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Physiology, Signaling, and Pharmacology of Galanin Peptides and Receptors: Three Decades of Emerging Diversity

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***Abstract*——Galanin was first identified 30 years ago as a "classic neuropeptide," with actions primarily as a modulator of neurotransmission in the brain and peripheral nervous system. Other structurally-related peptides—galanin-like peptide and alarin—with diverse biologic actions in brain and other tissues have since been identified, although, unlike galanin, their cognate receptors are currently unknown. Over the last two decades, in addition to many neuronal actions, a number of nonneuronal actions of galanin and other galanin family peptides have been described. These include actions associated with neural stem cells, nonneuronal cells in the brain such as glia, endocrine functions, effects on metabolism, energy homeostasis, and paracrine effects in bone. Substantial new data also indicate an emerging role for galanin in innate immunity, inflammation, and cancer. Galanin has been shown to regulate its numerous physiologic and pathophysiological processes through interactions with three G protein–coupled receptors, GAL_1, GAL_2, and GAL_3, and signaling via multiple transduction pathways, including inhibition of cAMP/PKA (GAL_1, GAL_3) and stimulation of phospholipase C (GAL_2). In**

ABBREVIATIONS: AC, adenylate cyclase; AD, Alzheimer's disease; AP, acute pancreatitis; ARC, arcuate nucleus; Aβ, β-amyloid; BNST, bed nucleus of the stria terminalis; BW, body weight; CeA, central amygdala; CNS, central nervous system; CREB, cAMP response element-binding protein; CRF, corticotropin-releasing factor; DCSV, dense core secretory vesicles; DH, dorsal horn; DR, dorsal raphe; DRG, dorsal root ganglia; EPSCs, excitatory postsynaptic currents; ERK, extracellular signal-regulated protein kinase; GAL_1, galanin receptor 1; GAL_1-KO, GAL_1 knockout; GAL_2, galanin receptor 2; GAL_2-KO, GAL_2 knockout; GAL_3, galanin receptor 3; GAL_3-KO, GAL_3 knockout; GALP, galanin-like peptide; GMAP, galanin message-associated peptide; GnRH, gonadotropin-releasing hormone; GPCR, G protein–coupled receptor; HNSCC, head and neck squamous cell carcinoma; 5-HT, 5-hydroxytryptamine, serotonin; IL-1α, interleukin 1α; IPSPs, inhibitory postsynaptic potentials; KO, knockout; LC, locus coeruleus; LDCVs, large dense-core vesicles; LepRb, leptin-induced p-STAT3 as a marker for leptin receptor; LH, luteinizing hormone; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCAo, middle cerebral artery occlusion; MPO, myeloperoxidase; NA, noradrenaline; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; OE, overexpressing; PAG, periaqueductal grey; PKC, protein kinase C; PNS, peripheral nervous system; PTX, pertussis toxin; PVN, paraventricular nucleus of hypothalamus; qRT-PCR, quantitative real-time polymerase chain reaction; SCLC, small-cell lung cancer; SFO, subfornical organ; SNP, single-nucleotide polymorphism; SON, supraoptic nucleus; SPX, spexin; SSSE, self-sustaining status epilepticus; 7-TM, 7-transmembrane; TNF-α, tumor necrosis factor-α; WT, wild-type.

this review, we emphasize the importance of novel galanin receptor–specific agonists and antagonists. Also, other approaches, including new transgenic mouse lines (such as a recently characterized GAL_3 knockout mouse) represent, in combination with viral-based techniques, critical tools required to better evaluate galanin system physiology. These in turn will help identify potential targets of the galanin/galanin-receptor systems in a diverse range of human diseases, including pain, mood disorders, epilepsy, neurodegenerative conditions, diabetes, and cancer.

I. Introduction—History of Galanin Systems

A. General Aspects of Neuropeptide Biology

1. Neuropeptides. The neuropeptide concept was coined by the late Dutch scientist David de Wied (for a review, see De Wied and De Kloet, 1987). In most mammalian nervous systems, neuropeptides are not the main chemical messengers but coexist with "classic" transmitters, e.g., acetylcholine, dopamine, noradrenaline (NA), serotonin (5-hydroxytryptamine; 5-HT), GABA, nitric oxide, and/or others. Thus, neurons release multiple messenger molecules (Hökfelt et al., 1986b; Merighi, 2002) (Fig. 1). However, peptides are the critical messenger molecules in hypothalamic neurosecretory cells. Here the magnocellular neurons produce inter alia oxytocin or vasopressin (Brownstein and Mezey, 1986; Bondy et al., 1989) and the parvocellular neurons synthesize corticotropin-releasing factor (CRF), thyrotropin-releasing hormone, gonadotropin-releasing hormone (GnRH), somatostatin, or/and others (Swanson and Sawchenko, 1983; Hökfelt et al., 1986a; Swanson et al., 1986; Kiss, 1988; Palkovits, 1992; Sawchenko et al., 1992). These peptides act as hormones and are released into the portal or general circulation.

Neuropeptides are different in several ways from classic transmitters (Strand, 1991). They are ribosomally synthesized as large precursor molecules in cell soma and dendrites and stored in and released from large dense-core (storage) vesicles (LDCVs) (Mains et al., 1987). The bioactive peptide is processed and then excised by convertase enzymes from larger prepropeptide precursors (Beinfeld, 1998; Seidah and Chretien, 1999). In contrast, classic transmitters are mainly stored in synaptic vesicles, although amines like NA and serotonin are also present in LDCVs. Neuropeptides are preferentially released when neurons fire in bursts or at high frequency (Adrian et al., 1983; Lundberg and Hökfelt, 1983; Dutar et al., 1989; Lundberg, 1996), so that under "normal" circumstances only the classic transmitter(s) is released and peptides remain in their storage vesicles. This

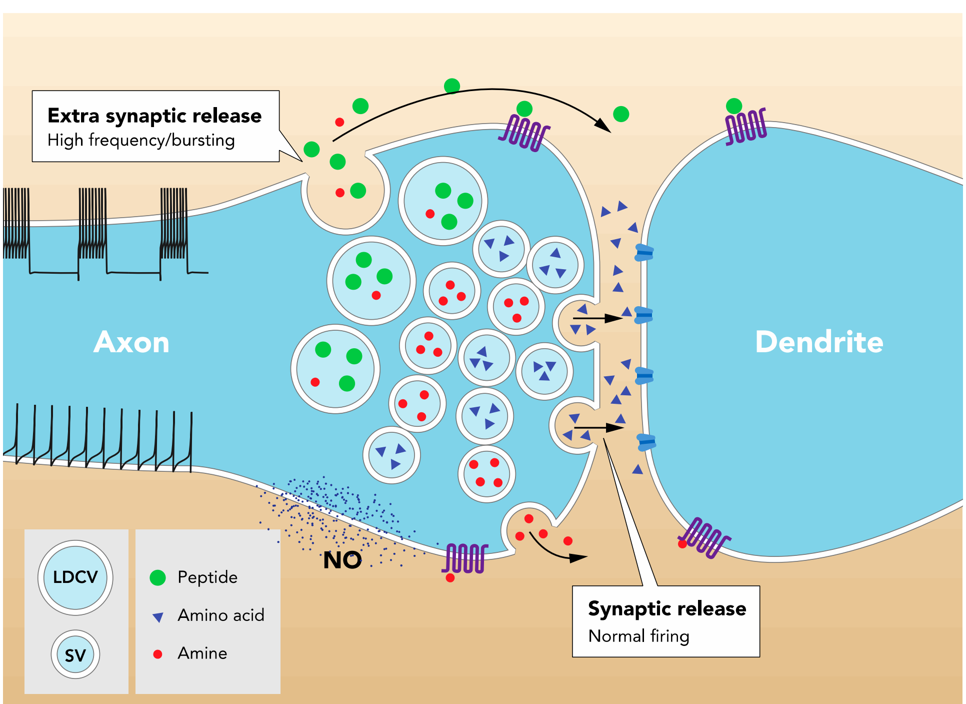

Fig. 1. Coexistence of a neuropeptide with classic and "unconventional" neurotransmitters in a nerve ending synapsing on a dendrite. Two types of storage vesicles are shown: synaptic vesicles (diameter 500 Å) storing classic transmitters (e.g., 5-HT, NA, GABA, or glutamate), mainly released at synapses; large dense-core vesicles (LDCVs) storing neuropeptides and, in amine neurons, NA or 5-HT, generally released extrasynaptically ("volume transmission") and after high-frequency or burst firing. Peptide receptors are essentially extrasynaptic or presynaptic, whereas ligand-gated receptors are mostly localized in the postsynaptic membrane. "Gaseous" (e.g., nitric oxide, NO) and other nonconventional transmitters are not stored in vesicles but are generated in neurons and/or nerve terminals upon demand. There is evidence that galanin can coexist with nitric oxide synthase and glutamate (or possibly GABA) in 5-HT neurons. Drawing by Mattias Karlén.

has been known for a long time also to apply to hypothalamic neurosecretory neurons. Thus, the release of oxytocin from magnocellular neurons is triggered by intermittent high-frequency burst firing (Wakerley et al., 1994), and this is also true for GnRH (Suter et al., 2000) and other hypothalamic releasing factors. Neuropeptides can be released both from nerve endings and soma/dendrites (Ludwig and Leng, 2006) in a similar way to some classic transmitters. After release they are usually degraded by extracellular peptidases (Roques et al., 1993), as there is no reuptake mechanism at the cell or storage vesicle membrane. In this way secreted neuropeptides have to be replaced by de novo synthesis, and thus transcript levels are generally elevated after release, followed by centrifugal transport of the newly synthesized peptide to nerve endings and/or dendrites. This results in dynamics that contrast with those of classic transmitters, which have a membrane reuptake mechanism (transporter) at both the cell and storage vesicle membrane (Liu and Edwards, 1997; Eiden et al., 2004; Torres and Amara, 2007). These transmitters can also be locally synthesized in nerve endings, allowing rapid reuse/replacement after release. In addition to replacing released peptide, peptide synthesis is also markedly altered by different physiologic and pathologic conditions. Thus, decreased or increased peptide expression may occur in response to, for example, nerve injury (Hökfelt et al., 1994; Zigmond and Sun, 1997; Costigan et al., 2002; Xiao et al., 2002).

Neuropeptides were initially monitored in native tissues using antibody-based technologies such as radioimmunoassay, Western blot analysis, enzyme-linked immunosorbent assay, or immunohistochemistry and, more recently, using advanced liquid chromatography mass spectrometry (Fricker, 2010). The cloning of genes encoding the neuropeptide precursors subsequently allowed their distribution and regulation to be characterized at the mRNA level by using molecular biologic techniques such as Northern blotting, quantitative real-time polymerase chain reaction (qRT-PCR), and in situ hybridization.

2. Neuropeptide Receptors. Evidence for neuropeptide receptors was first obtained using [^{125}I]-radioligand autoradiography, but there was still uncertainty about their existence/nature. This issue was resolved when Nakanishi and collaborators cloned the first neuropeptide receptor, a substance K receptor (tachykinin receptor; NK_2 receptor) (Masu et al., 1987). This receptor turned out to belong to the 7-transmembrane (7-TM), G protein–coupled receptor (GPCR) family. Subsequent research revealed that virtually all other neuropeptide receptors identified so far are GPCRs, with one exception, the peptide Phe-Met-Arg-Phe-NH_2 (FMRFamide), which induces a fast excitatory depolarizing response via direct activation of an amiloride-sensitive sodium channel (Green et al., 1994; Lingueglia et al., 1995). The cloning of neuropeptide receptors allowed their mapping and quantification at the mRNA level using in situ hybridization and qRT-PCR. At the protein level, the production of antisera permitted the identification of the exact subcellular localization and trafficking of neuropeptide receptors by using immunohistochemistry as well as quantification by Western blot analysis. However, the specificity of antibodies raised against neuropeptide receptors, and in fact also to 7-TM GPCRs in general, remains a serious problem.

3. Drug Development. The neuropeptide 7-TM GPCRs are potentially important targets for drug development, particularly as more than half of all drugs prescribed today act via this type of receptor (Hill, 2006). Moreover, neuropeptides and their receptors are often expressed in brain circuits/systems associated with conditions such as chronic pain and anxiety/depression. However, neuropeptide systems are prone to species variations (Bowers, 1994). Thus, drug targets based on animal experiments may not always be valid when designing drugs for treatment of human diseases. Another major obstacle is that neuropeptides are comparatively large molecules and pass through the blood-brain barrier to only a very limited extent. Moreover, due to the coexistence of multiple transmitters, it may not be sufficient to block only one receptor, if several transmitters are released from the same nerve ending. For example, although animal research indicated that substance P antagonists are analgesic, this effect was not reproduced in clinical trials (Hill, 2000). One reason could be that, in addition to substance P, several excitatory transmitters (glutamate and calcitonin gene-related peptide) are coreleased from central sensory nerve endings. Thus, glutamate and calcitonin gene-related peptide could still convey nociceptive signals, even if the substance P (neurokinin 1 [NK_1]) receptors are blocked. Another interesting issue is that peptide transmission is mostly "silent" under physiologic conditions. Therefore, intervention with antagonists is particularly attractive, because this should affect only deranged (upregulated) signaling systems, possibly resulting in fewer side effects. In contrast, agonists will act on receptors in the entire body, resulting in more side effects (e.g., the well known harmful effects of morphine, in addition to its unsurpassed antinociceptive action). For this reason, positive allosteric modulators are now increasingly being used as a way of reducing side effects attributable to receptor agonists.

B. History of Galanin Research

Galanin, a 29/30 amino acid peptide (Tatemoto et al., 1983), has been a relatively "anonymous" peptide during its 30-year-long research life, having been mentioned in just 3500 publications (PubMed, April

2014). Over this period a quite small number of galanin "aficionados" have gathered at four symposia, the last in 2013 in San Diego, California, with around 50 participants. In contrast, neuropeptide Y (NPY), discovered by the same group at the Karolinska Institutet around the same time as galanin (Tatemoto, 1982b), registers almost 13,000 hits in PubMed and more than a dozen scientific meetings. A much earlier discovered peptide, somatostatin, is associated with almost 30,000 articles in PubMed. Galanin can also be contrasted with the meteoric popularity of hypocretin/orexin (de Lecea et al., 1998; Sakurai et al., 1998), which has accumulated 3200 PubMed listings during its short, 15-year research life following its association with narcolepsy.

The galanin field or aspects of galanin biology have been frequently reviewed, e.g., the term "galanin *and* review" produces 460 hits in PubMed (April 2014), with 263 from 2001 and later, 91 of which have "galanin" in the title. From the latter, a representative collection covering the different galanin fields and research groups is provided here for further reading (Gundlach et al., 2001; Mazarati et al., 2001; Wiesenfeld-Hallin and Xu, 2001; Wynick et al., 2001; Zigmond, 2001; Crawley et al., 2002; Gundlach, 2002; Liu and Hökfelt, 2002; Vrontakis, 2002; Wynick and Bacon, 2002; Counts et al., 2003; Morilak et al., 2003; Ubink et al., 2003; Mazarati, 2004; Jacobowitz et al., 2004; Robinson, 2004; Lundstrom et al., 2005a; Hoyer and Bartfai, 2012). In addition, the proceedings of three of the galanin meetings (Hökfelt et al., 1991, 1998; Hökfelt and Crawley, 2005) and two multi-author reviews (Hökfelt and Tatemoto, 2008, 2010) have been published, with chapters by several authors who have been active in this field for many years. However, an up-to-date comprehensive review covering all aspects of the galaninergic system, including pharmacology, receptor signaling, major biologic functions, involvement in disease, epidemiology, and therapeutic implications, has not been published and is the rationale for the current review.

1. Discovery. Galanin was discovered by the Mutt group at the Karolinska Institutet in Stockholm around the early 1980s (Mutt, 1991). Viktor Mutt was a giant in the field of bioactive peptides (Jornvall et al., 1998). He died in September 1998, just months after attending the second galanin symposium. Viktor Mutt was an Estonian refugee from World War II and "found a home" at the Karolinska in the famous biochemical laboratory of Erik Jorpes, who had himself fled from Finland during World War I and then worked at the Karolinska, where he discovered heparin, in addition to other molecules (Åberg, 1991). Mutt over decades personally collected material from a slaughterhouse, serving as a starting point for purification of numerous peptides by him and his coworkers. While in initial studies the purity of the peptide was established in biologic assays, Mutt and his graduate student Kazuhiko Tatemoto developed a novel method for detection of biologically active peptides based on the C-terminal amide structure (Tatemoto and Mutt, 1978). This resulted in the discovery of several peptides, including peptide HI, peptide YY from porcine intestinal extracts, and NPY from porcine brain, published in papers included in Tatemoto's PhD thesis (Tatemoto, 1982a). The last in this peptide series was galanin, which was identified in porcine intestinal extracts (Tatemoto et al., 1983).

Viktor Mutt realized the problem of naming each new peptide after its first identified function and turned to an objective strategy based on the characteristic amino acid "signature" of the peptide. For example, galanin stands for N-terminal **g**lycine and C-terminal **alanin**e. NPY (Y for tyrosine) has tyrosine at both its C and N termini. As described by Tatemoto in a short article (Hökfelt and Tatemoto, 2010), the isolation of galanin was completed in 1980 but the structure was not determined until 1983. This was because, initially, no biologic activity was found. However, MacDonald at the University of Western Ontario demonstrated that galanin had an effect on plasma glucose levels, and Ake Rokaeus (Karolinska Institutet) demonstrated that galanin induced contraction of smooth muscle preparations, results that were included in the first publication on galanin (Tatemoto et al., 1983).

2. Rapid Expansion of Galanin Research. The rapid availability of galanin antibodies, first produced by Ake Rokaeus, allowed exploration of the galanin system using radioimmunoassay and, in particular, immunohistochemistry. A preliminary note (Rokaeus et al., 1984) reported the presence of galanin in widespread areas in the rat central nervous system (CNS) and in the intestine. This was promptly followed by major mapping studies (Skofitsch and Jacobowitz, 1985b, 1986; Melander et al., 1986c), an important finding being that galanin coexists in noradrenergic neurons in the locus coeruleus (LC) (high galanin levels), in serotoninergic neurons in the dorsal and medullary raphe nuclei (moderate levels), and with acetylcholine in cholinergic forebrain neurons (very low levels) (Melander et al., 1985b, 1986c). Subsequently, the distribution of galanin was reported in the mouse (Perez et al., 2001) and the primate brain (Gentleman et al., 1989; Chan-Palay et al., 1990; Kordower and Mufson, 1990; Kordower et al., 1992; Benzing et al., 1993). Peripheral tissues were also analyzed, including dorsal root ganglia (DRG) and the spinal cord (Ch'ng et al., 1985; Skofitsch and Jacobowitz, 1985a), as was the distribution of galanin neurons in the intestine (Ekblad et al., 1985; Melander et al., 1985a; Bishop et al., 1986), the respiratory tract (Cheung et al., 1985), and the genitourinary tract (Bauer et al., 1986a). However, in early studies, expression of galanin was also identified in endocrine tissues, e.g., the adrenal medulla (Bauer et al., 1986c) and anterior pituitary (Hulting et al., 1989; Steel et al., 1989), hence the designation of galanin as a "neuroendocrine" peptide.

3. The Galanin and Receptor Genes. A milestone in the field was the cloning of the rat *GAL* gene (Rokaeus and Brownstein, 1986; Vrontakis et al., 1987; Kaplan et al., 1988b) and the discovery of its estrogen-sensitivity (Kaplan et al., 1988a), later followed by the cloning of the mouse *GAL* gene (Kofler et al., 1996). These studies then allowed the mapping of galanin transcripts in the rat (Jacobowitz et al., 2004) and mouse brain (Cheung et al., 2001). Further exploration of the rat *GAL* gene revealed another peptide product encoded by it, galanin message-associated peptide (GMAP) (Rokaeus and Brownstein, 1986). Then, another related peptide, galanin-like peptide (GALP), was discovered, and although not a product of the *GAL* gene, GALP was originally described as a putative endogenous ligand of the GAL_2 receptor (Ohtaki et al., 1999), and its distribution in the rat and mouse brain has been widely reported (see section IV). Most recently, a further peptide product of the *GALP* gene, alarin, was described (Santic et al., 2006), demonstrating the existence of a small galanin peptide family.

Galanin receptors were initially mapped using radioligand binding autoradiography, first in the rat (Skofitsch et al., 1986; Melander et al., 1988) and then the primate brain (Kohler et al., 1989a,b; Kohler and Chan-Palay, 1990). However, in the mid-1990s the first galanin receptor gene, GAL_1, was cloned from a human melanoma cell line (Habert-Ortoli et al., 1994). Shortly thereafter, the rat GAL_1 gene was cloned from Rin14B insulinoma cells (Parker et al., 1995) and a rat cDNA library (Burgevin et al., 1995). These findings were followed by the identification and cloning of two more galanin receptors, GAL_2 and GAL_3 (Iismaa and Shine, 1999; Branchek et al., 2000; Lang et al., 2007). This allowed the mapping of galanin receptor transcripts using Northern blotting, qRT-PCR (Waters and Krause, 2000), and in situ hybridization (O'Donnell et al., 1999, 2003; Burazin et al., 2000; Mennicken et al., 2002; Le Maître et al., 2013). Thus far, no totally specific and reliable antigalanin receptor antibodies have been generated (Lu and Bartfai, 2009), so the exact regional and cellular localization of the three galanin receptor proteins in brain and other tissues remains to be elucidated, although studies of tagged receptors in transfected cell lines have provided some information on trafficking of GAL_1 and GAL_2 (Xia et al., 2004, 2008; Wirz et al., 2005).

4. Further Developments in the Galanin Field. These early basic research studies were then complemented by important advances in many areas, in particular the generation of mice carrying deletions of galanin and galanin receptor genes by several laboratories (Table 1), the synthesis of galanin receptor agonist and antagonist ligands, foremost by the Bartfai/Langel laboratories (see section III), as well as the resulting insights that galaninergic signaling is involved in a large number of disease states, including chronic pain, epilepsy, mood disorders, Alzheimer's disease and addiction, interestingly not confined to the nervous system but also involving the endocrine system, cancer, and inflammation—aspects that will be discussed in the following sections.

II. Galanin Genes and Peptides—Genomic Organization and Processing

The galanin family of peptides is encoded by two separate genes: galanin/GMAP prepropeptide (*GAL*) and galanin-like peptide (*GALP*). The human *GAL* gene is located on chromosome 11q13.2 (Evans et al., 1993), the rat gene on chromosome 1q42, and the mouse gene on chromosome 19 A. The human and mouse genes have six exons spanning 6.6 kb and 4.5 kb, respectively (Kofler et al., 1996), and the mRNAs encode precursor proteins of 124 (human) and 123 (mouse) amino acids (Rokaeus and Brownstein, 1986; Kofler et al., 1995; Blakeman et al., 2003). As is typical of regulatory peptides, galanin peptides are derived from a preproprecursor molecule (Fig. 2). First, the N-terminal signal sequence is cleaved, then further proteolytic cleavage at two pairs of basic amino acids results in the mature galanin peptide (30 amino acids in human, 29 amino acids in other species) and GMAP. In all species except humans, galanin is amidated on the C terminus. The N-terminal part of galanin is highly conserved throughout evolution. The first 19 amino acids display over 90% conservation from fish to humans, whereas the C-terminal portion of the peptide is less conserved (Fig. 2). The conservation of the N-terminal sequence is a strong indicator for the importance of this part of the peptide for receptor binding and biologic activity. Therefore, nearly all attempts to develop galanin receptor-selective peptides have used/are using galanin 1-13 as the core sequence (see section III.C on peptidergic ligands). Proteolysis of preprogalanin in cerebrospinal fluid leads to a variety of C-terminal, N-terminal, and internal peptide fragments (Nilsson et al., 2001). In certain types of tumors, processing of progalanin by plasmin results in production of galanin 1-20 (Yamamoto et al., 2011c). The half-life of galanin in plasma is around 5 minutes (Holmes et al., 2003). Biostability studies revealed that the half-life of synthetic galanin in plasma and cerebrospinal fluid is 60 to 120 minutes (Bedecs et al., 1995; Blakeman et al., 2001). Therefore, for potential therapeutic applications of galanin, analogs with increased biologic half-life are needed (see section III.C).

TABLE 1
Transgenic mice with altered levels of galanin/galanin receptor expression

Galanin/Galanin Receptor Overexpressing Transgenic Mice	
Promoter/DNA/Strain	Phenotype
Dopamine β-hydroxylase (Mazarati et al., 2000)/Human DBH (5.8 kb) driving 4.6 kb mouse genomic preprogalanin (10.4 kb transgene)/ C57BL/6J	Increased thresholds to noxious heat intact (Blakeman et al., 2001) Decreased neuropathic pain and shorter duration (Hygge-Blakeman et al., 2004) Reduced spinal excitability following c-fiber stimulation (Grass et al., 2003a) Galanin overexpression in neurons containing adrenaline or NA. Decrease in number of cholinergic neurons in the horizontal limbs of the diagonal band (Steiner et al., 2001) Increase in GAL_1 in specific brain regions (Hohmann et al., 2003a) Increased threshold for induction of after discharge (Mazarati et al., 2000) No difference in neuroendocrine profile (Hohmann et al., 2003b) Increased NA and 5-HT release after forced swim (learned helplessness—increase in depressive behavior) (Yoshitake et al., 2004) Reduced ACh release in the ventral hippocampus (Laplante et al., 2004) Decrease in opiate withdrawal behavior (Zachariou et al., 2003) Deficits in olfactory memory (Wrenn et al., 2003) Impaired response to trace cued fear conditioning (Kinney et al., 2002)
Galanin (Bacon et al., 2002)/20 kb murine genomic galanin upstream of the galanin gene/CBA/BL6 F1 hybrid	No difference in intact mechanical thresholds but higher after nerve injury, returned to intact values by day 7 (Bacon et al., 2007; Hulse et al., 2011) Reduction in acetone-induced pain-like behavior after PSNI (Hulse et al., 2012) Lower levels of cell death in vivo and in vitro (Elliott-Hunt et al., 2004)
Galanin (inducible) (Pope et al., 2010)/tTA under control of 20 kb murine genomic galanin, 4.6 kb murine genomic galanin under control of tetO/CBA/BL6 F1 hybrid	Decrease in opiate withdrawal behavior (Holmes et al., 2012) Increased mechanical thresholds after nerve injury reduced by galanin suppression (Pope et al., 2010)
Growth hormone (Perumal and Vrontakis, 2003)/320 bp rat GH promoter driving full-length rat preprogalanin cDNA including poly A tail (4.5 kb transgene)/C57BL6/SJL F2 × Swiss CD	Increased serum levels of galanin, prolactin and GH (GH in males only) Pituitary hyperplasia and adenomas in older mice (Perumal and Vrontakis, 2003) Reduced CPZ-induced myelin breakdown (Zhang et al., 2012)
Platelet-derived growth factor driving galanin (Holmberg et al., 2005a)/1.3 kb PDGF-β with galanin/GMAP gene construct, including intron 2 of the mouse galanin gene (genomic DNA and cDNA)/CBA/BL6 F1 hybrid	Increase in learned helplessness in old mice (Pirondi et al., 2005b). Increase in learned helplessness (Kuteeva et al., 2005) Reduced neuronal loss postaxotomy, 35% reduction in plasma extravasation, increased response in phase 2 of formalin test (Holmberg et al., 2005a) Elevated thermal thresholds but no difference in mechanical thresholds or cold thermal in intact adults (Blakeman et al., 2001) Decreased response to evoked seizures (Kokaia et al., 2001) Delayed reduction in NA after intracerebroventricular injection of galanin to ventral hippocampus. Increased NA and 5-HT release following forced swimming stress (Kehr et al., 2001)
Platelet-derived growth factor driving GAL_2 (Le Maitre et al., 2011)/1.3 kb PDGF-β driving mouse genomic GAL_2 with EGFP	Decreased immobility during the forced swim test (Le Maitre et al., 2011)
Prolactin (Cai et al., 1999)/2.5 kb rat prolactin promoter driving 4.6 kb murine genomic galanin (part of the first noncoding exon and all five coding exons for preprogalanin)/7.1 kb transgene/No details on strain	Increased prolactin synthesis and pituitary hyperplasia in older females (Cai et al., 1999). No increase in prolactin or hyperplasia in males.
Ret (Holmes et al., 2003)/12 kb murine c-ret cDNA driving 4.6 kb murine genomic galanin promoter (upstream of galanin gene)/ CBA/BL6 F1 hybrid	Elevated thermal and mechanical thresholds in intact mice and after injury (Holmes et al., 2003)
Reporters and Cre-expressing line	
Gal5.1-hβg-lacZ (Davidson et al., 2011)/5.1 kb human genomic galanin found 42 kb upstream of the galanin transcriptional start site with human β-globulin promoter and β-galactosidase reporter gene/CBA/BL6 F1 hybrid	Directed expression in galaninergic neurons of the PVN, ARC, and amygdala (Davidson et al., 2011)
20 kb Gal-lacZ (Bacon et al., 2007)/20 kb murine genomic galanin upstream of the *GAL* gene with 3.5 kb β-galactosidase reporter gene/CBA/BL6 F1 hybrid	Identical axotomy response to endogenous galanin in DRG neurons and in the developing DRG at embryonic day 17 (Bacon et al., 2007)
	Identical to 20 kb Gal-lacZ (Bacon et al., 2007)

(*continued*)

TABLE 1—*Continued*

Promoter/DNA/Strain	Phenotype
Galanin/Galanin Receptor Overexpressing Transgenic Mice	
4.6 kb Gal-lacZ (Bacon et al., 2007)/4.6 kb murine genomic galanin upstream of the galanin gene with 3.5 kb β-galactosidase reporter gene/CBA/BL6 F1 hybrid	
1.9 kb Gal-lacZ (Bacon et al., 2007)/1.9 kb murine genomic galanin upstream of the galanin gene with 3.5 kb β-galactosidase reporter gene/CBA/BL6 F1 hybrid	Loss of embryonic and intact adult DRG expression and axotomy response (Bacon et al., 2007)
4.6 Δ23,18 kb Gal-lacZ (Bacon et al., 2007)/4.6 kb murine genomic galanin upstream of the galanin gene but with deletion of the 23 bp 5′ putative Stat/Smad (−4326 to −4304) and 18 bp Stat/Smad/Ets (−2551 to −2534) binding sites, with 3.5 kb β-galactosidase reporter gene/CBA/BL6 F1 hybrid	No effect on embryonic or adult DRG expression but loss of axotomy response (Bacon et al., 2007)
GAL-Cre (Wu et al., 2014)/C56BL/6J	Use of galanin-Cre line to demonstrate that galanin neurons in the medial preoptic area govern parental behavior
GAL_2-OE-EGFP (Le Maitre et al., 2011)	High levels of GAL_2 expression in the presubiculum, subiculum, cingulate cortex, retrosplenial granular and agranular cortices, subregions of the prefrontal cortex and the olfactory bulb (Le Maitre et al., 2011)
Knockouts	
Galanin (Wynick et al., 1993)/129OlaHsd	Reduced intact thermal and mechanical pain thresholds. Reduced mechanical allodynia after nerve injury (Kerr et al., 2000a; Holmes et al., 2003)
	Increase in apoptosis in DRG at postnatal day 3–4 with reduction in number of small peptidergic neurons. Decreased regeneration in vivo and in vitro (Holmes et al., 2000; Sachs et al., 2007)
	Loss of one-third of cholinergic neurons in basal forebrain (O'Meara et al., 2000)
	Deficits in evoked ACh release (O'Meara et al., 2000; Kehr et al., 2001) and loss of spatial memory in aged mice (O'Meara et al., 2000; Massey et al., 2003)
	Increase in hippocampal cell death in vivo and in vitro (Elliott-Hunt et al., 2004, 2011)
	Increase in induced seizures (Mazarati et al., 2000)
	Marked reduction in levels of prolactin in the anterior pituitary and in plasma (Wynick et al., 1998)
	Decreased severity of cerulein-induced acute pancreatitis (Bhandari et al., 2010b)
	Reduced insulin secretion in response to non-neuronal stimulation and impaired glucose elimination (Ahren et al., 2004)
	Decreased food consumption on high-fat diet (Adams et al., 2008; Karatayev et al., 2010) Decreased ethanol intake and preference in female mice. Decreased orexin and melanin-concentrating hormone in the perifornical lateral hypothalamus (Karatayev et al., 2010)
	Increase in opiate withdrawal behavior (Zachariou et al., 2003)
	Decreased sensitivity to nicotine and no increase in ERK2 activation in mice that showed nicotine conditioned place preference (increase in WT) (Neugebauer et al., 2011)
	Increase in secreting sweat glands following thermal stimulation (Vilches et al., 2012)
GAL_1 (Jacoby et al., 2002)/C57BL/6J and 129T2/SvEmsJ	Increased sensitivity to both heat and cold intact. Increased duration of pain-like behavior after nerve injury (Blakeman et al., 2003)
	No difference in mechanical or thermal thresholds in intact animals but increased hyperalgesia after thermal injury and faster recovery after spinal nerve ligation (Malkmus et al., 2005)
	No difference in regeneration in vivo (Blakeman et al., 2003) or in vivo (Blakeman et al., 2003; Mahoney et al., 2003a)
	Increase in opiate withdrawal behavior (Holmes et al., 2012)
	Spontaneous seizures and reduced plasma levels of IGF-1. No sex difference but strain difference in seizures; not present in mice on 129/Sv background (Jacoby et al., 2002)
	Impaired response to trace cued fear conditioning (Wrenn et al., 2004)
	Mild glucose intolerance after feeding and impaired glucose elimination. Increased food intake on high-fat diet (Zorrilla et al., 2007)
	No inhibition of vagal activity after stimulation of the vagus nerve and administration of galanin, as seen in WT and galanin-KO. No inhibition of vagal activity after stimulation of the vagus nerve in the presence of propranolol and administration of an NPY Y_2 antagonist, as seen in WT and galanin-KO (Smith-White et al., 2003)

(*continued*)

TABLE 1—*Continued*

Galanin/Galanin Receptor Overexpressing Transgenic Mice	
Promoter/DNA/Strain	Phenotype
GAL$_1$ (Matkowskyj et al., 2000)/C57BL/6J	Decreased fluid secretion in the GI tract after infection with enteric pathogens (Matkowskyj et al., 2000)
	No different from WT in response to *Salmonella typhimurium* infection (Matkowskyj et al., 2009)
	Decreased diarrhea after infection with rhesus rotavirus (Hempson et al., 2010a)
GAL$_1$/Deltagen (San Carlos, CA)/129P2/OlaHsd × C57BL/6	Increased neuronal loss in hippocampus after kainic acid administration (Schauwecker, 2010)
GAL$_2$/Lexicon Genetics (The Woodlands, TX)/129/SvEvBrd × C57BL/6	15% less CGRP-IR neurons in DRG. No difference in thermal or mechanical thresholds in intact animals, but decreased response to neuropathic pain (no allodynia) and inflammatory pain (phase 2 of formalin test). Decrease of one-third in neurite outgrowth, decrease in phosphorylated ERK, increase in phosphorylated AKT (Hobson et al., 2006)
	Increased hippocampal cell death in vivo after glutamate treatment (Elliott-Hunt et al., 2011)
	Reduced levels of ERK and AKT after glutamate damage in vivo (Elliott-Hunt et al., 2007)
GAL$_2$/Deltagen (San Carlos, CA)/129 ⁄ Sv × C57BL/6	16–20% fewer neurons in DRG 7 days postaxotomy both intact and contralateral, no further loss ipsilateral (WT decrease of 26%). No difference in thermal or mechanical thresholds in intact animals or in hyperalgesia after injury (Shi et al., 2006)
	Persistent escape deficits after inescapable shock (persistent depressive-like phenotype) (Lu et al., 2008)
	Galanin had no effect on GABAergic IPSPs in CeA neurons (decreased in WT) (Bajo et al., 2012)
GAL$_2$/Nura Inc. (Seattle, WA)/129S1/SvImJ	No difference in motor and sensory function, reproduction, feeding behavior, mood, learning and memory, or susceptibility to seizures (Gottsch et al., 2005)
	Increased anxiety-like behavior in elevated plus-maze (Bailey et al., 2007)
GAL$_3$/Lexicon Genetics (The Woodlands, TX)/C57BL/6J	Increased cholesterol and triglyceride levels in homozygous males (Lexicon Genetics) (https://beta.infrafrontier.eu/sites/infrafrontier.eu/files/upload/public/lexicon/combined_lexicon_data/LEXKO-230-treeFrame.html)
	Anxiety phenotype but no depression-like behavior (Brunner et al., 2014)
Double GAL$_1$ × GAL$_2$-KO (Jacoby et al., 2002) × Deltagen (San Carlos, CA)/C57BL/6J × (129 ⁄ Svx C57BL/6)	Galanin had no effect on GABAergic IPSPs in CeA neurons (decreased in WT) (Bajo et al., 2012)

ACh, acetylcholine; bp, base pairs; CGRP, calcitonin gene-related peptide; CPZ, cuprizone; DBH, dopamine β-hydroxylase; EGFP, green fluorescent protein; GH, growth hormone; GI, gastrointestinal; Hβg, human β-globulin; IGF, insulin-like growth factor; lacZ, β-galactosidase; PDGF, platelet-derived growth factor; PSNI, partial saphenous nerve ligation injury; PVN, paraventricular nucleus of the hypothalamus; SNL, spinal nerve ligation.

The galanin sequence is followed by the GMAP sequence (60 amino acids in humans). No major in vivo functions for GMAP have been reported in mammals, but GMAP has antifungal activity (see section IX.B).

Galanin gene expression is regulated by estrogen within lactotrophs and somatotrophs of the rat anterior pituitary gland (Vrontakis et al., 1989; Hyde et al., 1991) and accordingly fluctuates during the estrous cycle in the rat (Kaplan et al., 1988a; Merchenthaler et al., 1991, 1993a; Bakker et al., 2002). Galanin expression is modulated in a cell type-specific manner in humans (Vrontakis et al., 1990; Kofler et al., 1995; Howard et al., 1997b), and tissue and cell type-specific hormonal regulators of the galanin gene include vasoactive intestinal peptide (Mohney and Zigmond, 1999), activity-dependent neuroprotective protein (Mandel et al., 2007), thyroid hormone (Hooi et al., 1997; Calza et al., 1998a,b), progesterone (Brann et al., 1993), GnRH (Marks et al., 1994), dexamethasone (Torsello et al., 1992), nerve growth factor, brain-derived nerve growth factor, and leukemia inhibitory factor (Corness et al., 1996; Corness et al., 1998; Kerekes et al., 1999).

Some of the most potent inducers of galanin gene expression are protein kinase C (PKC) after activation with phorbol ester, protein kinase A activated by forskolin (Rokaeus et al., 1990; Corness et al., 1997), and colchicine, which interferes with microtubules and alters intraneuronal transport (Dahlstrom, 1968; Kreutzberg, 1969) to produce a marked increase in *GAL* mRNA expression (Cortes et al., 1990). In vivo, galanin gene expression and peptide secretion in the nervous system are modulated by chronic stress (Holmes et al., 1995; Sweerts et al., 1999; Sergeyev et al., 2005; Sciolino et al., 2012), axotomy (Hökfelt et al., 1994; Burazin and Gundlach, 1998), ischemic brain damage (Liu and Hökfelt, 2000; Holm et al.,

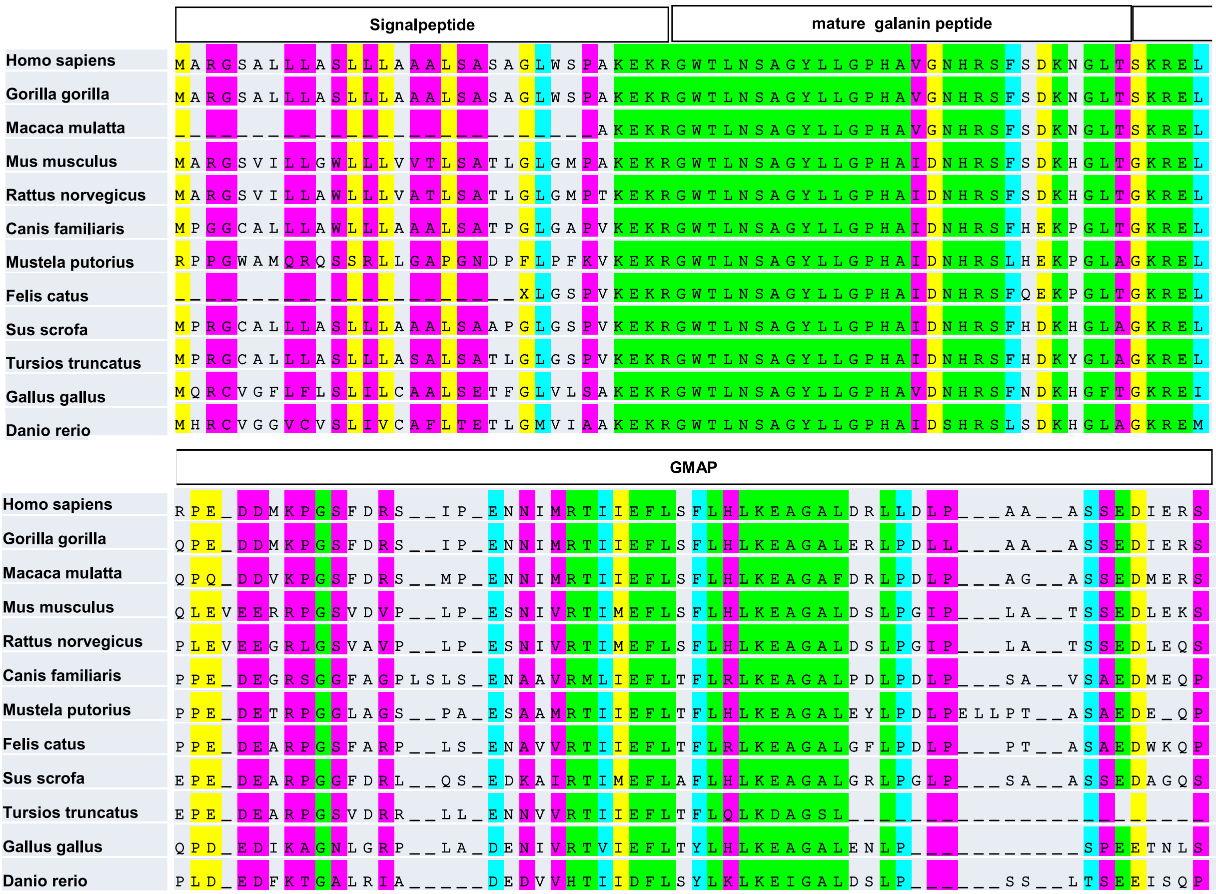

Fig. 2. Alignment of amino acid sequences of the galanin precursor peptides. The degree of conservation is indicated by color: gray < 50%, pink 50–70%, yellow 70–80%, blue 80–90%, and green > 90%.

2011, 2012), chronic constriction nerve injury (Nahin et al., 1994), orofacial pain (Tokunaga et al., 1992), exercise (Legakis et al., 2000), electroconvulsive stimulation (Christiansen, 2011), and herpes simplex virus infection (Henken and Martin, 1992).

The *GALP* gene is located on chromosome 19 in humans, 1q12 in rats, and 7 A1 in mice; it has 6 exons spanning 9.7 to 19 kb. The GALP prepropeptide consists of 115–120 amino acids, which includes a signal peptide followed by the GALP sequence. The C-terminal residual peptide is generated by cleavage at dibasic residues. The fact that the genomic organization of *GALP* is similar to that of *GAL* and that GALP amino acids 9–21 are homologous to the first 13 amino acids of galanin, indicate that these two genes evolved through gene duplication. In vivo experiments have revealed that *GALP* expression is regulated by insulin and leptin (Jureus et al., 2001; Fraley et al., 2004a), by fasting and osmotic stimulation (Shen et al., 2001), by thyroid hormone and lactation (Cunningham et al., 2004a), during endotoxin shock, and in adjuvant arthritis (Saito et al., 2003).

The high sequence conservation of GALP with the amino-terminal end of galanin provides the structural basis for GALP binding and activation of galanin receptors (see section III). However, it is very likely that GALP has other native receptors, despite actions at $GAL_{1\text{-}3}$, as it remains fully active in galanin receptor KO strains.

In contrast to *GAL* mRNA, the *GALP* primary transcript is characterized by extensive splicing (Santic et al., 2006, 2007). Transcript 2 of *GALP* excludes exon 3, which leads to a frame shift after the sequence encoding the first five amino acids of the mature GALP peptide, producing a putative "novel" peptide of 25 amino acids (Santic et al., 2006, 2007). Based on the naming of "galanin," this peptide was named "alarin" because of its N-terminal alanine and C-terminal serine residues. Analogously, other neuropeptides (e.g., vasoactive intestinal peptide and PHM-27) were also found to be derived from the same gene (Bodner et al., 1985).

Synthetic alarin inhibits neurogenic inflammation of the skin (Santic et al., 2007) and has actions typical of a neuropeptide in that it regulates food intake, metabolism, reproductive behavior, and hormone secretion (Boughton et al., 2010; Van Der Kolk et al., 2010; Fraley et al., 2012, 2013). Furthermore, alarin has antidepressant-like effects that are associated with reduced serum levels of corticotrophin-releasing hormone, adrenocorticotropic hormone, and corticosterone (Wang et al., 2014). Although alarin does not bind to galanin receptors, the peptide is regarded as a member of the galanin peptide family because it is derived from a gene with partial homology to *GAL*.

As will be emphasized in this review, galanin peptides have a wide range of nonneuronal functions as well as classic neuromodulatory roles. We therefore recommend that the galanin peptides be classified as *regulatory peptides* and not as neuropeptides, as the latter term is too narrow in scope and misleading in this context.

III. Galanin Receptors

A. Identification and Nomenclature

In this review we use the receptor nomenclature proposed by the International Union of Basic and Clinical Pharmacology Committee. Galanin exerts its biologic effects via three known GPCRs, GAL_1 (Habert-Ortoli et al., 1994), GAL_2 (Howard et al., 1997a), and GAL_3 (Wang et al., 1997b). The level of sequence homology among the three human receptors ranges between 33.2% (GAL_1 versus GAL_3) and 53.8% (GAL_2 versus GAL_3) (Liu et al., 2010) (Figs. 3 and 4). It has been speculated that GAL_2 genes may have evolved from GAL_1, and GAL_3 genes from GAL_2, because GAL_3 genes are found only in some mammals, whereas GAL_1 and GAL_2 genes are present in vertebrates as diverse as fish and primates (Liu et al., 2010).

In the CNS and in the periphery, all three galanin receptors display distinct but overlapping patterns of expression (see section IV); therefore, pharmacological studies using receptor-selective ligands are needed to help elucidate receptor-specific effects.

Studies using cell lines transfected with galanin receptors have demonstrated GAL_1 homodimerization and internalization (Wang et al., 1998b; Xia et al., 2004, 2005b, 2008; Wirz et al., 2005). GAL_2 also undergoes internalization upon ligand binding (Xia et al., 2004, 2005b). There is also increasing evidence that different galanin receptors can form heteromers, at least in the CNS (Fuxe et al., 2012), leading to altered recognition of galanin ligands. Moreover, putative heteromers of galanin receptors with other GPCRs have been described, including GAL_1 with a 5-HT receptor, Y_1 and Y_2 (NPY) receptors, α_2-adrenoceptor (Fuxe et al., 2008, 2012), and dopamine D_1-like receptors (D_1 and D_5), but not GAL_2 (Moreno et al., 2011). This latter study provides strong evidence that D_1-like/GAL_1 receptor heteromers integrate signals of the monoamine and neuropeptide transmitter systems to modulate hippocampal cholinergic neurotransmission. Such heteromeric receptors may present novel targets for therapeutic intervention.

Of the other members of the galanin peptide family, only GALP is a high-affinity ligand for the known galanin receptors. At present, there are no identified receptors for GMAP or alarin.

B. Galanin Receptor Signaling

The three galanin receptors share a number of characteristics as they are members of the 7-TM GPCRs, but their functional coupling and signal transduction pathways are substantially different, thus contributing to the diversity of galanin-mediated effects (Fig. 5), depending on the cell type and its particular G protein repertoire.

The majority of pharmacologic studies on GAL_1 signaling have been performed with cell lines transfected with rat or human GAL_1, where GAL_1 activation results in an inhibitory action on adenylate cyclase (AC), leading to reduced cAMP concentrations (Habert-Ortoli et al., 1994; Parker et al., 1995; Fitzgerald et al., 1998; Wang et al., 1998c), opening of G protein–regulated inwardly rectifying K^+

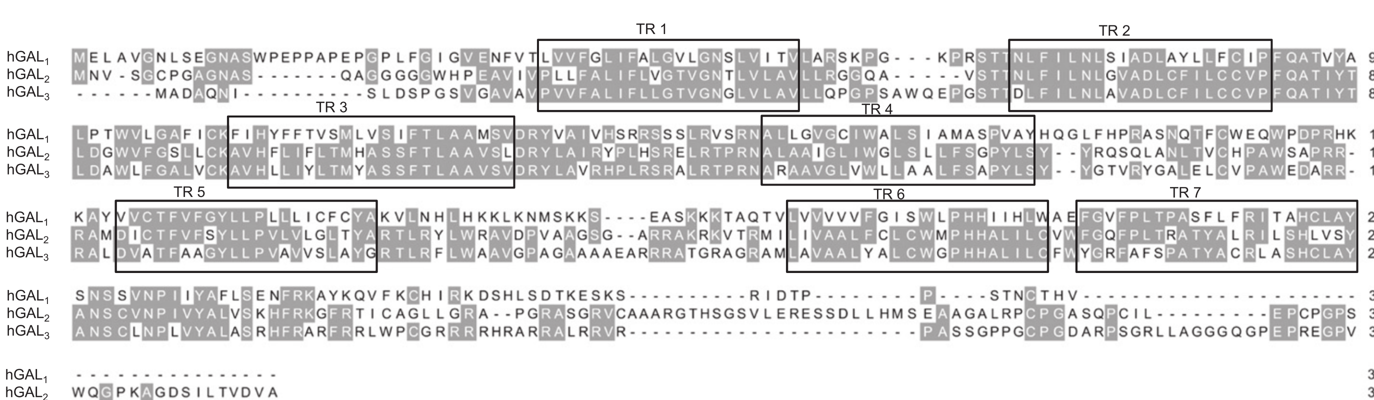

Fig. 3. Alignment of amino acid sequences of human GAL_1 (NP_001471.2), GAL_2 (NP_003848.1), and GAL_3 (NP_003605.1). Conserved amino acids of the aligned receptors are shown shaded. Transmembrane regions are boxed.

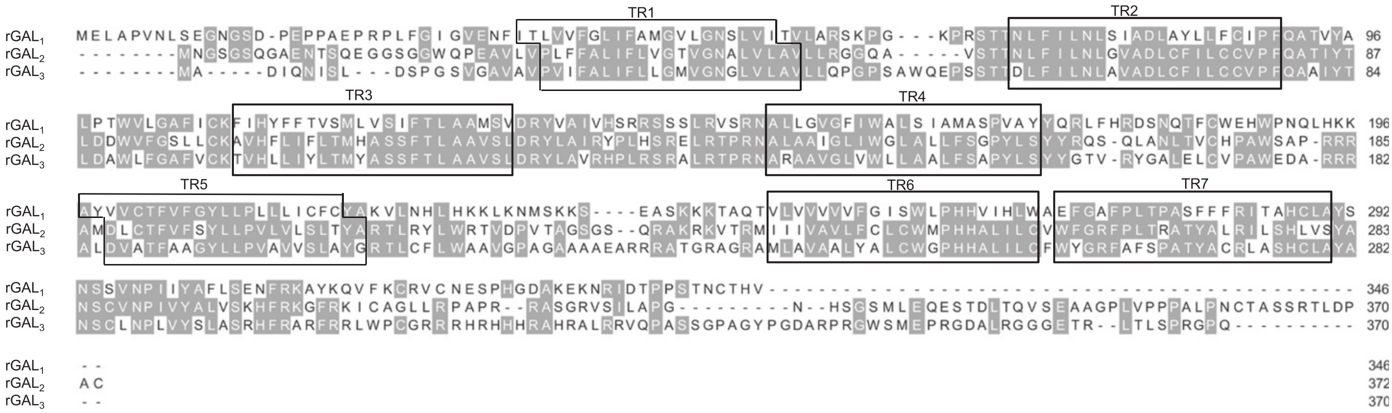

Fig. 4. Alignment of amino acid sequences of rat GAL_1 (NP_037090.2), GAL_2 (NP_062045.1), and GAL_3 (NP_062046.1). Conserved amino acids of the aligned receptors are shown shaded. Transmembrane regions are boxed.

channels (Smith et al., 1998), and stimulation of mitogen-activated protein kinase (MAPK) activity. All actions are regulated in a pertussis toxin (PTX)–sensitive manner and are mediated via a $G_{i/o}$-type G protein (Smith et al., 1998; Wang et al., 1998c). In rat neurons, a GAL_1-mediated effect on voltage-dependent Ca^{2+} channels has been reported (Endoh et al., 2008; Anselmi et al., 2009).

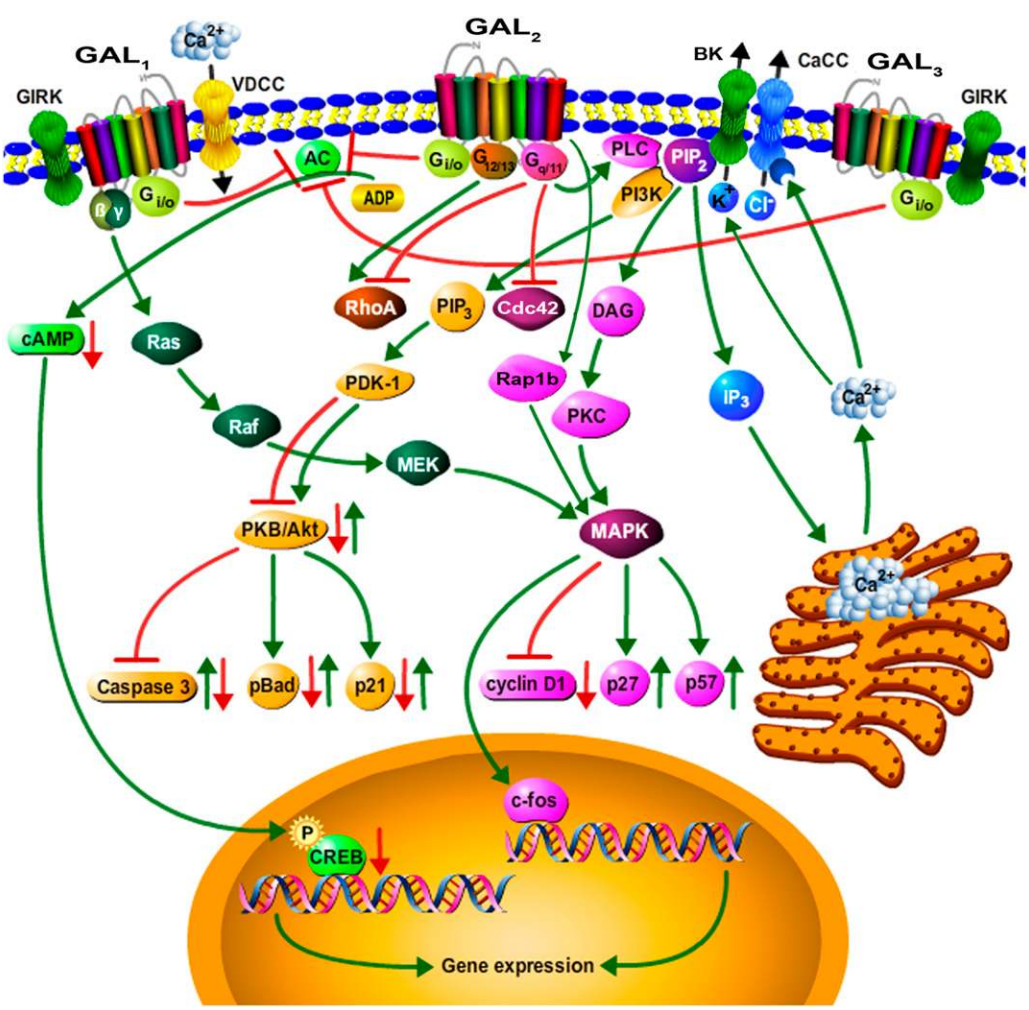

Fig. 5. Signaling pathways of galanin receptors. Abbreviations: AC, adenylate cyclase; BK, calcium-activated (big) potassium channel; CaCC, calcium-dependent chloride channel; (p)CREB, (phosphorylated) 3′,5′-cAMP response element-binding protein; DAG, diacylglycerol; GIRK, G protein–regulated inwardly rectifying potassium channel; IP_3, inositol triphosphate; MEK, mitogen-induced extracellular kinase; PDK-1, phosphoinositide-dependent protein-kinase 1; PIP_2, phosphatidylinositol bisphosphate; PIP_3, phosphatidylinositol trisphosphate; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; PLC, phospholipase C; VDCC, voltage-dependent calcium channel.

GAL_1-induced effects on the MAPK/extracellular signal-regulated protein kinase (ERK) 1/2 pathway have been described in human tumor cells (Henson et al., 2005; Kanazawa et al., 2007). Activation of the MAPK/ERK pathway via GAL_1 is not linked to the phosphatidylinositol 3-kinase pathway and leads to the induction of the cell-cycle control proteins $p27^{Kip1}$ and $p57^{Kip2}$ and suppression of cyclin D1 in GAL_1-transfected human squamous cell carcinoma cells (Kanazawa et al., 2007).

In vivo experiments in rodents suggest GAL_1 might be involved in the regulation of the transcription factors cAMP response element-binding protein (CREB) (Badie-Mahdavi et al., 2005; Kinney et al., 2009) and the immediate early gene c-*fos* (Blackshear et al., 2007) in specific brain regions.

However, phosphorylation of CREB is also mediated by activation of GAL_2 (Badie-Mahdavi et al., 2005), which may be because GAL_2 can inhibit AC activity through coupling to G_i-type G proteins similar to GAL_1 (Wang et al., 1997a; Fathi et al., 1998). In contrast to GAL_1, GAL_2 signals through multiple classes of G proteins to stimulate multiple intracellular pathways. Activation of GAL_2 is capable of stimulating the MAPK/ERK pathway in a PTX-sensitive, PKC-dependent fashion, indicative of coupling to a G_0 protein in GAL_2-transfected cell lines (Wang et al., 1998c). Endogenous GAL_2-induced activation of the MAPK/ERK pathway via PKC has been reported in rodent hippocampal neurons (Hawes et al., 2006; Elliott-Hunt et al., 2007), rat microglial cells (Ifuku et al., 2011), rat PC12 pheochromocytoma cells (Hawes et al., 2006), and human small-cell lung cancer (SCLC) cells (Seufferlein and Rozengurt, 1996), although in the latter, MAPK/ERK pathway activation can also occur independently of PKC (Wittau et al., 2000).

GAL_2 predominantly couples to a $G_{q/11}$-type G protein, leading to phospholipase C activation, which stimulates Ca^{2+} release via inositol phosphate hydrolysis and opens Ca^{2+}-dependent ion channels in a PTX-resistant manner, in both GAL_2-transfected cell lines (Smith et al., 1997b; Borowsky et al., 1998; Fathi et al., 1998; Pang et al., 1998; Wang et al., 1998c) and GAL_2-expressing rat microglial cells (Ifuku et al., 2011). GAL_2 activation led to a decrease in both Rho and Cdc42 GTPase activity and activation of cofilin in rat PC12 pheochromocytoma cells (Hobson et al., 2013). In SCLC cells, another signaling pathway has been proposed for GAL_2 involving functional coupling to a $G_{12/13}$-type G protein and subsequent activation of the small GTPase protein Rho A (Wittau et al., 2000).

In GAL_2-transfected human head and neck squamous carcinoma cells, GAL_2 activation affects the regulation of the cell-cycle control proteins $p27^{Kip1}$, $p57^{Kip2}$, and cyclin D1 and induces caspase-3–dependent apoptosis (Kanazawa et al., 2009), which has also been observed in GAL_2-transfected human SH-SY5Y neuroblastoma (Berger et al., 2004) and rat PC12 pheochromocytoma cells (Tofighi et al., 2008). In the latter cells, GAL_2 activation leads to reduced expression of pAkt, pBad, and $p21^{cip1}$, downstream of the G_{q11}/phosphatidylinositol 3-kinase pathway (Tofighi et al., 2008). The AKT signaling pathway also seems to be modulated by GAL_2 in rodent neurons in dorsal root ganglia (Hobson et al., 2006), hippocampus (Elliott-Hunt et al., 2007), and basal forebrain, where galanin-mediated AKT signaling leads to suppression of caspase-3 and -9 activity (Ding et al., 2006). In the human laryngeal carcinoma cell line HEp-2, GAL_2-mediated apoptosis is triggered independently of caspase by the induction of the proapoptotic Bcl-2 protein Bim (Uehara et al., 2014). A recent report indicates that activation of GAL_2 in human embryonic kidney (HEK293) cells leads to an elevation of intracellular Ca^{2+} due to Ca^{2+} efflux from the endoplasmic reticulum produced by IP3R sequentially opening BK channels (Pan et al., 2014).

GAL_1 and GAL_2 are the most studied of the three galanin receptors, and the signaling properties of GAL_3 are still poorly defined (Fig. 5). GAL_3 appears to act mainly via a PTX-sensitive $G_{i/o}$-type G protein, resulting in activation of G protein–regulated inwardly rectifying K^+ channels, as well as decreased AC activity and cytosolic cAMP levels (Kolakowski et al., 1998; Smith et al., 1998). Therefore, it seems likely that activation of GAL_3, similar to activation of GAL_1 and GAL_2, will affect phosphorylation of CREB. Also, potential heteromerization of GAL_3 with the other galanin receptors or other neuropeptide receptors cannot be excluded.

One explanation for the lack of information on GAL_3 signaling is that, so far, no cell line has been identified that expresses endogenous GAL_3. There are several GAL_3-transfected cell lines available (Lang et al., 2005; Lu et al., 2005b), but although they express *GAL_3* mRNA, they are not able to produce sufficient GAL_3 protein or GAL_3 in an appropriate form on the plasma membrane to allow galanin binding and stable signaling experiments to be performed (Robinson et al., 2013; R. Lang and A. Lang, personal communication). A possible reason for this is that the different cells used do not express the appropriate G proteins or other receptors to allow correct GAL_3 trafficking and/or signaling. Consistent with this hypothesis, GAL_3 overexpression in these cells has been shown to generate insoluble inclusion bodies which prevent the receptor being trafficked to and expressed on the cell surface (Robinson et al., 2013; B. Brodowicz, unpublished data). Robinson et al. (2013) reported that the GAL_3 carboxy tail has multiple overlapping motifs that target expression to the endoplasmic reticulum, inhibiting receptor transport and insertion at the cell membranes. Those authors showed that a modified GAL_3 construct (the C-terminal part of GAL_3 was replaced with that of GAL_1) facilitates cell surface expression while maintaining wild-type receptor pharmacology. This finding (Robinson et al., 2013) should allow the GAL_3 field to move forward, because the chimeric cell line can be used to study G protein coupling, the downstream signaling pathways, and to undertake high-throughput screening to identify novel GAL_3 ligands.

TABLE 3
Amino acid residues of galanin receptors involved in ligand binding determined in mutation studies

Receptor	Residues
GAL_1	Phe115[a,b], Phe186[b], His264[a], His267[a], Glu271[a,b], Phe282[a]
GAL_2	His252[c], His253[c], Ile256[c], Phe264[c], Tyr271[c]
GAL_3	Tyr103[d], His251[d], Phe263[d], Tyr270[d], Arg273[d], His277[d]

[a]Berthold et al. (1997).
[b]Church et al. (2002).
[c]Lundstrom et al. (2007).
[d]Runesson et al. (2010).

C. Galanin Receptor-Ligand Interactions

Some progress has been made over recent years toward the development of receptor-selective ligands to delineate the involvement of different galanin receptors in a variety of physiologic processes and associated diseases. Recent molecular docking studies have revealed several ligand-binding amino acid residues in galanin receptors, thus helping to identify the molecular interactions underlying the ligand selectivity and specificity at the different receptors (Xiong et al., 2005; Kothandan et al., 2013) (Table 2). Most of the residues identified by ligand-docking studies have been confirmed as crucial for these interactions in site-directed mutagenesis studies (Berthold et al., 1997; Church et al., 2002; Runesson et al., 2010) (Table 3) and these key interaction sites represent logical targets for drug-design studies.

1. Peptide Ligands. All three characterized galanin receptors have high affinity for the endogenous galanin peptide. Early pharmacological studies using a variety of galanin fragments from various species demonstrated minor importance of C-terminal amino acids beyond positions 15–16 but significant importance of the N-terminal region for galanin receptor affinity (Land et al., 1991; reviewed in Lang et al., 2007). N-terminal truncation of Gly^1 reduces the affinity of GAL_1 for galanin in comparison with GAL_2 and GAL_3, a finding that led to the introduction of the galanin fragment (2–11) (also known as AR-M1896) as a "non-GAL_1" galanin receptor ligand that was only able to activate GAL_2 and GAL_3 (Liu et al., 2001; Lu et al., 2005b). Although removal of further N-terminal amino acids from galanin (2–11) resulted in a loss of affinity for all three receptors in cell lines transfected with galanin receptors (Wang et al., 1997b; Bloomquist et al., 1998; Smith et al., 1998), the fragment galanin (3–29) is fully active in the anterior pituitary in vivo (Wynick et al., 1993; Kinney et al., 1998; Todd et al., 2000).

TABLE 2
Amino acid residues of galanin receptors involved in ligand binding found by docking studies

Receptor	Residues
GAL_1[a]	Gln92, Val95, Tyr96, Cys108, His112, Phe115, Thr116, Met119, Cys203, Val206, His263, His264, His267, Ile286, His289
GAL_2[a]	Gln82, Ile105, Phe106, Met109, Tyr160, Tyr163, Tyr164, Asn171, Thr173, Asp188, Thr191, Ser195, His253, Ile256, His278, Tyr282
GAL_3[a,b]	Gln79[a,b], Ile82[a,b], Asp86[b], Trp88[b], Cys95[a], Val98[a], His99[a,b], Ile102[a,b], Tyr103[a,b], Tyr161[a], Tyr166[a], Glu170[b], Pro174[b], Ala175[b], Asp185[b], His251[a], Tyr270[a], Arg273[a,b], His277[a,b], Tyr281[a]

[a]Jurkowski et al. (2013).
[b]Kothandan et al. (2013).

In the early 1990s, several chimeric, high-affinity but nonselective ligands were synthesized composed of mammalian galanin (1–13) as the N-terminal fragment and a carboxy-terminus modified with different (neuro) peptides, which mainly act as galanin receptor antagonists in vivo (Bartfai et al., 1991; Leibowitz and Kim, 1992; Wiesenfeld-Hallin et al., 1992; Crawley et al., 1993; Xu et al., 1995a) (see Table 4). However, many of these chimeric peptides have full or partial agonistic activity in vitro in cell lines expressing just one receptor type. To improve receptor selectivity further, chimeric peptide ligands were introduced with modifications at both the N and C termini. A modified M35 peptide called M617, in which the proline at position 14 was substituted by a glutamine (see Table 4 for sequence), was initially reported to be a GAL_1-specific ligand (Hobson et al., 2006), but was recently found to have agonist activity at GAL_3 (Sollenberg et al., 2010). Removal of the N-terminal glycine residue of galanin together with a C-terminal substitution resulted in the GAL_2-selective peptide M871, which acts as an antagonist in vivo (Sollenberg et al., 2006, 2010). Several other GAL_2-specific chimeric peptides (M1145 and M1151-M1153) with agonist properties in vitro have been described over recent years (Runesson et al., 2009; Saar et al., 2011). It was reported that the GAL_2-specific peptide M1160 is a potential agonist in vivo (Saar et al., 2013b) but generally the in vivo activity of these peptides is largely unknown. Stearoylation of M1145 resulted in a systemically active GAL_2-preferring ligand, J18 (Saar et al., 2013a).

Further chemical modifications of galanin have included the introduction of lipoamino acid and cationic acid residues as well as a palmitoyl moiety, which resulted in several high-affinity galanin analogs with potent anticonvulsant activities and improved systemic bioavailability (Bulaj et al., 2008). An 18-fold preference for GAL_2 was produced by altering the N terminus of these peptides (Robertson et al., 2010) (see

TABLE 4
Peptide ligands for galanin receptors with type of in vivo activity

Peptide Ligands	Sequence	Receptor Specificity	Activity	Species
Human galanin (1–30)	GWTLNSAGYLLGPHAVGNHRSFSDKNGLTS	none	agonist	
Rat galanin (1–29)	GWTLNSAGYLLGPHAIDNHRSFSDKHGLT	none	agonist	
Porcine galanin (1–29)	GWTLNSAGYLLGPHAIDNHRSFHDKYGLA	none	agonist	
Galanin (2–11) (AR-M1896)	WTLNSAGYLL	GAL$_2$/GAL$_3$[a,b]	agonist[a]	rat
C7 = galanin (1–13)-spantide I	GWTLNSAGYLLGPRPKPQQWFWLL	none	antagonist[c]	rat
M15 = galantide= galanin (1–13)-substance P (5–11) amide	GWTLNSAGYLLGPQQFFGLM	none	antagonist[d]	rat
M32 = galanin (1–13)-neuropeptide Y (25–36) amide	GWTLNSAGYLLGPRHYINLITRQRY	none	antagonist[e]	rat
M35 = galanin(1–13)-bradykinin(2–9) amide	GWTLNSAGYLLGPPPGFSPFR	none	antagonist[f]	rat
M40 = Galanin (1–13)-Pro-Pro-(Ala-Leu-)$_2$Ala amide	GWTLNSAGYLLGPALALA	none	antagonist[c,g]	rat
M617 = galanin(1–13)-Gln14-bradykinin(2–9) amide	GWTLNSAGYLLGPQPGFSPFR	GAL$_1$>GAL$_2$	agonist[h,i]	rat
M871 = galanin (2–13)-Glu-His-(Pro)$_3$(Ala-Leu)$_2$Ala amide	WTLNSAGYLLGPEHPPPALALA	GAL$_2$[j,k]	antagonist[i]	rat
M1160	RGRGNWLNSAGYLLGPVLPPPALALA	GAL$_2$[l]	agonist[l]	mouse
J18	RGRGNWTLNSAGYLLGPkkK(eNH_C(O)$_{stearic\ acid}$)k	GAL$_2$>GAL$_3$>GAL$_1$	agonist[m]	mouse
Gal-B2 (NAX 5055)	(Sar)WTLNSAGYLLGPKKK$_{palmitoyl}$K	GAL$_1$>GAL$_2$[n]	agonist[o]	mouse
[*N*-Me, des-Sar]Gal-B2	$_{N\text{-}Me}$WTLNSAGYLLGPKKK$_{palmitoyl}$K	GAL$_2$>GAL$_1$[n]	agonist[p]	mouse
Gal-S2	(Sar)WTLNSAGYLLGPXKKKX	none[n]	Agonist[q]	mouse
Human galanin-like peptide GALP (1–60)	APAHRGRGGWTLNSAGYLLGPVLHLP QMGDQDGKRETALEILDLWKAIDGL PYSHPPQPS	none[r]	agonist[s]	mouse
Human GALP (3–32)	AHRGRGGWTLNSAGYLLGPVLHLPQMGDQ	none[r,n]	agonist[s]	mouse

[a] Liu et al. (2001).
[b] Lu et al. (2005b).
[c] Crawley et al. (1993).
[d] Bartfai et al. (1991).
[e] Xu et al. (1995a).
[f] Wiesenfeld-Hallin et al. (1992).
[g] Leibowitz and Kim (1992).
[h] Lundström et al. (2005b).
[i] Jimenez-Andrade et al. (2006).
[j] Sollenberg et al. (2006).
[k] Sollenberg et al. (2010).
[l] Saar et al. (2013b).
[m] Saar et al. (2013b).
[n] Not tested for GAL$_3$; X = (*S*)-2-(4-pentenyl)alanine.
[o] Bulaj et al. (2008).
[p] Robertson et al. (2010).
[q] Green et al. (2013).
[r] Lang et al. (2005).
[s] Schmidhuber et al. (2007).

Table 4). Hydrocarbon stapling of galanin at its C terminus by incorporation of (*S*)-2-(4-pentenyl)alanine shifted the preference of the molecule from GAL$_1$ to GAL$_2$ (Green et al., 2013).

GALP, which has an amino acid sequence from position 9 to 21 that is identical to that of galanin (1–13), was originally described as a high-affinity agonist for rat GAL$_1$ and GAL$_2$ in receptor-transfected cells, with preferential binding to GAL$_2$ (Ohtaki et al., 1999). A later study demonstrated that human GALP can bind with high affinity to all human galanin receptor types expressed in human neuroblastoma cells, exhibiting a slight preference for GAL$_3$ (GAL$_1$<GAL$_2$<GAL$_3$) (Lang et al., 2005). Interestingly, in membranes derived from Chinese hamster ovary cells transfected with human GAL$_3$, GALP was 70-fold more effective at displacing [^{125}I]galanin binding than was galanin (Boughton et al., 2010). The putative proteolytic fragment GALP (3–32) had similar agonist activity to full-length GALP in functional assays in vitro and in vivo (Lang et al., 2005; Schmidhuber et al., 2007).

2. Nonpeptide Ligands. The antifungal metabolite Sch202596 (spirocoumaron) was described in 1997 as the first nonpeptide galanin-receptor ligand with antagonist activity in micromolar concentrations at membranes of human Bowes melanoma cells (Chu et al., 1997), which endogenously express GAL$_1$ and GAL$_3$ (Lang et al., 2001). In the same cell line, the compound RWJ-57408 (2,3-dihydro-2-(4-methylphenyl)-1,4-dithiepine-1,1,4,4-tetroxide) was shown to be an antagonist with submicromolar affinity (Scott et al., 2000). The antagonistic properties of RWJ-57408 have been confirmed in cultured rat myenteric neurons (Anselmi et al., 2009). The nonpeptide ligands galnon [7-((9-fluorenyl-methoxycarbonyl)cyclohexylalanyllysyl)amino-4-methylcoumarin] and galmic display low affinity (micromolar range) for galanin receptors in membranes of human Bowes melanoma cells and rat GAL$_2$-transfected Chinese hamster ovary cells (Bartfai et al., 2004), as well as agonist activity in functional studies in vitro and in vivo (Saar et al., 2002; Bartfai et al., 2004) (see Table 5). However, both compounds interact with a number of other GPCRs (Floren et al., 2005; Lu et al., 2005c).

The first genuinely effective nonpeptide ligands with selectivity for different galanin receptors are the 3-arylimino-2-indolones SNAP 37889 (1-phenyl-3-[[3-(trifluoromethyl)phenyl]imino]-1*H*-indol-2-one) and its more water-soluble analog SNAP 398299 (1-[3-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-3-(3-(trifluoromethyl) phenylimino)indolin-2-one), which act as specific antagonists at GAL_3 (Swanson et al., 2005; Konkel et al., 2006a,b). Recently, a potent, low molecular weight, positive allosteric modulator of GAL_2 named CYM2503 (9*H*-fluoren-9-yl)methyl((*S*)-1(((*S*)-6(*tert*-butoxycarbonyl) amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino])-3-cyclohexyl-1-oxopropan-2-yl) carbamate) was described and shown to potentiate the anticonvulsant activity of endogenous galanin in mouse seizure models (Lu et al., 2010). Other GAL_2-selective compounds with submicromolar affinity in vitro have been described—a series of 2,4,6-triaminopyrimidines (Sagi et al., 2011). Among these synthetic 2,4,6-triaminopyrimidine derivatives, two compounds displayed selective binding affinity for GAL_1 in the micromolar range (Table 5).

Although several peptidergic and nonpeptide ligands display some selectivity for the different galanin receptors, they are of limited use because typically they still bind to more than one receptor and/or they have not been tested for activity at GAL_3. Thus currently, to differentiate between the three galanin receptors, galanin (2–11) is used as a non-GAL_1 agonist and the SNAP compounds are useful GAL_3-selective antagonists (Tables 4 and 5).

IV. Galanin Family Peptide and Galanin Receptor Distributions

The distribution of *GAL* mRNA and galanin-immunoreactivity has been comprehensively mapped in adult rat and mouse CNS (brain and spinal cord) and to differing degrees in several other species, including primate and human brain (mentioned above and reviewed below), and several nonmammalian vertebrates, including fish (Mensah et al., 2010). Similarly, the distribution of *GALP* mRNA and GALP immunoreactivity was described in the rat brain by several groups soon after the peptide's discovery (Ohtaki et al., 1999) (see below), whereas its distribution in mouse brain was not as widely reported, possibly due to its relatively lower abundance in this species (Jureus et al., 2001). The distribution of *GALP* mRNA-positive neurons has also been reported in macaque brain (Cunningham et al., 2002, 2004b). Subsequent to early reports of the central distribution of [^{125}I]galanin binding sites (Skofitsch et al., 1986; Melander et al., 1988), the distribution of GAL_1, GAL_2, and GAL_3 mRNAs was reported in rat and mouse brain (and spinal cord), using both in situ hybridization and RT-PCR (see below). Although there are literature reports of the distribution of $GAL_{1\text{-}3}$ proteins using polyclonal antisera and immunohistochemistry, the validity of these data has been questioned and must be considered only putative mappings that require independent validation (see section IV.C).

The central distributions of galanin and/or GALP and the galanin receptors have been extensively reviewed, most recently by Lang et al. (2007) and Hökfelt and Tatemoto (2010) and references cited therein. The main aspects will be summarized in the following sections, and relevant aspects of galanin expression during brain development and/or in pathologic conditions will be referred to in subsequent sections.

A. Distribution of Galanin and Galanin-Like Peptide mRNA and Immunoreactivity in the Central Nervous System

1. Galanin mRNA and Galanin Immunoreactivity. *GAL* mRNA and galanin immunoreactivity have been characterized in the CNS of several mammalian

TABLE 5
Nonpeptidergic ligands for galanin receptors with type of in vivo activity

Nonpeptide Ligands	Name	Receptor Specificity	Activity	Species
Galnon	7-((9-Fluorenylmethoxycarbonyl)cyclohexylalanyllysyl) amino-4-methylcoumarin	none[a]	agonist[b]	mouse, rat
Galmic		GAL_1[a,c,d]	agonist[c]	mouse, rat
SNAP37889	1-Phenyl-3-[[3-(trifluoromethyl)phenyl]imino]-1*H*-indol-2-one	GAL_3[e]	antagonist[e]	mouse, rat, guinea pig
SNAP398299	1-[3-(2-(Pyrrolidin-1-yl)ethoxy)phenyl]-3-(3-trifluoromethyl) phenylimino)indolin-2-one	GAL_3[e]	antagonist[e]	rat
CYM2503	(9*H*-Fluoren-9-yl)methyl((*S*)-1(((*S*)-6(*tert*-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl) amino))-3-cyclohexyl-1-oxopropan-2-yl) carbamate	GAL_2[f,d]	agonist[f,g]	mouse, rat

[a]Interaction with other receptors.
[b]Saar et al. (2002).
[c]Bartfai et al. (2004).
[d]Not tested for GAL_3.
[e]Swanson et al. (2005).
[f]Lu et al. (2010).
[g]Positive allosteric modulator of endogenous galanin.

species, including rat (Skofitsch and Jacobowitz, 1985b; Everitt et al., 1986; Ryan and Gundlach, 1996), mouse (Cheung et al., 2001; Perez et al., 2001; Lein et al., 2007; see Allen Brain Institute [www.brain-map.org]), primate (Kordower et al., 1992), and human (Gentleman et al., 1989; Garcia-Falgueras et al., 2011), where it coexists with a complex, species-dependent array of classic neurotransmitters (Melander et al., 1986d; see Merchenthaler et al., 1993b, and Jacobowitz et al., 2004, for review) and other peptides (see below).

On a relative quantitative scale, *GAL* mRNA is highly abundant in the hypothalamic and brain stem areas of the rat (Ryan and Gundlach, 1996; Jacobowitz et al., 2004) and mouse (Cheung et al., 2001), with very high levels in the preoptic-, periventricular-, and dorsomedial-hypothalamic nuclei, bed nucleus of the stria terminalis (BNST), medial and lateral amygdala, LC, and nucleus of the solitary tract. Relatively low to medium *GAL* mRNA levels are present in the olfactory bulb, septal nuclei, thalamus, and the parabrachial and spinal trigeminal tract nuclei.

GAL mRNA is also detected in the proliferative zones of both the developing and adult brains—the subventricular zone, the rostral migratory stream, and the subgranular zone of the hippocampus (Shen et al., 2003)—where it may regulate the proliferation, differentiation, and/or migration of neural stem cells (Xia et al., 2005a; Agasse et al., 2013; Mansouri et al., 2013; Zaben and Gray, 2013) (see sections V.D and VIII)—and in oligodendrocyte precursor cells in the corpus callosum (Shen et al., 2003; Ubink et al., 2003), suggesting a role for galanin in normal myelination and responses to myelin injury (see Wraith et al., 2009, and Zhang et al., 2012).

Galanin is coexpressed with multiple different neurotransmitters and neuropeptides in different types of neurons. For example, in the rat, galanin was associated with four major ascending systems: 1) robustly in a majority of the noradrenergic LC neurons (Holets et al., 1988; Xu et al., 1998); 2) after colchicine in >50% of 5-HT neurons in dorsal raphe (DR) (Xu and Hökfelt, 1997); 3) in the histaminergic/GABAergic neurons in the tuberomammillary nucleus (Kohler et al., 1986; Melander et al., 1986c; Sherin et al., 1998); and 4) in the cholinergic basal forebrain neurons, which are known to degenerate in Alzheimer's disease (Davies and Maloney, 1976; Whitehouse et al., 1981). Notably, in the cholinergic basal forebrain neurons, galanin expression is low/undetectable in the normal rat (Miller et al., 1998) but is observed after colchicine treatment (possibly due to induction) (Melander et al., 1985b, 1986b; Dutar et al., 1989; Senut et al., 1989) and is highly expressed in monkeys (Melander and Staines, 1986; Kowall and Beal, 1989; Walker et al., 1989, 1991), whereas it has not been widely detected in humans (Walker et al., 1991), suggesting species differences even among primates (Kordower and Mufson, 1990).

Considerable evidence suggests that galanin expression in the brain, including the degree of co-expression with other transmitters and peptides, is species-specific. This is the case for galanin expression in 5-HT neurons in the DR nucleus, where there is strong coexpression in the rat, but none in the mouse (Larm et al., 1999; Cheung et al., 2001; Perez et al., 2001). This situation contrasts, however, with the LC, where galanin has been detected in several species, including rat, mouse (Cheung et al., 2001; Perez et al., 2001) and human (Chan-Palay, 1990; Kordower and Mufson, 1990; Fodor et al., 1992; Miller et al., 1999; Le Maître et al., 2013).

These species-based differences were further highlighted by a comparative study of the chemical neuroanatomy of the mouse DR nucleus with a focus on serotoninergic neurons (Everitt et al., 1986; Meister and Hökfelt, 1988). Despite evidence for the presence of several neuropeptides (including galanin and CRF) in nerve terminal networks close to DR serotonin neurons, indicative of direct or indirect influences on them, a relatively low number of coexisting transmitters was detected in mouse serotonin neurons compared with observations in the rat (e.g., Holets et al., 1988; Xu and Hökfelt, 1997; Larm et al., 2003). These data confirm the considerable species differences with regard to the chemical neuroanatomy of the DR (including galanin), which may also be observed in other brain areas, suggesting caution in any extrapolation of physiology or pathology from mouse to rat and/or human.

There are many other cases of galanin coexistence with a classic transmitter in the CNS and peripheral nervous system (PNS), for example, in GABAergic and dopaminergic neurons in the hypothalamic arcuate nucleus (ARC) (Everitt et al., 1986; Meister and Hökfelt, 1988), in GABAergic neurons in the spinal cord (Skofitsch and Jacobowitz, 1985a; Tuchscherer and Seybold, 1989; Klein et al., 1990; Carlton and Coggeshall, 1996), in cholinergic motor neurons (Lindh et al., 1989; Schreiber et al., 1994; Zhang et al., 1994), in glutamatergic DRG neurons (Skofitsch and Jacobowitz, 1985a; Tuchscherer and Seybold, 1989; Klein et al., 1990; Carlton and Coggeshall, 1996), and in noradrenergic sympathetic neurons (Lindh et al., 1989; Schreiber et al., 1994; Zhang et al., 1994), again with differing levels of cross-species fidelity.

Galanin immunoreactivity is normally low in mouse hippocampus but is abundant in this structure in the monkey (Kordower et al., 1992; Perez et al., 2001); and galanin cell bodies and dense galanin immunoreactive fibers in the nucleus accumbens of the monkey are not present in mouse or rat (Melander et al., 1986c; Kordower et al., 1992; Perez et al., 2001). Although rats and mice display a similar galanin distribution pattern, *GAL* mRNA and immunoreactivity are readily detected in the dorsal motor nucleus of the vagus of the mouse but not that of the rat; *GAL* mRNA is observed in inferior olive neurons of the mouse (in different subnuclei) (Cheung et al., 2001; Lein et al., 2007; unpublished data) but not of the rat (Ryan and Gundlach, 1996). These neurons also contain CRF and provide climbing fiber projections to the cerebellar cortex. In light of the involvement of hypothalamic and extrahypothalamic CRF (and galanin) systems in modulation of stress responses and evidence of cerebellar control of motor learning, these findings may imply that the olivocerebellar system is part of a larger peptidergic (CRF, galanin, others) functional system (Ito, 2009; Yu et al., 2014). In contrast *GAL* mRNA is not present in mouse cerebellum (Cheung et al., 2001), but abundant galanin transcripts are observed in the rat cerebellum in a subset of Purkinje cells in the flocculus, paraflocculus, and several lobules, with twice as many positive Purkinje cells in lobule 10 compared with the rest of the adult cerebellum (Ryan and Gundlach, 1996), which may be associated with cardiovascular-motor coordination (Ito, 2009).

Most recently, Laque et al. (2013) used reporter mice with green fluorescent protein expression driven from the galanin locus to identify the colocalization of galanin and leptin-induced p-STAT3 as a marker for leptin receptor (LepRb) expression in the lateral hypothalamus. They reported the existence of two populations of galanin- and LepRb-positive neurons (galanin-LepRb neurons)—in the hypothalamus spanning an extended perifornical area and in the nucleus of the solitary tract (Laque et al., 2013).

The application of such approaches, including mice displaying a reporter protein expression linked to specific genes (also see Table 1) should yield additional valuable information in the future about the putative neurochemical regulation of distinct populations of galaninergic neurons.

2. GALP mRNA and Immunoreactivity. In all species studied thus far, including the rat and mouse, *GALP* mRNA has a far more restricted distribution than *GAL* mRNA in the CNS, being detected by in situ hybridization histochemistry in neurons of the periventricular regions of the ARC and median eminence of the hypothalamus and in pituicytes (specialized astrocytes) in the posterior pituitary gland (Juréus et al., 2000, 2001; Larm and Gundlach, 2000; Shen et al., 2001). Subsequently, *GALP* mRNA was similarly detected in primate hypothalamus (Cunningham et al., 2004b), but there does not appear to be an equivalent human mapping study (see Lawrence and Fraley, 2011, for review).

In an important early study, GALP was detected by immunohistochemistry in neurons in the ARC, particularly the posterior-medial regions; GALP-immunoreactive fibers were observed in the arcuate and paraventricular nuclei, the lateral hypothalamus, the medial preoptic area, the BNST, and the lateral septum (Takatsu et al., 2001). Besides these initial reports, a range of immunohistochemical studies has demonstrated further characteristics of the hypothalamic GALP system in the rat brain. A majority (85%) of arcuate GALP neurons expresses leptin receptors and smaller numbers express orexin receptor-1 (OX_1R). There is also functional evidence for the presence of insulin receptors on GALP neurons (Lawrence and Fraley, 2011).

Some GALP neurons contain α-melanocyte-stimulating hormone, derived from pro-opiomelanocortin. NPY- and orexin-terminals contact GALP neurons in the ARC, whereas GALP-positive nerve terminals make contact with orexin- and melanin-concentrating hormone neurons in the lateral hypothalamus (Takenoya et al., 2005) and GnRH neurons and fibers in the medial preoptic area and the BNST of rats (Takatsu et al., 2001; Takenoya et al., 2006), as well as a putative association with kisspeptin neurons in the ARC (Lawrence and Fraley, 2011; Mohr et al., 2012). On the basis of these data, two major GALP pathways are identified—one to the paraventricular hypothalamic nucleus and a second to the medial hypothalamic area, the BNST and lateral septum (see Kageyama et al., 2005; Takenoya et al., 2006; Lawrence and Fraley, 2011).

B. Distribution of Galanin Receptors in the Brain and Spinal Cord

The distributions of *GAL₁* and *GAL₂* mRNA were extensively mapped by several independent laboratories soon after the cloning and pharmacological characterization of the receptors (see below), whereas only a single comprehensive report exists on the regional and cellular distribution of GAL_3 mRNA in the rat (Mennicken et al., 2002).

GAL_1 mRNA is widely expressed in the mammalian CNS. In the mouse and rat, expression is high in olfactory structures and subregions/nuclei of the amygdala, thalamus, hypothalamus, pons, medulla, and spinal cord (O'Donnell et al., 1999; Burazin et al., 2000; Mennicken et al., 2002; Hohmann et al., 2003a). GAL_2 mRNA is also broadly expressed in the CNS, with high levels present in the hippocampus, particularly in the dentate gyrus and the CA3 field, and in the supraoptic, arcuate, and mammillary nuclei of the hypothalamus (Gundlach and Burazin, 1998; O'Donnell et al., 1999; Burazin et al., 2000). In the hindbrain, GAL_2 mRNA is abundant in the spinal trigeminal tract and the dorsal vagal complex (O'Donnell et al., 1999; Burazin et al., 2000). GAL_3 mRNA is abundant in peripheral tissues, but has a more restricted distribution in the CNS than that of GAL_1 and GAL_2 mRNA, being confined to discrete areas of the hypothalamus (paraventricular, ventromedial, and dorsomedial nuclei) and areas of the forebrain (medial septum/diagonal band of Broca, bed nucleus of the stria terminalis, medial amygdaloid nucleus), midbrain (periaqueductal gray), and hindbrain (DR nucleus, LC and lateral parabrachial nucleus) (Mennicken et al., 2002).

Anatomic studies have identified the presence of *GAL_1* and *GAL_2* mRNA in the spinal cord, including data on labeled neuron types and regulation of expression (Brumovsky et al., 2006; Landry et al., 2006). For example, in the rat brain, *GAL_1* mRNA-positive neurons were detected in laminae I–III, and several *GAL_1* mRNA-positive neurons were seen in deeper layers, including the ventral horn, area X, and the lateral spinal nucleus (Brumovsky et al., 2006). In a separate study, putative GAL_1 immunoreactivity, which was absent in *GAL_1* knockout mice (*GAL_1*-KO), was detected in nerve endings in lamina II (Landry et al., 2006). In contrast, small and intermediate primary sensory neurons in the DRG express the highest levels of *GAL_2* mRNA in the rat CNS (see below); in the spinal cord, the large ventral horn alpha motor neurons are moderately labeled, and small, less intensely labeled cells are scattered throughout the gray matter, with scarce weakly labeled *GAL_2* mRNA-positive neurons in the ventral horns and area X and even fewer cells in the dorsal horn and the sympathetic and parasympathetic intermediate lateral cell columns (O'Donnell et al., 1999; Brumovsky et al., 2006). Finally, weak *GAL_3* mRNA expression is reported over laminae I–II, with a few moderately labeled cells distributed in laminae V and X (Mennicken et al., 2002).

Anatomic studies have also identified *GAL_1* and *GAL_2* mRNA in cells within the subventricular zone and the rostral migratory stream, regions associated with neurogenesis in the adult brain (Shen et al., 2003; Mazarati et al., 2004). The autoradiographic distribution of high-affinity [^{125}I]galanin binding sites best correlates with that of *GAL_1* mRNA in rat and mouse brain (Jacobowitz et al., 2004; Jungnickel and Gundlach, 2005; Lein et al., 2007), a finding consistent with a more limited and lower level of $GAL_{2/3}$ expression and a lower affinity of the radioligand for non-GAL_1 receptors (O'Donnell et al., 1999; Burazin et al., 2000; Mennicken et al., 2002; Hohmann et al., 2003a). The distribution of galanin receptors (and galanin) in the developing CNS (Ryan et al., 1997; Burazin et al., 2000; Jungnickel et al., 2005) (see Allen Brain Institute [www.brain-map.org]) suggests that galanin regulates developmental processes, including cell proliferation and survival, neurite growth, and synaptic maturation (Holmes et al., 2000; O'Meara et al., 2000; Jungnickel et al., 2005; Xia et al., 2005a; Hawes et al., 2006; see sections V.G and VIII).

In addition to their abundance in the adult mammalian CNS, galanin and its receptors are also present in the PNS and associated organs and have been implicated in functional regulation of various peripheral organ systems. For example, galanin and galanin receptors are present in DRG neurons and are known to participate in the control of pain processing at these associated sites (e.g., see Liu and Hökfelt, 2002; section V.C).

GALP was originally identified as a possible second native ligand for GAL_2 (Ohtaki et al., 1999) but is now known to bind to GAL_1 and to have high affinity for GAL_3 (see above; Lang et al., 2005). However, many in vivo and some in vitro studies have shown differences between the effects of GALP and galanin on neuronal activity and/or animal behaviors (Lawrence et al., 2002; Fraley et al., 2003; Krasnow et al., 2003; Dong et al., 2006; Lawrence and Fraley, 2011) as well as species differences in responses to GALP (Kauffman et al., 2005). These findings suggest the existence of a unique receptor for GALP that has yet to be discovered or that distinct profiles of GAL_1-GAL_3 exist on different populations of neurons, which might explain these various pharmacological findings.

C. Galanin Receptor Antibodies

Although several galanin receptor antibodies have been produced and used in experimental studies (e.g., Larm et al., 2003; Hawes and Picciotto, 2004), the specificity of these antibodies has often not been clearly demonstrated by using cells lines expressing the different galanin receptors and/or tissues from relevant galanin receptor KO mice as the preferred positive and negative controls. Specifically, the validity of several existing GAL_1 and GAL_2 antibodies has been questioned (Lu and Bartfai, 2009), and caution is required when interpreting immunohistochemical data on the presence and distribution of these galanin receptors. One reason for the lack of specificity of multiple commercially available galanin receptor antibodies is the fact that they are identical antibodies being sold by different vendors. Other technical issues may include the relatively low abundance of these particular peptide receptor proteins in native tissues relative to other proteins recognized by components of the polyclonal antisera when used at high concentrations, which can produce high levels of nonspecific staining of different neuron populations that can often appear "authentic," based on the distribution of the receptor mRNA species.

V. Neuronal Actions of Galanin in the Central and Peripheral Nervous Systems

Based on a large number of early studies with the native peptide or synthetic analogs, galanin was proposed to regulate numerous physiologic actions in the adult mammalian nervous system. More recent studies using receptor-selective agonists and antagonists (see section III.C) and various transgenic mouse models (Table 1) have helped to establish which galanin receptor(s) is/are primarily involved in these actions. In light of the considerable number of established and putative physiologic actions of galanin signaling, providing details of all of them and the relevant supporting studies is beyond the scope of this review. Importantly, a summary of much of the early data is available in a previous review (Lang et al., 2007) and in a series of chapters in a more recent multiauthor monograph (Hökfelt and Tatemoto, 2010). There have also been several more recent focused reviews of particular aspects of galanin actions (e.g., Fang et al., 2012a; Webling et al., 2012). However, the following sections provide a brief review of galanin actions in *some* major central processes, based largely on data from rats or from normal and transgenic mice. Galanin has been linked to the regulation of metabolic and osmotic homeostasis (Crawley, 1999; Landry et al., 2000; Gundlach, 2002), reproduction (Rossmanith et al., 1996; Gundlach, 2002), nociception (Liu and Hökfelt, 2002), arousal/sleep (Sherin et al., 1998; Steininger et al., 2001), and cognition (McDonald et al., 1998; Kinney et al., 2002), and these functions have been subsequently linked to the actions of specific galanin receptors. For example, GAL_1 has been linked strongly with the CNS and PNS and with modulatory actions on neurotransmission and anxiety, reward, and nociception (see details below), whereas GAL_2 is more broadly expressed and in the CNS is implicated in neurodevelopment (Burazin et al., 2000), modulation of both neurotransmission (Mazarati et al., 2004) and affective behaviors (Karlsson and Holmes, 2006; Lu et al., 2008), neurite outgrowth in normal hippocampus (Elliott-Hunt et al., 2004), and neuronal survival and neurogenesis in injured hippocampus (Elliott-Hunt et al., 2004; Mazarati et al., 2004; Pirondi et al., 2005a) (see details below). Galanin and galanin receptors have more recently been associated with neurogenesis and embryonic and adult neural stem cells (see section VIII).

A. Feeding and Energy Homeostasis

Early behavioral studies discovered that central administration of native galanin or biologically-active fragments such as galanin (1–16) consistently stimulated food intake. *Acute* intracerebroventricular administration or injection into multiple sites, including the hypothalamic paraventricular nucleus (PVN), lateral, and ventromedial nuclei and the central nucleus of the amygdala, produced a rapid increase in food and total caloric intake without markedly altering associated behaviors such as drinking, grooming, and motor activity (Kyrkouli et al., 1986, 1990b; Corwin et al., 1993; Schick et al., 1993; Crawley, 1999). Notably, *chronic* intracerebroventricular administration of galanin did not induce sustained obesity, but *chronic* daily administration of galanin into the PVN produced variable, complex changes in daily caloric intake, levels of obesity, and regional fat deposition, depending on the fat and carbohydrate content of the diet (Smith et al., 1994). Rats fed a high-fat, but not high- carbohydrate or -protein, diet displayed a marked increase in hypothalamic galanin levels (Leibowitz et al., 1998), and blockade of fatty acid metabolism reduced galanin expression in the anterior PVN (Wang et al., 1998a), suggesting galanin production is regulated by signals related to fatty acid metabolism (Barson et al., 2010).

Acute effects of galanin on feeding were abolished by galanin receptor (Corwin et al., 1993) and α_2-adrenoceptor (Kyrkouli et al., 1990a) antagonists. Inhibition of NA synthesis also blocked galanin-induced feeding, indicating that galanin modulates hypothalamic noradrenergic activity (Kyrkouli et al., 1990a). In rats, galanin was also reported to increase preference for a high-fat diet given a choice between fat, carbohydrate, and protein (Tempel et al., 1988), although other contemporary studies observed less of a difference in macronutrient choice (Smith et al., 1997a; Crawley, 1999; see Gundlach, 2002, for review). More recent studies in female rats also documented that ovarian steroids likely function together with galanin in a neural circuit, involving the medial preoptic nucleus, the anterior PVN, and the median eminence and anterior pituitary, to coordinate feeding behavior with reproductive function to promote consumption of a fat-rich diet at times of increased energy demand (Leibowitz et al., 2007).

Kyrkouli and colleagues (2006) further examined the influence of PVN galanin on dark/active phase nutrient intake in rats in a self-selection feeding paradigm—a choice between isocaloric diets enriched in protein, carbohydrate, or fat. Intra-PVN galanin significantly increased the 1-hour food intake but failed to increase intake of any particular nutrient. Analysis of "preference" relative to 24-hour baseline selection patterns over a 4-week period revealed that galanin increased "preferred nutrient" intake [i.e., galanin preferentially increased intake of the carbohydrate- *or* fat-rich diet in rats with high 24-hour intake of this particular nutrient ($>$ 40% of their total food intake)]. Additional analysis of plasma hormone levels revealed a significant increase in NA levels and a reduction in insulin with no effects on adrenaline, glucose, or corticosterone after intra-PVN galanin. The data suggest galanin in the PVN influences food intake and metabolic functioning, increasing sympathetic outflow and stimulating the intake of preferred macronutrients (Kyrkouli et al., 2006).

Since these early studies, considerable research has documented the interplay between fat and alcohol intake with regard to regulation by neuropeptides. In particular, hypothalamic galanin reportedly has a positive, reciprocal relationship with dietary fat and alcohol (see Barson et al., 2010, and Lewis, 2011, for review). It is well established that galanin increases consumption of fat or alcohol, which then stimulates galanin expression leading to overconsumption, with galanin facilitating intake by stimulating NA and dopamine release and reducing satiety by decreasing serotonin and acetylcholine signaling. In addition, hypothalamic galanin injection stimulates enkephalin expression throughout the brain, which also promotes alcohol consumption. Circulating triglycerides released by fat or alcohol correlate positively with hypothalamic galanin expression (see Barson et al., 2010).

Initially, neither GAL_1- or GAL_2-KO mice nor galanin-KO mice were reported to display any marked phenotype compared with littermates related to differences in body weight, feeding behavior, or responses to fasting or leptin (Jacoby et al., 2002; Wynick and Bacon, 2002; Gottsch et al., 2005). However, more detailed studies of galanin- and GAL_1-KO mice fed diets containing differing levels of energy and fat indicated that the endogenous galanin-GAL_1 system plays a role in adjusting food intake and/or metabolism to acute changes in dietary fat (Zorrilla et al., 2007; Adams et al., 2008). In response to an acute 3-day high-fat challenge, GAL_1-KO mice displayed an impaired adaptation, leading to increased food intake and weight gain compared with normal food intake and weight modulation on low-fat diets (Zorrilla et al., 2007). This latter finding is consistent with the phenotype reported for galanin-KO mice, which are more sensitive to leptin treatment (Ahren et al., 2004). In contrast to this acute response, over the subsequent 2 weeks on the high-fat diet, GAL_1-KO mice consumed less food and daily energy than when maintained on a low-fat diet and less food and energy than their heterozygous littermates, suggesting GAL_1 signaling may oppose positive energy balance or help maintain neutral balance (Zorrilla et al., 2007). Furthermore, heterozygous galanin-overexpressing (OE) mice displayed a >50% higher intake of a fat-rich diet relative to wild-type (WT) mice (Karatayev et al., 2009). Adams and others (2008) observed that WT mice consumed more energy and gained more weight than galanin-KO mice if only a high-fat diet was available; with macronutrient choice, WT mice ate ~3-fold more fat than galanin-KO mice. *Chronic* intracerebroventricular administration of galanin partially reversed the fat avoidance phenotype of galanin-KO mice (Adams et al., 2008). Macronutrient choices appear to be important, not only as potential factors influencing obesity, but as risk factors for diabetes and cardiovascular disease. Together, these data suggest galanin receptor antagonists may be of use in the treatment of some forms of obesity (Adams et al., 2008), although the precise nature of galanin signaling under different chronic dietary situations is still unclear.

Indeed, despite the widely reported and diverse effects of galanin on consummatory behavior, genetic linkage studies have to date revealed no strong impact of the galanin or galanin receptor genes on obesity (Kofler et al., 1998; Lapsys et al., 1999; Schauble et al., 2005; Sutton et al., 2006; section VII.C). However, it has become clear over recent years that common neural circuits can be involved in mediating different behaviors such as the regulation of feeding and fear/anxiety. For example, there is strong evidence for galanin and other peptides acting not only within parts of the hypothalamus but also within the extended amygdala to regulate feeding and reward aspects of food and to modulate the level of innate anxiety (e.g., Skibicka and Dickson, 2011; see section VII.C).

B. Osmotic Regulation and Water Intake

Very early studies of galanin dynamics in vasopressin neurons and the effects of central galanin administration revealed that galanin is involved in osmotic regulation within the hypothalamus. Vasopressin is pivotally involved in osmotic regulation, and vasopressin-deficient and salt-loaded rats with increased plasma osmolarity have reduced galanin levels in the median eminence and neurointermediate lobe of the pituitary (Koenig et al., 1989), suggesting increased galanin release. Furthermore, central administration of galanin reduced water intake (Brewer et al., 2005), inhibited osmotically induced increases in *vasopressin* mRNA in the PVN and supraoptic nucleus (SON) (Landry et al., 1995, 2000), and reduced vasopressin release and plasma vasopressin (Kondo et al., 1993). Infusion of the galanin antagonist M15 increased vasopressin mRNA in normal rats, further suggesting tonic inhibition by galanin (Landry et al., 2000). Galanin immunoreactivity in the SON is altered in diabetes mellitus, and salt-loading with 2% saline-drinking water increased *GAL* mRNA and GAL_1 mRNA in the PVN/SON of rats (Meister et al., 1990; Burazin et al., 2001). Water deprivation and salt-loading also increased galanin binding and putative GAL_1 protein immunoreactivity in these neurons (Burazin et al., 2001), suggesting salt-loading and dehydration increase vasopressin release and galanin levels, the latter acting as a negative feedback modulator of vasopressin release, via GAL_1 activation.

Circumventricular structures, including the subfornical organ (SFO), play a key role in control of water intake and vasopressin release (Miselis, 1981). Galanin has been identified in synapses in the SFO, and in brain slice preparations galanin dose dependently inhibited the activity of SFO neurons, many of which were activated by angiotensin II (Kai et al., 2006). The GAL_1 agonist M617 also inhibited SFO cells, whereas the $GAL_{2/3}$ agonist galanin (2–11) had no effect, suggesting galanin responses were largely mediated by GAL_1. Consistent with this conclusion, GAL_1 mRNA was detected in the SFO using RT-PCR (Kai et al., 2006) and an earlier study reported GAL_1 mRNA and putative GAL_1 immunoreactivity in SFO neurons

(Burazin et al., 2001). Any phenotypic differences in galanin- or galanin receptor-related transgenic and/or KO mice have not been widely reported. Furthermore, the possible role of galanin signaling in the SFO (Burazin et al., 2001; Mennicken et al., 2002) in the control of ingestive behavior (Fry and Ferguson, 2007) has not been investigated.

C. Pain

After nerve injury, under favorable conditions most nerve fibers successfully regenerate. However, in many clinically relevant circumstances, reduced or disordered axonal regeneration often results in a loss of sensation and/or the development of chronic neuropathic pain states. The pathophysiological mechanisms that underlie injury-induced axonal regeneration and the resulting pain states are therefore of considerable scientific and clinical importance. Neuropathic pain is characterized by spontaneous pain, allodynia (the perception of pain from a normally innocuous stimulus), and hyperalgesia (an exaggerated response to a given pain stimulus) and is often associated with depression, sleep disturbance, and interference with normal physical and social functioning (Tesfaye, 2009; Tesfaye et al., 2011).

Antidepressants and gabapentinoids are the drugs currently used to treat neuropathic pain in the United Kingdom and the United States. However, overviews of clinical trials (Saarto and Wiffen, 2007; Lunn et al., 2009; Moore et al., 2009) indicate that at best only 40% of patients gain control of their neuropathic pain with these drugs, even when used in combination with other available drugs, and very few obtain complete pain relief. Thus, there is still a huge unmet clinical need for the treatment of neuropathic pain, and more effective long-term therapies are urgently required. Galanin has been extensively studied in a number of physiologic systems, including regeneration of sensory neurons and nociception, and current data support the hypothesis that modulation of galanin receptor signaling cascades represents a novel therapeutic approach for treating sensory neuropathy and neuropathic pain.

Extensive research has been done to examine the function of the galanin system in pain processing in the intact nervous system and in models of neuropathic and inflammatory pain and the role played by galanin and its receptors in axonal regeneration and neurite outgrowth of sensory neurons. A number of reviews have addressed these topics (Wiesenfeld-Hallin and Xu, 1998; Kerr et al., 2000b; Xu et al., 2000b, 2008; Wynick et al., 2001; Liu and Hökfelt, 2002; Holmes et al., 2005; Hobson et al., 2008), so we will focus on more recent findings and place them in the context of previous data. Several experimental approaches have been used to study the function of galanin in pain processing and in axonal regeneration and neurite outgrowth, including in vitro and in vivo paradigms (almost all in rodents) in which anatomic, electrophysiological, and behavioral effects were assessed after administration of exogenous galanin or galanin receptor antagonists and/or agonists or antisense nucleotides. More recently, comparable studies have been completed in genetically modified mice.

1. Galanin and Galanin Receptor Expression in the Intact Adult Somatosensory System. In the adult rodent somatosensory system galanin is expressed at detectable levels in a small subset (<5%) of predominantly small fiber neurons in the DRG (Ch'ng et al., 1985; Skofitsch and Jacobowitz, 1985b; Hökfelt et al., 1987). However, ultrastructural studies suggest ongoing galanin synthesis in up to 40% of sensory neurons (Klein et al., 1990; Carlton and Coggeshall, 1996), most of which is transported to the afferent terminals within lamina II of the dorsal horn (DH) of the spinal cord (Villar et al., 1991; Zhang et al., 1993b; O'Donnell et al., 1999). *GAL_1* and *GAL_2* mRNAs are present in partially overlapping populations of DRG neurons: ~50% contain *GAL_1* mRNA (mostly larger neurons than those expressing *GAL_2*) and ~80% express *GAL_2* mRNA (with >60% of these being small- to medium-sized neurons) (Xu et al., 1996; Sten Shi et al., 1997; Zhang et al., 1998; O'Donnell et al., 1999; Liu and Hökfelt, 2002; Kerekes et al., 2003).

Galanin, GAL_1, and GAL_2 are also expressed in subsets of DH neurons where nociceptive information is integrated and transmitted. It has been shown that galanin-expressing neurons constitute a distinct population of GABAergic inhibitory interneurons, predominantly located in laminae I–II (Simmons et al., 1995; Zhang et al., 1995b; Tiong et al., 2011). *GAL_1* mRNA is expressed at relatively high levels, particularly in laminae I–III (Parker et al., 1995; Gustafson et al., 1996; Zhang et al., 1998; O'Donnell et al., 1999; Brumovsky et al., 2006; Landry et al., 2006) but also in the deeper DH, by numerous neurons that appear to be excitatory glutamatergic interneurons (Landry et al., 2006). Although present, *GAL_2* mRNA has a much sparser distribution (O'Donnell et al., 1999; Brumovsky et al., 2006), and it is not yet known by which populations of neurons it is expressed. Ablation of primary afferent innervation into the spinal cord does not appear to significantly decrease galanin binding (indicative of galanin receptor expression/levels) in the spinal cord, suggesting galanin receptors are present mainly on postsynaptic neurons (Kar and Quirion, 1994; Zhang et al., 1998). However, more recent studies imply that galanin also functions presynaptically in the DH, likely via GAL_2 (Alier et al., 2008; Yue et al., 2011). It is noteworthy that galanin and galanin receptor binding have also been detected in monkey DRG and spinal cord (Zhang et al., 1993a, 1995a), and galanin is expressed in human DRG (Landry et al., 2003). Expression of *GAL_3* in the rat and mouse DRG and spinal cord is very low, as determined by RT-PCR (Waters and Krause, 2000; Hobson et al., 2006), and undetectable using in situ hybridization (Mennicken et al., 2002).

Galanin and its receptors are also present in supraspinal regions implicated in the modulation and perception of pain, including the gracile nucleus (Ma and Bisby, 1999), LC, periaqueductal gray (PAG), DR nucleus, several hypothalamic nuclei (ARC and dorso- and ventromedial hypothalamus), the habenula, and amygdaloid nuclei (Skofitsch and Jacobowitz, 1985b, 1986; Melander et al., 1986a,b; Skofitsch et al., 1986; Melander et al., 1988; O'Donnell et al., 1999; Perez et al., 2001; Mennicken et al., 2002; Barreda-Gomez et al., 2005). Galanin receptors are also present in these brain areas in monkey and human (Kohler et al., 1989a,b).

2. Nociception in the Uninjured Rodent. Functional studies have demonstrated a role for galanin in the modulation of acute pain in intact adult rat and mouse. Administration of exogenous high-dose galanin to the peripheral receptive field of primary afferents modifies the firing of nociceptive fibers in response to noxious heat, with most being inhibited, but with some facilitated (Flatters et al., 2003), possibly due to activation of different receptors. Galanin also dose dependently modifies the response of mechanonociceptive C-fibers; low dose galanin facilitates, whereas high-doses inhibit nociceptor activity. Galanin (2–11) produces a similar effect, indicating that this nociceptive modulation is mediated in part via activation of peripheral GAL_2 (Hulse et al., 2011). Close intra-arterial infusion of galanin or galanin (2–11) both lead to the sensitization of C-fiber responses to mechanical stimulation. However, galanin, but not galanin (2–11), inhibits responses to cool stimuli, suggesting involvement of GAL_1 in mediating this inhibition (Hulse et al., 2012). Together these data support a role for galanin in modulating acute pain in the periphery via activation of GAL_1 and/or GAL_2.

Intrathecally administered galanin, which can potentially exert its actions on primary afferents presynaptically (via GAL_1 and/or GAL_2) or postsynaptically (on predominantly GAL_1-expressing excitatory interneurons), dose dependently exerts both facilitatory (Cridland and Henry, 1988; Kuraishi et al., 1991; Wiesenfeld-Hallin and Xu, 1998; Kerr et al., 2000a; Reeve et al., 2000; Liu et al., 2001; Flatters et al., 2003) and inhibitory (Post et al., 1988; Xu et al., 1991b; Yu et al., 2001; Flatters et al., 2003) effects on the electrophysiologic properties of DH neurons and nociception, with differential effects on sensory modalities (Kuraishi et al., 1991; Wiesenfeld-Hallin et al., 1993). Similar to the effects of peripheral administration, intrathecal galanin is facilitatory at low doses and inhibitory at higher doses, possibly via modulation of the actions of substance P (Xu et al., 1990) and opioids (Post et al., 1988; Wiesenfeld-Hallin et al., 1990; Reimann et al., 1994; Suh et al., 1994).

More recent in vitro studies, recorded from cells in lamina II of the spinal cord, reveal that low doses of galanin increase the frequency, but not the amplitude, of spontaneous excitatory postsynaptic currents (EPSCs) via a presynaptic calcium-dependent mechanism. This effect appears to be mediated by GAL_2, presumably located on terminals of primary afferents and DH neurons, because it is mimicked by low-dose galanin (2–11), but not the GAL_1 preferential agonist M617 (Yue et al., 2011). Conversely, it was demonstrated that galanin (2–11) decreases spontaneous EPSC frequency (Alier et al., 2008). Furthermore, galanin or galanin (2–11) both reduce nociceptor stimulation-evoked EPSC amplitudes, indicative of decreased primary afferent glutamate release (Alier et al., 2008; Yue et al., 2011). Galanin produces variable dose-dependent effects on postsynaptic currents in both excitatory and inhibitory lamina II neurons; GAL_1 agonism appears to predominantly cause hyperpolarization (Yue et al., 2011), and high-dose galanin (2–11) decreases membrane excitability (Alier et al., 2008; Yue et al., 2011). Overall, the effect of galanin in the spinal cord is likely to be determined by several factors, including the sensitivity of the receptors to galanin, the phenotype of the receptor-bearing neurons (e.g., neurotransmitter content and electrophysiological properties), and the local circuitry in the DH.

Several studies have demonstrated a potential role for galanin in supraspinal pain transmission or modulation in areas known to be innervated by galanin-positive nerve fibers and thought to be involved in pain modulation. Injection of galanin into the PAG, which has a well defined role in descending pain modulation, dose dependently decreases pain-related behavior in response to noxious stimuli, an effect that appears to involve the opioid system (Wang et al., 1999). Similarly, administration of high doses of galanin into the ARC decreases nociception by a PKC- and opioid-dependent mechanism, probably by influencing the PAG (Shi et al., 2011; Sun et al., 2003, 2007; Sun and Yu, 2005). Administration of galanin into the central nucleus of the amygdala (possibly by a GAL_1- and opioid-dependent mechanism) (Jin et al., 2010), the tuberomammillary nucleus (Sun et al., 2004), and the nucleus accumbens (Xu et al., 2012a) decreases pain-related behaviors. These effects are inhibited by the putative galanin receptor antagonist galantide, which blocks all galanin receptors. Although it appears galanin and its receptors are expressed in these regions, the cellular localization of the receptor proteins is as yet unknown.

In support of the effectiveness of *exogenous* galanin or its receptor ligands, there is increasing data to suggest that *endogenous* galanin plays a tonic inhibitory nociceptive role. The nonselective galanin receptor antagonist M35 potentiates the facilitation of intact C-fiber afferent activity (Wiesenfeld-Hallin et al., 1992). Furthermore, a decrease in *GAL₁* mRNA levels by intrathecal antisense administration attenuates the inhibitory effect of galanin (Pooga et al., 1998; Rezaei et al., 2001). Consistent with this, ablation of DH galanin receptor-expressing neurons (which are predominantly GAL_1 positive) reduces behavioral nocifensive responses to noxious temperature stimuli (Lemons and Wiley, 2011).

Results from genetically engineered mice provide further evidence for the role played by galanin in acute pain. Galanin-KO mice (Wynick et al., 1998) are more sensitive to noxious stimuli than WT controls (Kerr et al., 2000a), supporting an inhibitory function. However, GAL_1-KO mice have only a slightly increased sensitivity to noxious thermal, but not mechanical, stimuli (Blakeman et al., 2003), and GAL_2-KO mice display no differences in sensitivity to thermal or mechanical stimuli (Gottsch et al., 2005; Hobson et al., 2006; Shi et al., 2006). Several transgenic mouse lines have been generated that overexpress galanin in particular subsets of neurons, and their phenotypes support an inhibitory role for galanin (Table 1). Mice that constitutively overexpress galanin under the control of the c-*Ret* (Holmes et al., 2003), PDGF, platelet-derived growth factor subunit-β (Blakeman et al., 2001), or dopamine β-hydroxylase (Hygge-Blakeman et al., 2004) promoters, all display reduced sensitivity to thermal stimulation, and in the case of the c-*Ret* transgenic mice, also to mechanical stimulation.

3. Models of Neuropathic Pain. Nerve injury induces pronounced changes in the expression of *GAL* mRNA and peptide, and many other genes are also affected, as shown in gene array studies (Costigan et al., 2002; Xiao et al., 2002). It was initially shown that total peripheral nerve transection (axotomy) induced an increase in galanin to the extent it was detectable in 40–50% of DRG neurons, with peak levels at 10–14 days after injury and elevated levels during nerve regeneration (Hökfelt et al., 1987, 1994). Concomitant with this is a marked increase in galanin transport, both toward the site of injury and to the DH (Villar et al., 1991), although levels were little changed within intrinsic DH neurons (Villar et al., 1989). Such postinjury changes were also demonstrated in monkey, where there is also reorganization of afferents in the DH (Zhang et al., 1995a; Wang et al., 2007). Furthermore, there is increased galanin release in the DH after nerve injury (Duggan and Riley, 1996; Colvin et al., 1997; Colvin and Duggan, 1998). After axotomy, the levels of mRNA for GAL_1, and to a lesser extent for GAL_2, in the DRG are reduced (Xu et al., 1996; Sten Shi et al., 1997), with no change in DH neurons (Brumovsky et al., 2006). More recently, specific and highly sensitive, semiquantitative RT-PCR (Taqman) was used to demonstrate that the levels of GAL_1 and GAL_2 mRNA in mouse DRG were reduced by 37 and 28%, respectively, 1 week after nerve section (Hobson et al., 2006).

Galanin is also upregulated to a variable extent in several models of neuropathy that are accompanied by abnormal pain-like behaviors in vivo (Ma and Bisby, 1997; Shi et al., 1999; Coronel et al., 2008). These models include partial sciatic nerve transection (Ma and Bisby, 1997), tibial transection (Hofmann et al., 2003; Garry et al., 2005), nerve crush/pinch (Villar et al., 1991; Xu et al., 2012b), and chronic nerve constriction (Villar et al., 1989, 1991; Nahin et al., 1994; Ma and Bisby, 1997; Shi et al., 1999), in which it has been suggested the extent of galanin upregulation is inversely proportional to the development of pain behavior (Shi et al., 1999; Liu and Hökfelt, 2000) and single ligature nerve constriction (Coronel et al., 2008), partial sciatic (Shi et al., 1999) or saphenous nerve ligation (Hulse et al., 2008), photochemically-induced ischemic nerve injury (Hao et al., 1999; Shi et al., 1999), spared nerve injury (Holmes et al., 2003), spinal nerve ligation (Fukuoka et al., 1998; Honore et al., 2000), the cisplatin model of neurotoxicity (Barajon et al., 1996), as well as after skin incision, which is preceded by inflammation (Peters et al., 2005; Hill et al., 2010). In contrast, galanin does not appear to increase in models of painful diabetic neuropathy (Zochodne et al., 2001; Burnand et al., 2004; Shi et al., 2013). After nerve injury, galanin is also increased in trigeminal (Zhang et al., 1996) and superior cervical ganglia (Zhang et al., 1994), which may have implications in pain modulation.

Upregulation of galanin is also seen in disease models associated with neuropathic pain, including bone cancer pain (Peters et al., 2005), although some caution is required when interpreting the data (Honore et al., 2000), herpes simplex (Henken and Martin, 1992) or varicella zoster virus infection (Garry et al., 2005), and perineural HIV-1 gp120 infection (Wallace et al., 2007).

In the periphery, similar to observations in naive rodents, local injection into the primary afferent receptive field or intra-arterial perfusion of low doses of galanin reduced peripheral nerve injury-induced cooling-evoked nociceptor activity but increased mechanical sensitivity, likely mediated via activation of GAL_1 and GAL_2, respectively (Hulse et al., 2011, 2012). However, higher doses of galanin markedly inhibited mechanonociceptor activity via activation of GAL_2 (Hulse et al., 2011). Furthermore, injection of galanin into the peripheral receptive fields of spinal nerve-ligated rats reduced evoked responses in the vast majority of DH neurons to mechanical and thermal stimuli (Flatters et al., 2003) to a significantly greater extent than in naive rats.

In the spinal cord, the inhibitory effect of exogenous galanin [delivered intrathecally or released from transplanted galanin-expressing cells (Eaton et al., 1999; An et al., 2010)] is also enhanced after nerve injury, both in terms of effects on the electrophysiological properties of neurons (Wiesenfeld-Hallin et al., 1989; Xu et al., 2000a; Flatters et al., 2002) and on neuropathic pain-like behaviors (Hao et al., 1999; Yu et al., 1999; An et al., 2010; Eaton et al., 2000; Liu and Hökfelt, 2000; Xu et al., 2012b,c). In support of an inhibitory role for endogenous galanin, the administration of galanin antisense nucleotides increased pain behavior after nerve injury (Wiesenfeld-Hallin et al., 1992; Verge et al., 1993; Liu and Hökfelt, 2000). M35 (Wiesenfeld-Hallin et al., 1992; Verge et al., 1993; Liu and Hökfelt, 2000) or galanin, but not galanin (2–11), decreased nerve constriction injury-induced mechanical allodynia, suggesting GAL_1 may play a dominant role in the analgesic effect of galanin after nerve injury (Liu et al., 2001). However, GAL_1-KO mice demonstrate only a slightly enhanced sensitivity to noxious temperature and increased duration of pain behavior after nerve injury (Blakeman et al., 2003), and no differences are seen between GAL_1-KO and WT mice in neuronal excitability in the C-fiber stimulation-induced facilitation of flexor reflex model (Grass et al., 2003b).

After nerve injury, galanin increases in several brain areas associated with pain modulation (Imbe et al., 2004; Gu et al., 2007). Application of high doses of galanin into the medulla oblongata decreased behavioral pain-like responses and the activity of gracile nucleus neurons (Jung et al., 2009). Similarly, galanin injected into the PAG (Wang et al., 2000) reduces pain behavior, possibly involving the endogenous opioid system (Zhang et al., 2000a,b). Galanin injected into the ARC (Gu et al., 2007) also has analgesic effects.

Finally, several genetically modified mouse strains have provided information regarding the role of galanin and its receptors within pain circuits after peripheral nerve injury. Mouse lines have been generated that overexpress galanin (either constitutively or inducibly under the control of different promoters; see Table 1), and their electrophysiologic and behavioral phenotypes further support a strong analgesic role for galanin after nerve injury (Blakeman et al., 2001; Grass et al., 2003a; Holmes et al., 2003; Hygge-Blakeman et al., 2004; Pope et al., 2010; Hulse et al., 2011, 2012) due to peripheral *and* central actions of the peptide (Hulse et al., 2011). However, contrary to initial predictions, galanin-KO mice display attenuated pain-like behaviors in several nerve-injury models (Kerr et al., 2000a, 2001b; Holmes et al., 2003; Hulse et al., 2008). This result is likely due, however, to the fact that galanin-KO mice lack a subset of sensory neurons that may be critical for mediating pain after nerve injury (Holmes et al., 2000; see Hobson et al., 2008, for review). This neurotrophic effect of galanin is mediated via activation of GAL_2, and consequently GAL_2-KO mice also display neuronal deficits in the DRG (Hobson et al., 2006; Shi et al., 2006); consistent with this, GAL_2-KO mice have attenuated neuropathic pain-like behavior after spared sciatic, but not spinal, nerve injury (Hobson et al., 2006; Shi et al., 2006). Unfortunately, the impact of the developmental changes evident in these findings confounds the interpretation of pain data obtained in adult galanin-KO and GAL_2-KO mice.

4. Models of Inflammatory Pain. The distributions of galanin and its receptors are altered throughout pain circuits in experimental inflammation conditions and this has functional implications for the modulation of inflammatory pain. Galanin levels decrease in DRG sensory neurons but increase in DH neurons in response to peripheral injection of carrageenan (Ji et al., 1995; Zhang et al., 1998). In this model, GAL_1 is transiently downregulated in the DRG (Xu et al., 1996), whereas GAL_2 is increased (Sten Shi et al., 1997), and there is no significant change in *GAL_1* or *GAL_2* mRNA expression within DH neurons (Brumovsky et al., 2006). Similarly, in a model of chronic experimental arthritis, peripheral adjuvant injection causes an initial decrease in DRG galanin (after 3 days), but this is followed by a later increase (~21 days), suggesting a transition from an inflammatory to a nerve injury state, and *GAL* mRNA levels also increase in DH neurons (Calza et al., 1998a, 2000). However, in this model, galanin peptide levels have been shown to decrease in spinal cord by 28 days (Qinyang et al., 2004). Galanin is released into the spinal cord of rats with ankle inflammation (Hope et al., 1994; Garry et al., 2005), and inflammatory orofacial pain increases galanin in the *trigeminal nucleus caudalis* (Tokunaga et al., 1992). The peptide is also present in neurons innervating the Achilles tendon in a rupture model (Ackermann et al., 2003). Galanin levels are reported to increase in sensory neurons in models of chemically induced ileitis (Pidsudko et al., 2003) and cystitis (Callsen-Cencic and Mense, 1997), although a similar study reported no significant change (Zvarova and Vizzard, 2006). In this model, galanin also increased in the hypothalamus and amygdala (Nishii et al., 2007). Galanin also increases after noxious colorectal distension (in the absence of inflammation) (Lu et al., 2005a) and in chronic diverticular disease (Simpson et al., 2009), indicative of a role in visceral as well as somatic pain modulation.

Peripheral intraplantar injection of low doses of galanin enhances capsaicin-induced neuronal activity and spontaneous inflammatory pain-related behavior, an effect that appears to be mediated via GAL_2 and modulation of transient receptor potential vanilloid 1 (TRPV1) function (Jimenez-Andrade et al., 2004) by a PKC-dependent signaling pathway (Jimenez-Andrade et al., 2005), whereas activation of GAL_1 is antinociceptive in this experimental paradigm (Jimenez-Andrade et al., 2006). Similarly, in adjuvant-induced inflammation, both interarterial galanin and galanin (2–11) decrease mechanical activation thresholds. However, galanin, but not galanin (2–11), reduces cooling-evoked nociceptor activity (Hulse et al., 2012), suggesting this antinociceptive effect is mediated via GAL_1. The same dose of galanin has variable effects on primary afferent responses in an acutely inflamed knee joint subjected to movement, as does blocking the actions of endogenous galanin. However, the mechanosensitivity of most of the affected afferents is inhibited by galanin (Heppelmann et al., 2000).

Early studies investigating the effects of galanin in the spinal cord suggested it had pronociceptive actions in models of inflammation, even at high doses, possibly by modulating substance P release (Lundeberg et al., 1993). However, later studies revealed that intrathecal administration of high doses of galanin is antinociceptive in both intraplantar formalin-induced nociception (Hua et al., 2004) and carrageenan-induced inflammation (Hua et al., 2005; Xiong et al., 2005), partially via mechanisms involving the opioid system (Hua et al., 2004; Xiong et al., 2005) and the modulation of substance P release (Hua et al., 2005). This effect may be mediated via both GAL_1 (Hua et al., 2004) and pre- and postsynaptic GAL_2 (Hua et al., 2005). In contrast, galanin-KO mice are hyporesponsive to formalin and to thermal stimuli after carrageenan inflammation and have attenuated spinal excitability, arguing for a pronociceptive role for endogenous galanin (Kerr et al., 2001a). However, galanin-KO mice, as described, are deficient in a population of nociceptors, which likely contributes to their impaired pain phenotype (Holmes et al., 2000). GAL_2-KO mice also have impaired pain-like behavioral responses to formalin (Hobson et al., 2006) but, like galanin-KO mice, have sensory neuron deficits, which confounds interpretation of the data (Shi et al., 2006). At the supraspinal level, exogenous galanin appears to be antinociceptive in the ARC after inflammation (Sun et al., 2003).

D. Regeneration and Neurite Outgrowth

Damage to sensory neurons of the DRG induces major and long-lasting changes in expression of a large number of genes that promote neurite outgrowth and axonal regeneration (see Navarro et al., 2007, for review). Thus the upregulation in galanin expression in the DRG after nerve injury led to the hypothesis that galanin has a trophic role during regeneration. Adult galanin-KO mice demonstrate a 35% reduction in regeneration after a crush injury to the sciatic nerve compared with WT controls, associated with long-term sensorimotor functional deficits (Holmes et al., 2000). Consistent with these findings, studies using the rat facial nerve lesion model demonstrate that treatment with galanin substantially increases the number of neurons regenerating into identified branches of the facial nerve (Suarez et al., 2006) compared with vehicle-treated rats [possibly via GAL_2 (Burazin and Gundlach, 1998), see below]. However, despite increased regeneration, the authors observed a decrease in functional recovery compared with vehicle-treated animals that they suggested was due to collateral axonal branching (Suarez et al., 2006). A role for galanin in regeneration is further supported by a recent report that there are more regenerative fibers in rats treated with exogenous galanin compared with control rats after a sciatic nerve-pinch injury (Xu et al., 2012b). Furthermore, this increase in regeneration is associated with increased functional recovery as measured by both motor and sensory nerve conduction velocities (Xu et al., 2012b). In contrast, galanin-OE mice did not display an increase in functional recovery after a sciatic nerve crush injury (Hygge-Blakeman et al., 2004). However, these mice ectopically overexpress galanin under the control of the dopamine β-hydroxylase promoter (Steiner et al., 2001), and it remains to be determined whether galanin levels in the DRG after nerve injury are higher in these mice than in WT mice.

The impaired regenerative capacity in galanin-KO mice is paralleled by a reduction in neuritogenesis of adult mouse dispersed DRG neurons in vitro. The number of neurons producing neurites is reduced by a third and the neurite length almost halved after 8 hours in culture (Holmes et al., 2000). Importantly, these deficits in both neurite numbers and length in galanin-KO DRG cultures can be rescued by the addition of exogenous galanin (Mahoney et al., 2003a,b). Furthermore, after a conditioning nerve lesion, neurite outgrowth in adult mouse dispersed DRG neurons from galanin-KO mice was significantly lower than in WT controls (Sachs et al., 2007). Consistent with these findings, treatment of adult rat DRG with exogenous galanin increases neurite length and the number of branch points (Suarez et al., 2006). Subsequent studies demonstrated that treatment with a gradient of exogenous galanin significantly increased the velocity of DRG growth cone advancement by 1.9-fold without inducing a turning response, suggesting galanin is not an attractant or repellent cue but a "pure" promoter of neurite advance (Sanford et al., 2008).

Many studies of neurite outgrowth have used the rat adrenal pheochromocytoma (PC12) derived cell line (Greene and Tischler, 1976) that when treated with nerve growth factor differentiates to resemble sympathetic neurons. An early study reported that treatment with galanin failed to induce neurite outgrowth in PC12 cells (Klimaschewski et al., 1995), whereas a more recent study demonstrated that galanin significantly increased the percentage of PC12 cells exhibiting neurite outgrowth (Hawes et al., 2006; Hobson et al., 2013).

Existing data suggest that the proregenerative and neuritogenic effects of galanin are mediated by GAL_2. Treatment of dispersed DRG neurons with the nonpeptide GAL_1-specific antagonist RWJ-57408 (Scott et al., 2000) failed to suppress neurite outgrowth (Mahoney et al., 2003a). Consistent with this, GAL_1-KO mice have no reduction in regenerative capacity after a nerve crush injury (Blakeman et al., 2003) nor a deficit in neuritogenesis in vitro (Mahoney et al., 2003a). Together these results suggest GAL_1 is not responsible for the proregenerative effects of galanin. Furthermore, the deficits in neurite outgrowth of neurons from the galanin-KO mouse can be rescued by addition of the $GAL_{2/3}$ specific agonist galanin (2–11) (Mahoney et al., 2003b), suggesting GAL_2 mediates the neuritogenic effects of galanin. This is confirmed by the finding that GAL_2-KO mice have a one-third reduction in neurite outgrowth consistent with that observed in galanin-KO mice (Hobson et al., 2006), which cannot be rescued by the addition of galanin or galanin (2–11). Most recently, Hobson et al. (2013) showed that, in adult sensory neurons and PC12 cells, galanin decreases the activation state of Rho and Cdc42 GTPases, both known regulators of filopodial and growth cone motility. Consistent with this, the levels of activated Rho and Cdc42 are increased in the DRG of galanin-KO mice compared with WT controls. Furthermore, exogenous galanin increases the activation of cofilin, which is a downstream effector of many of the small GTPases, in the cell bodies and growth cones of DRG and in PC12 cells. A reduction in the activation of cofilin and an alteration in growth cone motility were also observed in cultured galanin-KO neurons.

In summary, strong evidence has been obtained over the last 20 years for a pivotal role for galanin in the response of the nervous system to injury (see also section V.E), particularly with respect to regeneration and chronic pain caused by various sensory neuropathies. However, the precise mechanisms of action that underlie these roles remain to be fully elucidated.

E. Physiologic and Pharmacologic Actions of Galanin in the Diseased Brain

A marked alteration in galanin expression in the brain is observed under a number of different pathologic conditions, suggesting a role for the neuropeptide/receptor system in the development, pathology, or response to neuronal damage and neurodegeneration. More generally, epidemiologic and genetic data are starting to reveal the contribution of neuropeptides to multifactorial disorders, such as Alzheimer's disease (AD), seizures and epilepsy, psychiatric disorders, obesity, and substance abuse (section VII).

1. Alzheimer's Disease. AD is characterized by a progressive loss of cognitive function accompanied by neuronal loss in cerebral cortex, hippocampus, basal forebrain, and brain stem areas. AD brains are characterized by neurofibrillary tangles and neuritic plaques composed of neurites, astrocytes, and glial cells around an amyloid core (e.g., Pearson, 1996; Hyman, 2001), a historically "characteristic' loss of cholinergic neurons in the nucleus basalis of Meynert, and reduced choline acetyltransferase and acetyl cholinesterase levels in the basal forebrain. In postmortem brains from AD victims, a twofold increase in galanin receptor binding sites was observed in the hippocampal CA1 region, the stratum radiatum of CA3, the hilus of the dentate gyrus, and the substantia nigra (Rodriguez-Puertas et al., 1997). Increased galanin receptors were also observed in the central nucleus of the amygdala and the corticoamygdaloid transition area in the early stages of AD, but levels decreased by the end stages of the disease (Perez et al., 2002). Notably, galanin-positive fibers and terminals are present at a higher density in the basal forebrain and hyperinnervate the remaining cholinergic cell bodies (Chan-Palay, 1988; Mufson et al., 1993).

It was initially proposed based on early studies that degeneration of a collateral network induced by AD leads to upregulation of galanin production in the remaining, "unaffected" nerve terminals (Chan-Palay, 1988), similar to models of neuronal injury. In contrast, in Down's syndrome, which also produces cholinergic neuron degeneration, no galanin hyperinnervation occurred (Mufson et al., 1993). Thus, degeneration per se is not sufficient to induce galanin upregulation, an idea supported by a lack of correlation between galanin fiber hypertrophy and the level of cholinergic cell loss resulting from lesions of the septum in rats (de Lacalle et al., 1997). In more recent studies in human brain, single neuron gene expression profiles in postmortem samples of cholinergic basal forebrain from AD and control patients (i.e., from subjects who died with a clinical diagnosis of no cognitive impairment compared with nucleus basalis neurons from AD cases lacking galanin hyperinnervation or those displaying prominent hyperinnervation) indicated that galanin hyperinnervation in this area was associated with a "neuroprotective" gene expression profile (Counts et al., 2009, 2010).

In recent years there has also been renewed interest in aspects of galanin activity in AD and in animal models of AD or beta-amyloid (Aβ) toxicity. These studies are beginning to reveal the functional consequences of galanin system plasticity in AD. Several studies have explored the neuroprotective role of galanin using in vitro and in vivo paradigms. Cheng and Yu (2010) demonstrated that galanin inhibited the neurotoxicity and associated gene expression induced by amyloid-β (25–35) (Aβ (25–35)) or Aβ (1–42) in rat primary cultured hippocampal neurons, with activity associated with $GAL_{2/3}$ activation using galanin (2–11)

(Cheng and Yu, 2010). Similar results were also reported independently (Elliott-Hunt et al., 2011) and using cultured human primary neurons (Cui et al., 2010) and a mouse cholinergic cell line, SN56 (Pirondi et al., 2010), with $GAL_{2/3}$-mediated effects on cell death-related gene expression (e.g., caspase-3) implicated.

In the study by Cheng and Yu (2010), galanin inhibited spatial learning deficits in the Morris water maze task produced by Aβ (25–35) injection into CA1 of the hippocampus as well as the associated disruption of gene expression (p53, Bax, and MAP2) caused by the amyloid (Cheng and Yu, 2010). New studies have confirmed the ability of exogenous galanin to attenuate spatial memory impairment and to decrease hippocampal Aβ levels in a rat AD model (Li et al., 2013). In these comprehensive studies, galanin and the $GAL_{2/3}$ agonist galanin (2–11) improved spatial memory and decreased hippocampal Aβ levels produced by intracerebroventricular Aβ injection, and the levels of galanin and GAL_2 mRNA and peptide/protein were increased significantly in the hippocampus after Aβ administration, whereas GAL_1 mRNA and protein levels were not altered. Together these results implicate galanin signaling via GAL_2 in the protective effects against spatial memory impairment and hippocampal Aβ aggregation.

In related studies the relationship between galanin and Aβ has been further explored. Aβ peptides are secreted from neurons, resulting in extracellular accumulation of Aβ and neurodegeneration. A study that assessed the hypothesis that Aβ undergoes corelease with neurotransmitters demonstrated regulated cosecretion of Aβ (1–40) and Aβ (1–42) with galanin and other peptides (enkephalin and NPY) and with the catecholamine transmitters (dopamine, NA) (Toneff et al., 2013). Aβ and both neuropeptide and catecholamine neurotransmitters were found colocalized in dense core secretory vesicles (DCSVs), which also contained amyloid-precursor protein and its processing proteases, β- and γ-secretases, required for production of Aβ, suggesting Aβ can be generated in transmitter-containing DCSVs. Regulated secretion of Aβ (1–40) and Aβ (1–42) with galanin was observed in human neuroblastoma cells. This demonstration that Aβ peptides are present in transmitter-containing DCSV and undergo cosecretion with galanin (and other neuropeptide and catecholamine neurotransmitters; Toneff et al., 2013) raises questions about the nature of the interaction between galanin and Aβ.

Recently, small peptides were shown to modulate the aggregation and toxicity of Aβ. A screen of neuropeptides using ion mobility-mass spectrometry to search for such naturally occurring peptides with direct Aβ binding properties, revealed that galanin and the neuropeptide leucine enkephalin interact strongly with both monomeric and small oligomeric forms of Aβ (1–40) to create a range of complexes. These data indicate that galanin may modulate fibril generation and produce shorter fibrillar aggregates when present in "excess" concentrations (Soper et al., 2013). As such, this may contribute to a therapeutic effect of endogenous or exogenous galanin in AD.

In a study in rats, the effects of antidiabetic drugs that were postulated to inhibit galanin production (glibenclamide and pioglitazone, orally for 3 weeks) were examined on the behavioral and neurochemical changes produced by intracerebroventricular Aβ injection (Baraka and ElGhotny, 2010). Administration of Aβ produced a predicted impairment in spatial cognition, evaluated in the Morris water maze task, and in learning and memory performance, in a passive-avoidance learning task, and glibenclamide and pioglitazone treatment resulted in significant improvement in spatial cognition and in learning and memory performance, as well as a decrease in hippocampal galanin and hyperphosphorylated tau protein levels (Baraka and ElGhotny, 2010). These findings have potential implications for improving the major symptoms in AD.

Several studies using transgenic mice have attempted to further explore the relationship between galanin systems and AD pathology and symptomology. Notably, DβH-galanin-OE mice displayed performance deficits in memory tests, analogous to deficits seen in AD (Steiner et al., 2001). On this basis, it was proposed that the inhibitory activity of galanin might inhibit acetylcholine release and worsen symptoms, although later studies indicated otherwise. In electrophysiological studies of acutely dissociated rat cholinergic neurons from basal forebrain, galanin inhibited K^+ currents but not Ca^{2+} or Na^+ currents (Jhamandas et al., 2002). Hence, galanin may excite and augment acetylcholine release from any remaining cholinergic neurons in the AD brain. Thus, it is still unclear if upregulation of galanin is a contributing factor to AD or a compensatory change to maintain cholinergic and noncholinergic transmission. In this regard, a recent study reported that galanin-mediated spatial learning deficits may be unrelated to its modulation of the cholinergic system (Sabbagh et al., 2012).

2. Cerebral Ischemia and Stroke. A distinctive feature of galanin expression established over many years of research is the dramatic increase in its expression produced by neuronal injury and during development (see sections V.D and VIII). Although stroke is a major clinical cause of neuronal injury, very little research has investigated the galanin system in human stroke or experimental models of cerebral ischemia. Cerebral cortex contains few if any strongly galanin-positive neurons under normal conditions but receives galanin-positive inputs from subcortical areas. Apart from an early study on the response to cortical spreading depression (Shen et al., 2003), little is known about the presence and function of galanin in normal or injured cortex. However, some data on alterations in galanin gene expression and peptide levels and galanin receptor plasticity over the time course of ischemic damage are available.

In a comparative gene expression study that evaluated changes in rat cerebral cortex at 6 and 24 hours after reperfusion after transient middle cerebral artery occlusion (MCAo), increased mRNA levels of genes involved in stress, inflammation, transcription, and plasticity were observed, in association with decreased mRNA levels of genes that control neurotransmitter function and ionic balance. Galanin was one of many genes found to be increased (12- to 15-fold) in the ischemic cortex (Raghavendra Rao et al., 2002).

In a later study, the effect of transient MCAo on the tissue concentrations of galanin peptide was examined in rats (Theodorsson and Theodorsson, 2005). The concentrations of galanin and NPY were measured after 3, 7, and 14 days in tissue extracts from the lesioned and the contralateral hemisphere. Galanin levels were not changed in any of the brain regions studied except in the hippocampus, where levels were lower in the ischemic compared with the intact contralateral hemisphere. Thus, although neuronal injury/lesions in the CNS generally produce an upregulation of galanin, this study did not obtain evidence that galanin is involved in the response within the ischemic penumbra (Theodorsson and Theodorsson, 2005). However, a potential confound is the use of regional tissue extracts, because changes in specific populations of neurons may not be detected. In this regard, no significant changes were observed in the concentration of NPY in response to the lesions in this study, but previous studies of the effect of different types of ischemia (focal and transient) have reported changes in NPY levels in hippocampal interneurons and in cortical and striatal neurons. For example, in an MCAo study with the ischemic region centered in the insular cortex, significant increases in NPY immunostaining were detected within the peri-infarct region (Allen et al., 1995). Also, transient (30 minutes) forebrain ischemia by four-vessel occlusion produced a decreased number of the NPY immunoreactive neurons in the frontoparietal cortex at 4 hours and at 1 and 7 days after reperfusion followed by recovery after 40 days. A rapid reduction in NPY immunoreactive neurons and an almost complete recovery by 7 days after reperfusion were also observed in the striatum (Grimaldi et al., 1990).

In a later study, the presence of galanin immunoreactive cells was investigated in the core and peri-infarct zone at 1, 4, 24, and 72 hour after *permanent* MCAo in the rat (De Michele et al., 2006). Seventy-two hours after MCAo, a population of morphologically intact galanin-positive neurons was observed in the peri-infarct zone, but galanin cells were not observed at earlier time points. However, galanin immunoreactive myelinated nerve fibers were observed 4 and 24 hours after the focal ischemia (De Michele et al., 2006), perhaps reflecting expression in damaged neurons with their soma outside the area of ischemia.

Hwang et al. (2004) investigated chronological changes in galanin immunoreactivity and peptide levels in the hippocampus at various times after 5 minutes of transient forebrain ischemia in the gerbil. At 12 hours after ischemia/reperfusion, the number of galanin immunoreactive neurons and galanin immunoreactivity were significantly increased in the hippocampus compared with 3 hours after ischemic insult, especially in the CA1 region (Hwang et al., 2004). Thereafter the number of hippocampal galanin immunoreactive neurons and immunoreactivity decreased in a time-dependent fashion. Galanin immunoreactivity was also identified in microglia in the CA1 region associated with delayed death of CA1 pyramidal cells. The authors speculated that these changes (early increases) in galanin in pyramidal cells may be associated with reduction of excitotoxic damage, the enhanced expression between 0.5 to 2 days after ischemia may be associated with increased extracellular potassium and neuronal depolarization, and galanin expression in microglia 4 days after ischemia may be associated with a possible reduction of ischemic damage (Hwang et al., 2004).

The temporal effects of focal ischemia induced by unilateral MCAo on the expression of galanin receptors as well as galanin in the rat was also investigated (Shen and Gundlach, 2010). *GAL* and GAL_1 mRNAs in penumbral/undamaged areas were increased on the first and second day postischemia, whereas increased GAL_2 mRNA was observed in the same regions only on day 2. Galanin immunoreactive neurons were detected in the frontal/cingulate cortex and abundant galanin-immunoreactivity in nerve axons/fibers within the penumbral areas between the third and the seventh day after ischemia. *GAL* mRNA and immunoreactivity were also increased in a population of putative oligodendrocyte precursors (Shen and Gundlach, 2010). Upregulation of galanin and receptors in various cell populations after severe ischemic injury further demonstrates the plasticity of galanin/receptor expression after brain injury, consistent with a functional role for galanin signaling in such pathophysiological conditions (see also section V.E). Despite their widespread investigation in other experimental paradigms, galanin and galanin receptor KO and OE mice do not appear to have been studied in relation to cerebral ischemia/stroke.

3. Seizures and Epilepsy. Neuropeptide modulators are ideal candidates to influence epileptic tissue overexcited during seizures, because they have longer half-lives allowing modulation of neuronal and network activity over prolonged periods, potentially setting the seizure threshold. Neuropeptides, stored in LDCVs, are released upon high frequency stimulation that occurs during seizures (Kovac and Walker, 2013; Dobolyi et al., 2014; see section I). Indeed, galanin and a number of other neuropeptides are implicated in epilepsy pathology and many are considered to participate in endogenous neuroprotective actions via receptors in the hippocampus, a focus of seizures in temporal lobe epilepsy (Lerner et al., 2010; Kovac and Walker, 2013).

Galanin immunoreactivity in nerve fibers in the hippocampus is markedly depleted in all hippocampal areas for up to a week after experimental stimulation of the perforant path-dentate gyrus pathway to induce self-sustaining status epilepticus (SSSE) in rats, a state of nearly continuous seizure activity lasting for hours to days (Mazarati et al., 1998; see Lerner et al., 2010, for review). Galanin-positive fibers reappear at a reduced density in the hippocampus, an effect caused by "release fatigue" induced by over activation of galanin-containing projections to the hippocampus. Administration of galanin receptor agonists into brain areas pertinent to the initiation and propagation of epileptic activity attenuate seizure responses in multiple animal models of epilepsy and pharmacological blockade of galanin receptors exerts proconvulsant effects. For example, the duration of SSSE can be markedly shortened by injection of galanin into the dentate hilus before stimulation of the perforant path, an effect reversible by injection of a GAL_1 antagonist, M35. Furthermore, M35 alone promotes the establishment of seizures and prolongs their duration, indicating that galanin can affect the maintenance phase of established SSSE, possibly via GAL_1 (Mazarati et al., 1998; Lerner et al., 2010).

Functional deletion of both *GAL* and *GAL_1* genes in mice results in either a spontaneous seizure phenotype or an enhanced susceptibility to seizure stimuli. Despite their development by two laboratories (Gottsch et al., 2005; Hobson et al., 2006; Lu et al., 2008), the profile of GAL_2-KO mice in terms of seizures and epilepsy has not be reported. In contrast, overexpression of galanin in seizure pathways, using both transgenic and virus vector transfection methods, retards the epileptic process. Galanin-OE mice display a retarded seizure-threshold and duration during hippocampal kindling, presumably due to increased release of galanin from hippocampal mossy fibers, which interacts with presynaptic GAL_2 to reduce glutamate release and seizure activity (Kokaia et al., 2001). Galanin-KO mice are more susceptible to perforant path stimulation-induced SSSE than WT mice, suggesting that endogenous galanin modulates the excitability of the perforant path-dentate granule cell complex and hippocampal excitability (Mazarati et al., 2000). Galanin-KO mice display a similar increase in susceptibility to seizures induced by pentylenetetrazole, which acts on brain stem and medial thalamic nuclei (Mazarati et al., 2000) that contain galanin fibers and receptors. Galanin-KO mice do not have spontaneous seizures (Mazarati et al., 2000), whereas GAL_1-KO mice do (Jacoby et al., 2002; McColl et al., 2006). Although the reason for this difference is not known, there are morphologic dissimilarities between brains of WT and GAL_1-KO mice, with a decrease in galanin-positive fibers in the hippocampal granule cell layer of GAL_1-KO mice (Fetissov et al., 2003). Generally, galanin exerts anticonvulsant effects via GAL_1 and GAL_2 and their distinct downstream signaling cascades (see Lerner et al., 2010, and Webling et al., 2012, for review).

Although activation and inhibition of receptors by oral application of peptides is typically not efficient because of low bioavailability, rapid degradation, and insufficient penetration of peptides through the blood-brain barrier, several synthetic agonists of galanin receptors with optimized bioavailability and allosteric modulators of GAL_2 inhibit experimental seizures upon systemic administration (Lerner et al., 2010; Lu et al., 2010). Together with recent progress in gene therapy approaches leading to the local production of agonists and antagonists within the CNS (McCown, 2009) and encapsulated cell biodelivery (Nikitidou et al., 2014), these approaches offer a realistic opportunity for the development of galanin-based antiepileptic treatments (Lerner et al., 2010).

4. Anxiety Disorders, Depression, Substance Abuse, and other Pathologic States. In animal studies, both exogenous and endogenous galanin have been shown to modulate anxiety- and depressive-like behaviors, both basal levels of anxiety and anhedonia, and those induced experimentally by different stimuli such as acute or chronic stress. For example, in rodent models of depression-related behavior, treatment with galanin or galanin receptor agonists has been shown to affect these behaviors and alter the behavioral and neurochemical effects of antidepressants. Conversely, treatment with clinically efficacious antidepressants alters galanin and galanin receptor gene expression in rodents (Karlsson and Holmes, 2006; Rovin et al., 2012).

The pathophysiology of depression remains unclear, but is thought to involve stress-related disturbances in brain monoaminergic transmission. Specific reports on changes in galanin or galanin receptors associated with the pathology of clinical anxiety disorders and/or major depression in patient groups remain elusive (Murck et al., 2004; Serafini et al., 2013; Juhasz et al., 2014), although galanin is coexpressed with and modulates NA and serotonin transmission, both implicated in depression, and there are some relevant genetic association studies (see section VII). Indeed, on the basis of existing knowledge, Juhasz and colleagues (2014) recently provided an excellent synthesis of data that supports an integrated role of galanin and galanin receptors in the pathology and potential treatment of major depression disorder.

Similarly, several peptides that affect stress-related and innate motivated behavior and associated common neural circuits have been shown to be involved in drug reward behavior and substance abuse and addiction (Nestler, 2005; Koob and Volkow, 2010). These peptides include CRF (Koob, 2010), NPY (Ciccocioppo et al., 2009), and galanin (Picciotto et al., 2010). Galanin receptor binding sites are present in brain regions implicated in drug addiction in rats (Skofitsch et al., 1986) and mice (Hawes and Picciotto, 2004; Jungnickel and Gundlach, 2005; but see Lu and Bartfai, 2009), including the dopaminergic neuron systems within the substantia nigra/caudate putamen and ventral tegmental area/nucleus accumbens. They are also present in the LC, which contains galanin-positive noradrenergic neurons that express different profiles of galanin receptors in rodents (Rovin et al., 2012) and humans (Le Maître et al., 2013), with GAL_3 most abundant in human LC (and DR nucleus), an important consideration for therapeutic drug development. Lastly GAL_3, which has a more restricted expression pattern in the brain than GAL_1 and GAL_2, is strongly associated with anxiety- and depressive-like behaviors (Swanson et al., 2005; Karlsson and Holmes, 2006; Rovin et al., 2012; Brunner et al., 2014).

In terms of neuropeptide regulation of alcohol (ethanol) intake, experimental studies indicate a relationship between hypothalamic galanin and the consumption of ethanol. Injection of galanin into the PVN or the cerebral ventricles increases the amount of ethanol consumed (Lewis et al., 2004; Rada et al., 2004), and voluntary ethanol intake and systemic injection of ethanol stimulate the expression of *GAL* mRNA in the PVN (Leibowitz et al., 2003). GAL3 antagonism by SNAP 37889 reduces the motivation to work for alcohol (Ash et al., 2014). There are also more recent experimental studies in transgenic mice demonstrating a link between galanin signaling and alcohol preference and intake—galanin-KO mice displayed a marked (35–45%) decrease in ethanol intake and preference at the highest (15%) ethanol concentration provided, which was stronger in female than male mice, compared with littermate and nonlittermate WT mice (Karatayev et al., 2010).

Other recent studies addressed the nature of galanin signaling in the central amygdala (CeA), a key site of alcohol action and production of anxiety-like behavior. Bajo and colleagues (2012) examined the effects of galanin in the CeA using slices from WT and both GAL_2-KO mice and GAL_1/GAL_2 double-KO mice. Galanin had dual effects on GABA transmission, decreasing the amplitudes of GABAergic inhibitory postsynaptic potentials (IPSPs) in a majority of CeA neurons but augmenting IPSPs in others. The increase in IPSP size was blocked by the GAL_3 antagonist SNAP 37889, whereas the IPSP reduction was absent in CeA neurons of $GAL_1 \times GAL_2$ double-KO *and* GAL_2-KO mice, suggesting postsynaptic augmentation of GABA transmission in some CeA neurons via GAL_3, whereas GAL_2 receptors are involved in the depression of IPSPs (Bajo et al., 2012). Galanin in combination with ethanol, which augments IPSPs presynaptically, caused summated effects in those CeA neurons displaying galanin-augmented IPSPs, suggesting the two agents act via different mechanisms in this population. However, in neurons displaying diminished IPSPs in response to galanin, ethanol effects were blunted, suggesting a pre-emptive effect of galanin (Bajo et al., 2012). These findings illustrate the complex cellular mechanisms that underlie the interaction of galanin and ethanol with inhibitory transmission in a key brain region related to anxiety-related behavior and the demonstrated involvement of GAL_3 is consistent with genetic linkage data. A link between galanin and abnormal levels of alcohol craving or elevated consumption is suggested by a reported association of galanin and GAL_3 with alcoholism. Galanin haplotypes and increased alcoholism risk were identified in two distinct populations (Belfer et al., 2006), whereas there was no effect of GAL_1 or GAL_2 haplotypes on alcoholism risk (see section VII).

There are also experimental studies in both rats and WT and transgenic mice demonstrating a link between galanin receptor signaling and nicotine (see Jackson et al., 2011, for review), and opiates (see Picciotto, 2010, and Holmes et al., 2012, for review). For example, galanin-KO mice have reduced sensitivity to nicotine reward, and galanin-mediated signaling via GAL_1 blocks nicotine reward (Jackson et al., 2011; Neugebauer et al., 2011).

Galanin was also shown in a series of studies to alter the rewarding properties of morphine. Specifically, galanin opposes the actions of morphine that lead to opiate dependence and withdrawal, an effect that is mediated via GAL_1 (Holmes et al., 2012). Both morphine administration and withdrawal increased galanin gene transcription in the LC. Increasing galanin levels in the brain reduced signs of opiate withdrawal. GAL_1-KO mice undergo more severe opiate withdrawal, whereas mice lacking GAL_2 display no significant difference in withdrawal signs compared with matched WT controls (Holmes et al., 2012).

A recent study investigated the potential cellular mechanisms involved in the ability of galanin to modulate opiate reward (Einstein et al., 2013). Excitatory postsynaptic potentials were measured using both field and whole-cell recordings in striatal brain slices from WT mice and mice lacking specific galanin receptors. Galanin decreased excitatory postsynaptic potentials amplitude in the dorsal striatum and nucleus accumbens in WT mice, whereas this ability of galanin was absent in slices from mice lacking either the GAL_1 or GAL_2 gene, suggesting that both receptors are required for this effect. In studies to determine whether behavioral responses to opiates were dependent on both receptors, GAL_1- and GAL_2-KO mice were tested for morphine conditioned place preference, which was significantly attenuated in both KO strains. These data suggest that mesolimbic excitatory signaling is significantly modulated by galanin in a GAL_1- and GAL_2-dependent manner, and morphine conditioned place preference is dependent on the same receptors (Einstein et al., 2013).

5. Other Neuronal Actions. In addition to the neuronal actions of galanin already discussed, there are many other actions that, because of space restrictions, cannot be covered in detail. These include roles in arousal and sleep regulation (see Gaus et al., 2002; McGinty and Szymusiak, 2003; Saper, 2006), reproduction and associated behavior, neuroendocrine mechanisms, and hormone release, which are reviewed elsewhere, along with similar GALP actions (see, e.g., Gundlach, 2002; Gottsch et al., 2004; Crown et al., 2007; Kalló et al., 2012; see section VI).

There is also good evidence for a role for galanin signaling in processes of myelination and responses to myelin injury (Wraith et al., 2009; Zhang et al., 2012) along with proliferation, differentiation, and/or migration of oligodendrocyte precursor cells (Shen et al., 2003; Ubink et al., 2003; Butzkueven and Gundlach, 2010) and neural stem and progenitor cells (the latter topic is covered in section VIII). It is highly likely that ongoing research in these areas will produce further evidence of the pleiotropic actions of galanin and the associated receptor mechanisms.

VI. Actions of Galanin-Like Peptide in the Normal Brain and in Pathology

Since its discovery, >100 peer-reviewed articles and reviews have appeared on GALP biology or closely related topics, and most of these have provided consistent anatomic, physiologic, and pharmacological evidence for its potential role in affecting and integrating metabolism and reproduction via actions in the hypothalamus and pituitary (reviewed in Gundlach, 2002; Cunningham, 2004; Gottsch et al., 2004; Shiba et al., 2010; Lawrence and Fraley, 2011). However, unfortunately for the field and for the important aspects of drug development and therapeutic applications, it is also thought that GALP mediates these actions via an as yet unknown receptor(s) rather than via $GAL_{1\text{-}3}$ (see, e.g., Krasnow et al., 2004; Lawrence and Fraley, 2011).

Initially it was reported that central GALP infusion altered feeding in rats (acute stimulation and subsequent inhibition; Lawrence et al., 2002; Matsumoto et al., 2002) and mice (inhibition only; Krasnow et al., 2003). In rats maintained on a high-fat diet associated with greater caloric intake (>2-fold) and body weight (BW) (~30% higher) compared with chow-fed control rats, central administration of GALP induced rapid feeding in both dietary groups over 30 minutes post-injection. A 0.3 nmol dose of GALP led to ~40% larger increases in caloric intake in high-fat-fed rats than in chow-fed controls (Tan et al., 2005).

A more recent study determined whether energy metabolism in spontaneously exercising mice could be promoted by intracerebroventricular GALP administration (Ito et al., 2013). Changes in the respiratory exchange ratio in response to GALP indicated that lipids were primarily consumed followed by a continuous consumption of glucose throughout the dark period in nonexercising mice. In mice permitted to spontaneously exercise on a running wheel, intracerebroventricular GALP administration increased oxygen consumption and heat production levels for 5 to 11 hours after administration, independent of the total running distance. GALP administration and spontaneous exercise decreased BW within 24 hours, and energy metabolism-related enzymes in liver and skeletal muscle were altered, including phosphoenolpyruvate carboxykinase, which regulates gluconeogenesis, and glucose transporter-4 (Ito et al., 2013).

Studies of *acute* and *chronic* GALP infusion in leptin-deficient *ob/ob* obese mice revealed that *acute* GALP induced a long-lasting (4 days) decrease in food intake and BW, whereas *chronic* GALP produced a sustained decrease in BW and an increase in core body temperature, despite significant recovery of food intake. In a pair-fed model, *chronic* GALP treatment resulted in a decrease in BW and an increase in body temperature and thermogenesis in brown adipose tissue, suggesting that leptin activation of the sympathetic nervous system and ultimately thermogenesis may be partially mediated by GALP (Hansen et al., 2003).

Data from more recent in vivo and in vitro studies suggest GALP elicits thermogenesis via a prostaglandin E_2-mediated pathway in CNS astrocytes (Kageyama et al., 2013). Central injection of GALP (intracerebroventricular) caused biphasic thermogenesis that was blocked by pretreatment with central (intracerebroventricular), but not peripheral (intravenous), administration of the cyclooxygenase inhibitor diclofenac. Astrocytes in the periventricular zone of the third ventricle were activated by GALP, and the peptide also increased *cyclooxygenase-2* and *cytosolic prostaglandin E_2 synthase* mRNA levels in cultured astrocytes (Kageyama et al., 2013).

Fasting reduces *GALP* mRNA expression in the ARC (Fraley et al., 2004a), and as GALP is also present in the gastrointestinal tract (Ohtaki et al., 1999), levels of immunoreactive GALP in the blood are also decreased by food deprivation. Fasting also decreased a rapid blood-to-brain influx of intact GALP induced by glucose treatment (Kastin et al., 2001).

In regulatory studies to determine if and how GALP expression was modulated by pituitary hormones in the rat, it was reported that hypophysectomy induced a reduction in *GALP* mRNA levels in the ARC, and although this was not associated with alterations in levels of gonadal or adrenal steroids, thyroidectomy led to a significant reduction in *GALP* mRNA expression compared with intact controls, and thyroidectomized rats treated with thyroxine displayed *GALP* mRNA levels similar to intact controls, suggesting a selective regulation of arcuate GALP neurons by thyroid hormone (Cunningham et al., 2004a). In contrast, *GALP* mRNA was increased in neurohypophyseal pituicytes of lactating compared with nonlactating rats (ARC levels were unaffected), likely associated with the lactation-induced activation of oxytocin and vasopressin secretion (Cunningham et al., 2004a).

In relation to the reproductive axis, central infusion of GALP activated GnRH neurons (reflected by Fos staining) and increased plasma luteinizing hormone (LH) levels post-treatment in male rats, mice, and macaques, and the LH response was blocked by pretreatment with a $GnRH_1$ antagonist (Takatsu et al., 2001; Krasnow et al., 2003; Cunningham, 2004; Cunningham et al., 2004a,b; Seth et al., 2004). In a later study, the magnitude of increases in serum LH in response to GALP administration was heightened in pubertal versus adult male rats, and negligible LH responses were detected in pubertal or adult female rats at diestrus (Castellano et al., 2006). Short-term fasting amplified rather than reduced LH responses to GALP in pubertal males. These findings suggest the LH response to GALP is sexually differentiated and the relative responsiveness of the GnRH/LH system may relate to the metabolic-reproductive axis crosstalk during puberty (Castellano et al., 2006).

Furthermore, in vitro studies demonstrated that GALP induced GnRH release from rat hypothalamic explants and GALP antiserum inhibited leptin-induced GnRH release (Seth et al., 2004). Further in vitro studies suggested additional targets for GALP in the hypothalamus, with activation of growth hormone-releasing hormone neurons isolated from the ARC, reflected by increased cytosolic Ca^{2+} levels (Kuramochi et al., 2005). In electrophysiologic studies of ARC neurons in hypothalamic slices, GALP was shown to inhibit excitatory and inhibitory postsynaptic currents in a similar way to galanin, whereas the two peptides differentially affected the intrinsic membrane properties, with galanin inducing hyperpolarization of the resting membrane potential and GALP having no effect (Dong et al., 2006). Galanin also suppressed the spontaneous firing of arcuate neurons, whereas GALP produced a mixture of suppression and enhancement of firing and appeared to antagonize galanin effects (Dong et al., 2006).

Further to its effects on reproductive hormones, GALP was shown to increase male sexual behavior in rats, whereas galanin inhibited it, and the effect of GALP was maintained in castrated rats, suggesting effects independent of testosterone secretion (Fraley et al., 2004b). In more recent comparative studies in adult, ovariectomized, female mice primed with estradiol and progesterone, GALP infusion increased LH secretion, and the response was blocked by pretreatment with a $GnRH_1$ antagonist. GALP infusion significantly increased the latency with which sexually experienced female mice displayed receptivity and slightly reduced lordosis behavior (Kauffman et al., 2005). In contrast to effects in rats, GALP inhibited sexual behavior in male mice. These authors also observed a dose-dependent reduction in motor control (on rotarod) and open-field locomotor activity in female mice acutely treated with GALP (Kauffman et al., 2005), effects not reported in rats.

The absence of leptin signaling in obese Zucker rats and hypoleptinemia in streptozotocin-induced diabetic rats are associated with decreased hypothalamic GALP expression, and this reduction can be reversed by treatment with either leptin or insulin (Fraley et al., 2004a). In fact, the downregulation of hypothalamic GALP and the upregulation of NPY may act in concert to promote hyperphagia in these rats. These findings are consistent with a tonic influence of leptin and insulin signaling on hypothalamic GALP expression under normal conditions and abnormalities in GALP neuronal signaling and their putative targets—thyrotropin-releasing hormone and GnRH neurons—-under pathologic conditions such as diabetes and obesity (Takatsu et al., 2001; Kumano et al., 2003; Fraley et al., 2004b; Seth et al., 2004).

In this regard, another report provided further evidence for the trophic support by endogenous GALP of the neuroendocrine reproductive axis, including sexual behavior (Stoyanovitch et al., 2005), demonstrating firstly that central immuno-blockade of GALP reduced serum LH levels and blocked sexual behavior in normal male rats and also that central GALP infusion increased (restored) serum LH levels and sexual behavior in diabetic rats (Stoyanovitch et al., 2005). These authors also found that treatment of diabetic rats with leptin and insulin normalized LH and sexual behavior, and this effect could be attenuated by intracerebroventricular GALP antibody infusion.

In relation to puberty, *GALP* mRNA was first detected in the ARC on day 8. *GALP* mRNA was gradually increased between days 8 and 14 and markedly increased between days 14 and 40, which is the weaning and pubertal period in rats. After day 40, there were no significant differences in *GALP* mRNA and there was no sexual dimorphism in *GALP* mRNA during postnatal development (Kawagoe et al., 2008). In food-restricted weanling rats of both sexes, GALP treatment restored the timing of puberty onset to that observed in ad libitum-fed controls, and a reduction of GALP translation in ad libitum-fed, prepubertal females, but not male rats, significantly delayed the onset of puberty (Mohr et al., 2012). Studies of a potential mechanism revealed that, in food-restricted rats, kisspeptin mRNA in the ARC was significantly reduced compared with ad libitum-fed controls, and this effect was prevented by central GALP administration via indirect effects on the kisspeptin neurons (Mohr et al., 2012).

In mice that were overfed during breastfeeding (by rearing in a small litter) and/or during adolescence (adolescent mice fed a high-fat diet), possible alterations in *GALP* and other neuropeptide mRNA levels were investigated after 50 days of a high-fat diet (high-fat challenge) at 19 weeks of age. In developmentally overfed mice, the high-fat challenge significantly decreased *GALP* mRNA levels compared with control challenged mice. Thus, in mice overfed during critical developmental periods, hypothalamic neuropeptide systems (GALP and galanin, NPY, and AgRP) are altered and respond differently to a high-fat diet in adulthood (Ferretti et al., 2011).

GALP-KO mice are reported to be physiologically indistinguishable from WT mice in several assessed aspects of growth, sexual development, body weight, food and water consumption, and motor activity when allowed unlimited access to standard chow. However, in response to changes in diet, GALP-KO mice consumed less food during refeeding after a fast than WT mice (male only) and gained less weight on a high-fat diet than WT controls, despite having consumed equal amounts of food (male and female). These findings suggest GALP signaling may not be essential for the maintenance of energy homeostasis under steady-state nutritional conditions but plays a role in readjusting energy balance under changing nutritional circumstances (Dungan Lemko et al., 2008).

Overall, considerable independent evidence indicates that GALP is a key modulatory factor that integrates metabolism and reproduction during puberty and in adulthood under different nutritional conditions and is an important mediator of the physiologic effects of leptin and insulin on GnRH/LH secretion and the reproductive axis. Comparative data also suggest some sex-based and species differences in the nature of GALP actions (see Gottsch et al., 2005; Kauffman et al., 2005; Stoyanovitch et al., 2005; Castellano et al., 2006). Therefore, the identification of the GALP receptor(s) and further developments in the field are eagerly awaited.

VII. Genetic Association Studies of Galanin and Galanin Receptors

A. Anxiety- and Depression-Related Behavior

In animal studies, both exogenous and endogenous galanin have been shown to modulate anxiety- and depressive-like behavior (see section V.E). In human studies, the sex-specific association of polymorphisms in the promoter region of the *GAL* gene in patients with anxiety disorder or major manic depression with the severity of anxiety symptoms, supports a role for galanin in the pathophysiology of clinical anxiety and depression and demonstrates the importance of sex- and hormone-status-specific genetic associations (Unschuld et al., 2008, 2010) (Table 6). Specifically, a meta-analysis of genome-wide association studies on over 10,000 individuals revealed a significant association between the *GAL* gene (rs2156464) and major depressive disorder (Wray et al., 2012). The rs2156464 single-nucleotide polymorphism (SNP) is in linkage disequilibrium with two other SNPs in the promoter region of *GAL* that have been shown to influence promoter activity and therefore galanin expression in the amygdala and hypothalamus (Davidson et al., 2011). In the Chinese Han population, a different *GAL* SNP also has a positive correlation with major depressive disorder (Wang et al., 2013). Race-associated differences may, at least partially, explain why depression is correlated with different SNPs in the *GAL* gene in different studies. Further evidence was recently described of potential involvement of alterations in the galanin peptide *and* receptor genes with an increased risk of depression and anxiety in people who experienced childhood adversity or recent negative life events (Juhasz et al., 2014). Bayesian multivariate analysis revealed a greater relevance of galanin system genes in highly stressed subjects than in subjects with moderate or low life stress, suggesting galanin pathways play an important role in the pathogenesis of depression in humans by increasing the vulnerability to early and recent psychosocial stress (Juhasz et al., 2014).

B. Addiction-Related Behavior

Considerable experimental evidence has been obtained that implicates galanin signaling in reward and addictive processes. Neural circuits that affect both stress-related and feeding behavior have been shown to be involved in drug reward behavior and substance abuse and addiction (Nestler, 2005; Koob and Volkow, 2010) and are known to be modulated by neuropeptides, including galanin (Picciotto et al., 2010; Ubaldi et al., 2013). Galanin can increase the release of dopamine and norepinephrine (Melnikova et al., 2006; Robinson and Brewer, 2008), a likely mechanism for its influence on reward behavior and drug seeking. All three galanin receptors are reported to be present in brain regions implicated in drug addiction in mice (Hawes and Picciotto, 2004; Lu and Bartfai, 2009), including the dopamine neuron systems within the substantia nigra/caudate putamen and ventral tegmental area/nucleus accumbens, and in the LC, which contains noradrenergic neurons that are galanin and NPY positive, with similar or partial indications in rats

TABLE 6
Association of gene variations of the galanin system with multifactorial diseases

Disease	Cases/Controls	Population	Gene	SNP	*P* Value	Reference
Smoking cessation	486	European American	*GAL_1*	rs2717162	<0.001	Lori et al., 2011
Heroin addiction	412/184	Caucasian ancestry	*GAL*	rs694066	0.001	Levran et al., 2008
Opioid addiction	142/142	Western European	*GAL*	rs948854	0.001	Beer et al., 2013
Heroine addiction	314/208	African American	*GAL_1*	rs5376/(Asn334Ser) rs2717162	0.02	Levran et al., 2014
			GAL	rs3136541	0.04 0.04	
Cocaine addiction	281/208	African American	*GAL_1*	rs5374 rs2717162	0.001 0.03	Levran et al., 2014
Pharmacogenetic association with smoking cessation	1025/192	European American	*GAL_1*	rs2717162	0.003	Gold et al., 2012
Alcoholism	522/489	Finnish Caucasians	*GAL_3*	rs3091367	0.012	Belfer et al., 2007
Alcoholism	263/251	Finnish Caucasians	*GAL*	HT A/B rs31336540 rs4930241 rs6940066 rs3136541	0.001	Belfer et al., 2006
Alcoholism	193/138	Plains American Indians	*GAL*	HT A/B rs31336540 rs4930241 rs6940066 rs3136541	0.045	Belfer et al., 2006
Ventral striatum reactivity/problem drinking	77 Female	Caucasian	*GAL*	HT GAL5.1	0.002	Nikolova et al., 2013
Anxiety	268/541	Caucasian	*GAL*	rs948854 rs4432027	<0.05 (female)	Unschuld et al., 2008, 2010
Major depressive disorder/HAMD score	541/541	Caucasian	*GAL*	rs948854	<0.05 (female)	Unschuld et al., 2010
Major depressive disorder	5673/6901	Meta analysis	*GAL*	rs2156464	<0.001	Wray et al., 2012
Major depressive disorder	376/360 Female	Chinese Han	*GAL*	rs694066	0.0005 (female)	Wang et al., 2013
Major depressive disorder	324/313 Male	Chinese Han	*GAL*	rs694066	0.054 (male)	Wang et al., 2013
Life time depression	1641 female/720 male	Caucasian	*GAL*	rs3136541	<0.05	Juhasz et al., 2014
Life time depression with childhood adversity interaction	1641 female/720 male	Caucasian	*GAL_1*	rs5375 HT 2:GAGTAG HT 6:GAGTGA HT12:GGTCGG	<0.05	Juhasz et al., 2014
Life time depression with recent negative life events interaction	1641 female/720 male	Caucasian	*GAL_1* *GAL_2*	rs1893829 HT 10:AAGCAG rs8836	<0.05	Juhasz et al., 2014
Current depression score with childhood adversity interaction	1641 female/720 male	Caucasian	*GAL_1*	rs11665337	<0.05	Juhasz et al., 2014
Current depression score with recent negative life events interaction	1641 female/720 male	Caucasian	*GAL_1* *GAL_2*	rs5375 rs8836	<0.05	Juhasz et al., 2014
Current anxiety score with childhood adversity interaction	1641 female/720 male	Caucasian	*GAL_1* *GAL_3*	rs11665337 rs2285179 HT 1:GA	<0.05	Juhasz et al., 2014
Current anxiety score with recent negative life events interaction	1641 female/720 male	Caucasian	*GAL_1*	rs11662010	<0.05	Juhasz et al., 2014

HT, haplotype.

(Rovin et al., 2012) and humans (Le Maître et al., 2013). Galanin-KO mice have a decreased sensitivity to nicotine reward, and galanin-mediated signaling via GAL_1 blocks nicotine reward (Jackson et al., 2011; Neugebauer et al., 2011). In a clinical context, craving for tobacco (nicotine) is a major challenge for individuals with nicotine dependence, and craving is one of the most important factors contributing to smoking relapse. Two studies on smokers of European ancestry reported an association of an intronic SNP in the *GAL_1* gene with smoking cessation (Lori et al., 2011; Gold et al., 2012) (Table 6).

In Finnish and American Plains Indian men, an association of *GAL* haplotypes with alcoholism has been reported (Belfer et al., 2006). Furthermore, the *GAL_3* gene, but not the *GAL_1* and *GAL_2* genes, was associated with alcoholism in Finnish Caucasians (Belfer et al., 2007), whereas in the same study, no association of the *GAL_3* locus with alcoholism was observed in American Plains Indians. This difference might be due to the fact that the frequency of SNP rs3091367 differed significantly between the two populations (Belfer et al., 2007). Furthermore, the GAL_3/*GAL* risk diplotypes display a significant association with alcoholism, more than *GAL* or GAL_3 alone (Belfer et al., 2007).

A significant association of a SNP in intron 2 of the *GAL* gene and heroin addiction was observed in US Caucasians (Levran et al., 2008), and more recently the involvement of galanin in opioid addiction was further suggested by a candidate gene association study conducted including >100 well phenotyped long-term opioid addicts undergoing opioid maintenance therapy and well matched healthy controls. The most significant association with opioid addiction was for the rs948854 SNP in the *GAL* gene (Beer et al., 2013).

C. Obesity

The increased prevalence of obesity and "overweight" is a major health problem, because these conditions can cause metabolic complications, including elevated cholesterol, hyperlipidemia, type 2 diabetes mellitus, coronary artery disease, and hypertension. Clear evidence exists that galanin is involved in the regulation of food intake and body weight (see section V.A). For example, central administration of galanin increases food and ethanol consumption (Leibowitz et al., 2003), and galanin-OE mice display an increased intake of dietary fat and ethanol (Karatayev et al., 2009). Indeed, the actions of central and peripheral galanin and its receptors in the regulation of metabolism, obesity, and appetite, including galanin receptor-linked mechanisms in experimental obesity, were recently reviewed in detail (Fang et al., 2012a), with the authors recommending development of GAL_1 antagonism as a novel antiobesity strategy. However, in early clinical studies, there was no strong association reported between GAL or GAL_1 genetic variants and obesity or dietary fat intake in obese children and adolescents (Schauble et al., 2005) and no evidence for a GAL_2 linkage to obesity (Sutton et al., 2006) (Table 6).

VIII. Stem Cells

In recent years, much interest has been generated in stem cells because of their ability to extensively proliferate, self-renew, and differentiate into different types of cells and tissues, offering the possibility to treat multiple diseases and disorders. Embryonic stem cells are pluripotent cells with the ability to differentiate into all types of cells of an adult individual. Notably, gene expression analysis revealed abundant expression of galanin in mouse embryonic stem cells (Anisimov et al., 2002). The presence of galanin during mouse embryonic development has been further confirmed via immunolocalization of the peptide in tissues of mesenchymal and neural crest origin (Jones et al., 2009). Human embryonic stem cell lines and embryonic carcinoma cells also express galanin at high levels (Assou et al., 2007). Moreover, galanin is considered to be a "stemness" gene in human embryonic stem cells, related to the fact that its expression level declines during differentiation (Bhattacharya et al., 2005). Murine bone marrow mesenchymal stem cells (Louridas et al., 2009), neural stem cells of the subventricular zone (Shen et al., 2005), oligodendrocyte progenitor cells (Shen et al., 2005), and human cultured pulp-derived odontoblast-like cells (Paakkonen et al., 2009) also express *GAL* mRNA and/or peptide.

Data on the expression patterns of different galanin receptors in stem cells are largely lacking in humans and are scarce for mice. Although all three galanin receptor transcripts are expressed in mouse R1 embryonic stem cells (Anisimov et al., 2002), GAL_2 and GAL_3 seem to be more strongly expressed in these cells and may mediate the decrease in cell number after incubation in high levels of galanin in the presence of leukemia inhibitory factor (Tarasov et al., 2002). Similar galanin receptor expression patterns were observed in murine bone marrow mesenchymal stem cells, with GAL_1 the least abundantly expressed (Louridas et al., 2009). Hence, it is likely that GAL_2 and GAL_3 are involved in mediating the promigratory effects of galanin on murine bone marrow mesenchymal stem cells (Louridas et al., 2009). The same scale of galanin receptor expression (GAL_2>GAL_3>GAL_1) was reported in a murine oligodendrocyte progenitor cell line (Shen et al., 2005).

However, in murine neural stem cells, GAL_1 displays a more prominent expression level (Shen et al., 2003) and might contribute to the antiproliferative effects of galanin observed on murine neural stem cells isolated from the subventricular zone (Shen et al., 2005). However, a recent study did not confirm galanin-mediated effects on proliferation of cultured murine neural stem cells derived from the subventricular zone but did demonstrate that galanin treatment had antimigratory as well as proneurogenic effects on these cells (Agasse et al., 2013). Furthermore, GAL_3 activation promotes survival of these cells in response to diabetes (Mansouri et al., 2013).

IX. Endocrine and Neuroendocrine Functions

A. Glucose Metabolism and Diabetes

Diabetes mellitus is a multifactorial disease associated with genetic and environmental factors. Notably, a study that analyzed affected sib-pair families identified the *GAL* gene as a possible candidate gene for type 1 diabetes, although the *GAL* polymorphisms investigated did not provide any evidence for association (Eckenrode et al., 2000) (Table 6).

In patients with type 1 diabetes with no autonomic neuropathy, plasma galanin levels were not different from those of healthy control subjects (Tallroth et al., 1992), whereas significantly lower plasma galanin concentrations were detected in type 1 diabetic patients with autonomic dysfunction, and these increased during exercise (Sundkvist et al., 1992). In addition, higher plasma concentrations of galanin were detected in children with type 1 diabetes compared with healthy children. Furthermore, there was a positive association between galanin levels and body mass index (Celi et al., 2005). In another study, elevated serum levels of galanin were associated with a gain in body mass index in epileptic children treated with valproate (Cansu et al., 2011). Similarly, plasma galanin levels were increased in female patients with obesity and obese women with type 2 diabetes (Baranowska et al., 1997), although a separate study reported comparable plasma galanin concentrations in obese and normal weight women (Invitti et al., 1995). Hormonal status also appears to have an impact on galanin levels in obese women (Baranowska et al., 2000; Milewicz et al., 2000a).

Results from experiments with galanin-OE mice indicate that chronically elevated galanin levels induce obesity and alter lipid metabolism (Poritsanos et al., 2009) and therefore may contribute to the development of metabolic disorders leading to type 2 diabetes. This idea is further supported by findings that plasma galanin levels are significantly increased in patients with type 2 diabetes (Legakis et al., 2005) and pregnant women with gestational diabetes mellitus (Fang et al., 2013a). Moreover, galanin was recently postulated as a biomarker for the prediction of gestational diabetes mellitus (Zhang et al., 2014).

Galanin and other members of the galanin family of peptides have actions in brain and peripheral tissues involved in the complex circuits controlling metabolism, appetite, and obesity (see Fang et al., 2012a, for review). Various studies provide evidence for a relationship between galanin and glucose levels. In humans, a positive correlation between blood galanin and glucose levels was observed in children with type 1 diabetes (Celi et al., 2005), patients with type 2 diabetes (Legakis et al., 2005), and pregnant women with gestational diabetes mellitus (Fang et al., 2013a; Nergiz et al., 2014; Zhang et al., 2014) as well as in healthy volunteers during an oral glucose tolerance test (Tatemoto et al., 1983; McDonald et al., 1985; Manabe et al., 2003). Furthermore, galanin infusions induced hyperglycemia in fasted dogs, and galanin-OE mice show impaired glucose tolerance (Poritsanos et al., 2009). Unexpectedly, galanin-KO mice also had higher glucose levels after glucose administration than WT mice (Ahren et al., 2004). Moreover, in humans, galanin infusions had no effect on plasma intravenous glucose tolerance (Gilbey et al., 1989; Holst et al., 1993; Mazziotti et al., 2008) and did not suppress the postprandial rise in glucose plasma concentrations (Bauer et al., 1989).

It is currently unclear which galanin receptor(s) mediate the glucoregulatory effects of galanin. GAL_1-KO mice had significantly higher circulating glucose levels than control when subjected to a high-fat diet (Zorrilla et al., 2007), indicating possible involvement of GAL_1. On the other hand, mice on a high-fat diet displayed significantly increased expression of all three galanin receptor transcripts in epididymal and subcutaneous fat tissues, but levels were significantly downregulated in skeletal muscle (Kim and Park, 2010).

In humans with type 1 or type 2 diabetes, plasma galanin levels were also positively correlated with hemoglobin A1c, which is frequently used as a marker to guide therapy in diabetes (Celi et al., 2005; Legakis et al., 2005), whereas in gestational diabetes mellitus conflicting results have been reported (Fang et al., 2013a).

Several studies indicate that galanin might regulate insulin release in some species. For example, galanin administration lowers plasma insulin levels in various species, including rats and pigs (McDonald et al., 1985; Lindskog et al., 1990; Manabe et al., 2003). However, different results were reported in humans, and although suppressed insulin levels were detected after galanin infusion in one study (Bauer et al., 1989), other studies observed no effect of galanin administration on basal plasma insulin secretion (Gilbey et al., 1989; Ahren, 1990). Plasma galanin levels were found to be negatively correlated with plasma insulin levels in obese postmenopausal women, whereas a positive correlation between galanin and insulin plasma levels was observed in controls (Milewicz et al., 2000b).

Galanin directly inhibited glucose-stimulated insulin secretion from isolated pancreatic tissues from several species (Lindskog et al., 1990; Olkowicz et al., 2007; Ruczynski et al., 2010). In rodents, inhibition of insulin release from pancreatic islets by galanin is mediated by a G_{o2} G protein via regulation of potassium and calcium channels (Lindskog and Ahren, 1991; Tang et al., 2012). Conversely, genetically obese, hyperinsulinemic mice had a reduced pancreatic galanin content (Dunning and Ahren, 1992). Interestingly, diabetic rats also displayed a significant reduction of galanin-expressing pancreatic islet cells (Adeghate and Ponery, 2001).

Conflicting data were derived from experiments with galanin-KO mice, which display impaired glucose-stimulated insulin secretion in pancreatic islets compared with WT mice (Ahren et al., 2004). Furthermore, a possible "insulinostatic" effect of galanin in human pancreatic islets in vitro remains uncertain, because an inhibitory effect of galanin on glucose-stimulated insulin secretion, as well as no effect, has been reported (Ahren et al., 1991; Straub et al., 1998).

Data from several studies suggest galanin reduces insulin resistance by increasing glucose transporter 4 content in skeletal muscle cells and adipocytes of healthy and type 2 diabetic rats (Jiang et al., 2009; Guo et al., 2011; He et al., 2011; Fang et al., 2012b; Liang et al., 2012). Exercise decreased insulin resistance and significantly elevated plasma galanin levels in these rats (Jiang et al., 2009; Guo et al., 2011; He et al., 2011; Liang et al., 2012). However, exercise alone seems not to be sufficient to increase plasma galanin levels in rats, and the effect also requires glucose (Milot and Trudeau, 1997). Data on the influence of exercise on plasma galanin levels in humans are scarce and inconclusive, with both an increase in plasma galanin levels and no change after exercise being reported (Ceresini et al., 1997; Legakis et al., 2000).

Galanin appears to have beneficial effects in some animal models of diabetes (see Fang et al., 2014, for review), so further genetic and other studies of galanin *and* GALP are warranted to elucidate their exact role in human metabolic disorders and diabetes (Fang et al., 2013a). A recent whole-genome profile study revealed that 30 genes from the hippocampus, including galanin, and 22 genes from the prefrontal cortex, including GAL_2, were found to exhibit altered expression levels in type 2 diabetic rats compared with nondiabetic control rats, shedding further light on the complex role of insulin signaling in fine-tuning brain functions and its interactions with galanin systems (Abdul-Rahman et al., 2012).

B. Skin

The skin is the largest organ of the body and the first barrier against external environmental factors/influences. The skin is able to "communicate" with the endocrine, immune, and central nervous systems via different mediators. Among these mediators are neuropeptides, including members of the galanin peptide family, the importance of which for skin function has been highlighted previously (Bauer et al., 2010). Here we will review the most important influences of the galanin peptide family on skin biology.

1. Epidermis. As the outermost layer of the skin, the epidermis is involved in a multitude of processes such as barrier formation, maintenance and repair, immune functions, and sensory transduction. In human epidermis, galanin immunoreactivity has been localized in sensory Merkel cells (Fantini and Johansson, 1995) and follicular and interfollicular keratinocytes (Pincelli et al., 1990; Kofler et al., 2004). Additionally, galanin secretion has been detected in cultures of human primary foreskin and oral keratinocytes (Kofler et al., 2004; Henson et al., 2005). Keratinocytes play a crucial role in the innate immune responses of skin, including the production of proinflammatory cytokines and antimicrobial peptides (Metz and Maurer, 2009). It has been shown that galanin upregulates the production of the proinflammatory cytokines interleukin 1α (IL-1α) and tumor necrosis factor-α (TNF-α) in cultured keratinocytes (Dallos et al., 2006a) and that galanin expression is increased in inflamed epidermis (Ji et al., 1995).

Recently, it was demonstrated that GMAP, the peptide derived through proteolytic cleavage of the galanin precursor peptide, possesses antimicrobial activity against *Candida albicans* and other *Candida* species (Rauch et al., 2007; Holub et al., 2011). The discovery that alarin, another member of the galanin family of peptides (see section II), has antimicrobial activity against *Escherichia coli* (Wada et al., 2013) is also consistent with the idea that the galanin peptide family has important functions and therapeutic potential in the regulation of cutaneous innate immune responses.

Although galanin receptors are expressed in epithelia of other organ systems (Matkowskyj et al., 2000), data on galanin receptor expression in the epidermis are controversial. In rats, galanin binding sites have been detected in the basal layer of the epidermis (Ji et al., 1995), whereas no substantial galanin binding could be detected in human epidermis from different anatomic sites (Kofler et al., 2004). However, putative GAL_2-like immunoreactivity has been localized in the epidermis of a human breast skin specimen and in cultured primary keratinocytes derived from this specimen, where GAL_2 seems to be functional (Dallos et al., 2006b). Interestingly, human immortalized oral keratinocytes express mRNA for all three galanin receptors (Henson et al., 2005), reflecting either different galanin receptor distributions at different anatomic sites or differential galanin receptor expression due to malignant transformation. In malignant oral keratinocytes, GAL_1 likely produces antiproliferative effects, because treatment of the cells with an anti-GAL_1 antibody resulted in increased proliferation and MAPK activation (Henson et al., 2005). Antiproliferative effects of galanin have also been reported after GAL_2 re-expression in p53-mutant oral carcinoma, and galanin treatment caused morphologic changes and a marked reduction in cell number (Kanazawa et al., 2009).

2. Skin Appendages. Galanin immunoreactivity was detected in different parts of human scalp hair follicles and, in agreement with this immunohistochemical analysis, *GAL* mRNA was detected in microdissected hair follicles and isolated outer root sheath keratinocytes (Holub et al., 2012). Galanin treatment of cultured human hair follicles resulted in inhibition of hair-shaft elongation and shortening of the hair growth phase (Holub et al., 2012). The presence of GAL_2 and GAL_3 mRNA in outer root sheath keratinocytes and some hair follicle samples (Holub et al., 2012) suggests these galanin receptors mediate the hair growth-inhibitory properties of galanin. Because normal human scalp hair follicle epithelium possesses a functional antimicrobial defense system (Reithmayer et al., 2009), galanin and other members of the galanin peptide family produced by hair follicles presumably also belong to this armory.

In human skin, galanin-like immunoreactivity was first detected in nerves innervating eccrine sweat glands (Tainio et al., 1987) and later in ductal cells of eccrine sweat glands (Kofler et al., 2004). Recently, it was shown that the NCL-SG3 cell line derived from human eccrine sweat gland secretory epithelia expresses *GAL* mRNA (Bovell et al., 2013). Because this cell line produces galanin peptide immunoreactivity (B. Holub and R. Lang, unpublished data) and galanin is present in human sweat at concentrations up to 10-fold higher than in serum (Bovell et al., 2013), it is likely that members of the galanin peptide family are secreted by eccrine sweat glands and transported to the skin surface to exert their antimicrobial activity, similar to other cutaneous antimicrobial peptides (Schittek et al., 2001; Murakami et al., 2002).

Galanin also plays a key role in eccrine sweat gland physiology, because galanin-KO mice exhibit a significantly altered sweating response to thermal stimulation (Vilches et al., 2012). Furthermore, galanin and GALP can regulate transepithelial chloride ion transport and fluid secretion in NCL-SG3 cells (Bovell et al., 2013). Although a possible contribution of GAL_2 could not be excluded, the effects of galanin and GALP on anion movement were shown to be mediated via GAL_3 (Bovell et al., 2013), establishing GAL_3 as an important component of normal eccrine sweat gland physiology.

3. Dermis. In the human dermis, galanin is present in sensory nerve fibers and nerve fibers innervating anatomic structures in the dermis, including blood vessels and eccrine glands (Tainio et al., 1987; Johansson et al., 1988; Kofler et al., 2004), as well as in dermal mechanoreceptors called Meissner corpuscles (Johansson et al., 1999). Galanin is also present in nonneuronal locations in the dermis, including in smooth muscle cells of human blood vessels (Kofler et al., 2004) and immune-competent cells of the rat hindpaw (Ji et al., 1995). After the observation that carrageenan injection into rat hindpaw evoked a marked increase of galanin-expressing cells (likely macrophages) in the inflamed dermis (Ji et al., 1995), it was apparent that galanin is involved in skin inflammatory processes. Postcapillary venules in the dermis are associated with migration of inflammatory cells from vessels into the tissue and increased vascular permeability during acute inflammation, which can be induced in response to stimulation of peripheral sensory nerves in a process termed neurogenic inflammation (Holzer, 1998).

Galanin has been shown to inhibit inflammatory edema formation induced by antidromic C-fiber stimulation, substance P (Xu et al., 1991a), or histamine (Jancso et al., 2000). A significant reduction in cutaneous plasma extravasation produced by coinjection of substance P and calcitonin-gene–related peptide into mouse skin was produced by galanin, GALP, and alarin (Santic et al., 2007; Schmidhuber et al., 2007), demonstrating an apparent functional redundancy of the galanin family peptides. The antiedema effects were attributed to vasoconstrictive properties of galanin peptides (Santic et al., 2007; Schmidhuber et al., 2007), which have also been described in pigeon skin (Santha et al., 1998) and in the microvasculature of the hamster cheek pouch (Dagar et al., 2003). In accordance with the proposed vasoconstrictor activities of galanin peptides, galanin binding sites have been detected around dermal blood vessels in human skin (Kofler et al., 2004) and, as mentioned, increased galanin binding sites are present in the inflamed dermis of rat hindpaw skin (Ji et al., 1995).

There is evidence that, in murine dermal microvasculature, the vasoconstrictive effects of galanin on inflammatory edema formation are mediated by GAL_3 (Schmidhuber et al., 2009). But because GAL_2 mRNA is present in murine dorsal skin (Schmidhuber et al., 2007) and putative GAL_2 protein has been localized around blood vessels in human skin (Dallos et al., 2006b), it seems GAL_2 may also be involved in the vasoactive actions of galanin peptides.

Data from transgenic mice supported the proposed anti-inflammatory function of galanin in the skin. Galanin-OE mice displayed a significant reduction in cutaneous plasma extravasation induced by mustard oil (Holmberg et al., 2005a). In addition, galanin-KO mice exhibited a deficit in neutrophil accumulation in skin after exposure to noxious heat, carrageenan, or TNF-α (Schmidhuber et al., 2008).

Interestingly, galanin expression was reported to be downregulated in psoriasis, a chronic inflammatory skin disease (Gudjonsson et al., 2009), and reduced galanin levels were observed in inflamed ears in a mouse model of allergic contact dermatitis (El-Nour et al., 2004). Together, findings to date suggest the galanin peptide family and its receptors (known and unknown) should be considered as potential targets for the development of better treatment of inflammatory skin diseases.

Recently, a possible role of galanin in the angiogenic process during granulation tissue formation was revealed in an experimental rat model, whereby galanin injections after subcutaneous implantation of cotton threads increased granulation and hemoglobin content. The proangiogenic effects of galanin are thought to be mediated by GAL_1/GAL_2 in this model (Yamamoto et al., 2011a), although a possible role of GAL_3 has not been investigated.

Overall, the presence of galanin family peptides throughout whole skin and recent discoveries of their diverse actions via specific receptors have opened a new area of research in skin biology and could lead to therapeutic applications in cutaneous pathophysiology.

C. Heart and Central Cardiovascular Control

There is substantial evidence that galanin participates in the central control of cardiovascular function (see Diaz-Cabiale et al., 2010, for review). Central administration of galanin affects heart rate and blood pressure in rats via complex mechanisms (Harfstrand et al., 1987; Narvaez et al., 1994; Diaz-Cabiale et al., 2005; Abbott and Pilowsky, 2009). In humans, galanin infusion ranging from 33 to 132 pmol/kg per minute dose dependently induced an increase in heart rate (Carey et al., 1993; degli Uberti et al., 1995), although in an early study galanin infused at a lower doses (7.8 and 32 pmol/kg per minute) did not affect heart rate (Bauer et al., 1986b).

The *nucleus tractus solitarius* (NTS) in the brain stem is a complex neuroanatomical site for the integration of peripherally initiated sensory neural information regarding the status of blood pressure, heart rate, and respiratory function (see Lawrence and Jarrott, 1996, for review). Galanin is expressed by neurons in the NTS of young and adult rats (Burazin et al., 2000), and experimental hypertension in rats decreases *GAL* mRNA levels in the NTS (Coelho et al., 2004).

In situ hybridization data suggest GAL_1 mRNA, but not GAL_2 mRNA, is abundantly expressed in the NTS (Burazin et al., 2000), suggesting the galanin-induced inhibition of voltage-dependent calcium channels in rat NTS neurons is GAL_1-mediated (Endoh et al., 2008). Recently, it was postulated that GAL_1 interacts with GAL_2 to form heterotrimers with the Y_2 receptor or angiotensin II type I receptor in the NTS to integrate cardiovascular responses (Fuxe et al., 2012). Furthermore, it was proposed that galanin receptors form heteromers with other neuromodulatory receptors involved in central cardiovascular regulation such as 5-HT_{1A} receptor, α_2-adrenoceptor or Y_1 receptor (Diaz-Cabiale et al., 2010).

Exogenous galanin has been shown to modulate the cardiac sympathovagal crosstalk that leads to bradycardia in mice (Potter and Smith-White, 2005), guinea pigs (Herring et al., 2012), and cats (Ulman et al., 1992), but this effect has not been observed in rats (Smith-White et al., 1999) or dogs (Moriarty et al., 1992). Although both GAL_1 and GAL_3 are present in cardiac ganglia, it was suggested that GAL_1-activation reduces acetylcholine release from atrial cholinergic neurons in guinea pigs (Herring et al., 2012). Experiments with GAL_1-KO mice support the view that GAL_1 acts to reduce acetylcholine release from cardiac parasympathetic neurons after peripheral sympathetic stimulation (Smith-White et al., 2003; Potter and Smith-White, 2005). Furthermore, analysis of human heart tissue revealed prominent GAL_1 and GAL_3 expression (Sullivan et al., 1997; Kolakowski et al., 1998).

Galanin immunoreactivity has been localized in all major regions of the heart in rats and other mammalian species (Xu et al., 1995b) and *GAL* mRNA has been detected in mouse cardiovascular cells (Chalmers et al., 2008). After myocardial infarction and after ischemia-reperfusion in rodents, galanin content was elevated in the left ventricle (Habecker et al., 2005; Ewert et al., 2008; Alston et al., 2011), indicating a role for galanin in the response of the heart to injury. In other organs, including the brain, ischemia increases GAL_1 expression (Shen and Gundlach, 2010; Holm et al., 2012), suggesting that an increase of GAL_1 expression might also occur in the heart after myocardial infarction.

Galanin has been shown to regulate the contractility of guinea-pig cardiomyocytes and their sensitivity to hypoxic conditions (Kocic, 1998). Furthermore, it was recently suggested that galanin promotes glucose uptake into cardiac muscle of diabetic rats by increasing glucose transporter 4 expression in cardiomyocytes (Fang et al., 2013b). In addition to a role in the central and peripheral regulation of cardiovascular function, galanin is also involved in heart development (Schweickert et al., 2008; Jones et al., 2009). Interestingly, galanin expression decreases during cardiomyocyte differentiation (Beqqali et al., 2006). Additional studies are necessary to elucidate the relative contribution of central and peripheral galanin and the receptor(s) involved in the complex regulation of cardiovascular processes.

D. Cancer

Neuropeptide expression has been detected in a variety of tumors, and the expression levels were shown to correlate with differentiation level or tumor aggressiveness (Rauch and Kofler, 2010). In vivo identification of neuropeptide receptors in various diseases plays an important role in the development of suitable neuropeptide analogs as imaging agents and for the evaluation of the main indications for which these agents should be used. Apart from the use of neuropeptide receptors for tumor imaging, neuropeptides can have pro- or antiproliferative activity on cancer cells, thereby having direct therapeutic implications.

1. Expression of Galanin Peptides in Tumor Tissues and Cell Lines. Human pheochromocytoma was the first tumor in which galanin was identified (Bauer et al., 1986c; Hacker et al., 1988), and later galanin-like immunoreactivity was detected in other neuroendocrine tumors, including human pituitary adenoma (Bauer et al., 1986c; Hacker et al., 1988). Subsequently, galanin-like immunoreactivity was detected in human pituitary adenoma particularly associated with adrenocorticotrophic hormone-secreting cells (Hulting et al., 1989; Vrontakis et al., 1990; Bennet et al., 1991; Hsu et al., 1991; Sano et al., 1991; Leung et al., 2002; Grenback et al., 2004) and in gangliocytoma (Sano et al., 1991; Felix et al., 1994), paraganglioma (Fried et al., 1994; Tadros et al., 2003), and neuroblastoma (Tuechler et al., 1998). Alarin was subsequently detected in differentiated neuroblastoma cells (Santic et al., 2006) and was recently detected in a variety of human CNS tumors and suggested to be a diagnostic marker for ependymoma to differentiate them from other gliomas (Eberhard et al., 2013).

Galanin expression in neuroblastoma may depend on the differentiation state of the tumor, because a human undifferentiated tumor transplanted into nude mice did not express galanin, whereas all transplants derived from tumors with different types of differentiation expressed galanin (Hoshi et al., 2008). Indeed, a correlation between the amount of galanin in neuroblastoma and their differentiation status was reported (Perel et al., 2002), although a similar study could not confirm this correlation (Berger et al., 2002)

Galanin was also detected in a variety of non-neuroendocrine human tumors of different origin, including glioblastoma and other brain tumors (Berger et al., 2003), melanoma (Gilaberte et al., 2007), head and neck squamous cell carcinoma (HNSCC) (Sugimoto et al., 2009), basal cell carcinoma (Kepron et al., 2009), colon cancer (Kim et al., 2007; Godlewski and Pidsudko, 2012; Stevenson et al., 2012), and embryonic carcinoma (Skotheim et al., 2005). Interestingly, the majority of these tumors exhibited significantly higher galanin levels than corresponding noncancerous tissue (Skotheim et al., 2005; Gilaberte et al., 2007; Kim et al., 2007; Sugimoto et al., 2009; Stevenson et al., 2012), similar to observations of human pheochromocytoma (Bauer et al., 1986c). In colon cancers, *GAL* mRNA levels were observed to increase significantly with tumor size and stage (Kim et al., 2007), and a recent study found a significant correlation between high galanin expression and poorer disease-free survival in colon cancer patients, identifying galanin as a potential biomarker for certain cancer types (Stevenson et al., 2012).

In HNSCC, current data are conflicting, with significant upregulation of galanin reported in tumor samples from HNSCC patients (Sugimoto et al., 2009), whereas a more recent study proposed galanin as a tumor suppressor and correlated galanin promoter methylation with significantly lower disease-free survival in HNSCC patients (Misawa et al., 2013). In basal cell carcinoma, a type of tumor arising from keratinocytes, two different studies reported reduced galanin expression (Kepron et al., 2009).

Galanin expression was reported in several human tumor cell lines, including SH-SY5Y neuroblastoma (Berger et al., 2004), several breast cancers (Ormandy et al., 1998; Yamamoto et al., 2011b), HNSCC (Henson et al., 2005; Sugimoto et al., 2009), colon carcinoma (Kim et al., 2007), embryonic carcinoma (Skotheim et al., 2005), and SBC-3A small lung carcinoma (Yamamoto et al., 2011b). In xenografts generated from the latter cells and implanted in mice, galanin was processed from the longer precursor peptide progalanin by plasmin (Yamamoto et al., 2011b) and it induced the release of the proprotein forms of matrix metalloproteinase-2 and -9 (Yamamoto et al., 2011c). Overall, the expression of galanin in different tumor tissues suggests that further studies of the potential of galanin as a target for therapeutic interventions in cancer are warranted.

2. Therapeutic Implications of Galanin Receptors in Cancer Biology. Initially, galanin receptors were identified in a hamster pancreatic cell tumor and a rat insulinoma cell line (Amiranoff et al., 1987; Lagny-Pourmir et al., 1989). In humans, galanin receptors were first discovered in pituitary tumors (Hulting et al., 1993) and were subsequently identified in pheochromocytoma (Berger et al., 2005), neuroblastoma (Tuechler et al., 1998), glioma (Berger et al., 2003), prostate carcinoma (Berger et al., 2005), colon carcinoma (Stevenson et al., 2012), HNSCC (Misawa et al., 2008), and SCLC cell lines (Wittau et al., 2000).

In 1994, GAL_1 was cloned from the human Bowes melanoma cell line (Habert-Ortoli et al., 1994) and is the most prominently expressed galanin receptor in human meningioma, glioblastoma (Berger et al., 2003) and neuroblastoma (Berger et al., 2002), and elevated GAL_1 expression is associated with increased malignancy (Perel et al., 2002). Increased GAL_1 expression was also observed in human pituitary adenomas relative to levels in normal human pituitaries (Tofighi et al., 2012), suggesting cancer-promoting properties for GAL_1, at least in these tumors. Recently, GAL_1 was proposed to contribute to resistance to chemotherapeutic drugs in colon cancer, because GAL_1 silencing led to enhanced chemosensitivity of human colon cancer cell lines (Stevenson et al., 2012). This is somewhat contrary to the finding that advanced colorectal carcinomas often display chromosomal alterations with a loss of the GAL_1 locus on 18q (Knosel et al., 2002). Chromosomal imbalances also occur in HNSCC cell lines, similarly affecting the GAL_1 locus (Takebayashi et al., 2000). Additionally, epigenetic inactivation of GAL_1 via promoter methylation was found to occur frequently in HNSCC and to correlate with reduced disease-free survival. Therefore, GAL_1 was suggested to be a tumor suppressor gene in HNSCC (Misawa et al., 2008, 2013). GAL_1 methylation was also reported as one of the most common molecular alterations in endometrial cancer (Doufekas et al., 2013). Furthermore, activation of GAL_1 induces cell-cycle arrest and suppresses proliferation of HNSCC cell lines (Henson et al., 2005; Kanazawa et al., 2007; Misawa et al., 2008). Antiproliferative effects via GAL_1 signaling have also been observed in human SH-SY5Y neuroblastoma cells transfected with GAL_1 (Berger et al., 2004).

In contrast, the presence of GAL_2 is less common in human glioma (Berger et al., 2003) and neuroblastoma (Tuechler et al., 1998). GAL_2 expression is low in the majority of human pituitary adenomas compared with levels in normal human pituitaries (Tofighi et al., 2012). However, elevated GAL_2 expression was observed in human pheochromocytoma tissue (Tofighi et al., 2008). Although analysis of tumor tissues of HNSCC patients revealed no differences in GAL_2 mRNA levels compared with normal tissue (Sugimoto et al., 2009), elevated GAL_2 expression was reported in several HNSCC cell lines along with increased cell proliferation and survival and growth of xenografts in mice (Banerjee et al., 2011). These results are discrepant with earlier reports of silencing of detectable GAL_2 expression (Kanazawa et al., 2007) due to methylation in a *p53* mutant HNSCC cell line and inhibition of cell proliferation and induction of apoptosis in these cells by GAL_2 re-expression (Kanazawa et al., 2009). Interestingly, the same group reported detectable GAL_2 expression levels in this cell line in an earlier publication (Kanazawa et al., 2007). Recently, GAL_2 promoter methylation was associated with a statistically significant decrease in disease-free survival and higher odds ratio for recurrence in HNSCC patients (Misawa et al., 2014).

GAL_2 promoter methylation leading to suppressed levels of GAL_2 mRNA was also observed in breast, prostate, and colorectal cancer as well as in a panel of prostate cancer, breast cancer, leukemia, and colon cancer cell lines (Chung et al., 2008). In the colon cancer cells, GAL_2 methylation was found to reduce chemosensitivity to certain therapeutic regimens, whereas GAL_2 overexpression was correlated with enhanced sensitivity to these chemical regimens (Kim et al., 2011).

It is noteworthy that transfection of GAL_2 into human SH-SY5Y neuroblastoma cells, which do not endogenously express galanin receptors, and into human HNSCC cells, which naturally express one or more galanin receptors (Kanazawa et al., 2007), and into rat pheochromocytoma cells (Cheng and Yuan, 2007) led to suppressed cell proliferation and induction of caspase-dependent apoptosis (Berger et al., 2004; Tofighi et al., 2008; Kanazawa et al., 2009, 2014). On the other hand, in SCLC, where GAL_2 is the only endogenous galanin receptor (Wittau et al., 2000), activation of GAL_2 resulted in growth-promoting effects, possibly via pathways involving the protein tyrosine kinase 2β and proto-oncogene protein tyrosine kinase Src (Sethi and Rozengurt, 1991; Roelle et al., 2008).

The impact of GAL_3 signaling on the biologic activity of cancer cells is less well studied. GAL_3 mRNA is expressed in human HNSCC cell lines (Henson et al., 2005; Kanazawa et al., 2007), human Bowes melanoma cells (Lang et al., 2001), and rat PC12 pheochromocytoma and rat B104 neuroblastoma cell lines (Cheng and Yuan, 2007). GAL_3 expression was also detected in clinical tumor samples, including neuroblastoma (Berger et al., 2002; Perel et al., 2002) and glioma (Berger et al., 2003). Analysis of human HNSCC revealed significantly increased GAL_3 expression in the tumors compared with normal tissue (Sugimoto et al., 2009). Similarly, GAL_3 expression was detected in human pituitary adenomas associated with tumor relapse, whereas it was absent in postmortem pituitaries (Tofighi et al., 2012). These data suggest a role for GAL_3 in cancer biology and support the idea that, like GAL_2, this galanin receptor deserves further experimental investigation, not only as a potential diagnostic tool but as a drug target to modify the activity of certain tumor types, particularly as a specific GAL_3 antagonist (SNAP-37889) is available.

Efficacious therapeutic application of galanin agonists or antagonists will likely depend on the respective expression levels of the different galanin receptors and on the downstream signaling pathways in different tumor types. This is reflected in an animal model, in which exogenous application of galanin in a triple therapy with serotonin and the somatostatin analog octreotide was effective in the treatment of human colon cancer xenografts (El-Salhy and Dennerqvist, 2004; El-Salhy, 2005) either via direct antiproliferative effects (El-Salhy and Starefeldt, 2003) and/or reduction of the tumor blood supply (El-Salhy and Dennerqvist, 2004; El-Salhy, 2005). Notably, a significant reduction in the vascularization of transplanted rat colon carcinoma was achieved only when galanin was added to the therapy regimen (El-Salhy et al., 2003). In contrast, this same therapeutic regimen was without any discernible effects in human pancreas cancer xenografts in terms of apoptotic index, necrosis, and number of tumor blood vessels, but significantly increased the proliferation index (El-Salhy et al., 2005). An increased number of viable cells and higher proliferation index was also observed with the aforementioned human pancreatic cancer cells in vitro when galanin was added to the treatment regimen containing octreotide and/or serotonin (Tjomsland and El-Salhy, 2005).

X. Emerging Role of the Galanin Peptide Family in Inflammation

The regulation of inflammatory processes by galanin family peptides was reviewed recently (Lang and Kofler, 2011), and therefore only key aspects will be highlighted here.

A. Innate Immunity

Innate immunity is the first line of defense against microbes. The skin, the respiratory tract, the gastrointestinal tract, and the genitourinary tract are the main interfaces between the environment and the body and are a common portal of entry for a variety of microbes. Specialized epithelia in these sites not only provide a physical barrier to microbes and produce an array of antimicrobial substances but also perform many physiologic functions.

The presence of galanin has been demonstrated in epithelial cells of human skin (Kofler et al., 2004) and human colon (I. Rauch and B. Kofler, unpublished data), and treatment of human primary cultured keratinocytes with lipopolysaccharide (LPS) or live *C. albicans* led to an increase in *GAL* mRNA levels (Rauch et al., 2007), which was also observed in the human colonic T84 epithelial cell line (I. Rauch and B. Kofler, unpublished data). Treatment of adult cultured mouse microglia with LPS resulted in a significant increase of the responsiveness of the microglia to galanin (Pannell et al., 2014). Two other members of the galanin family of peptides, GMAP and alarin, have been identified as components of the innate immune system with different spectra and mechanisms of antimicrobial activity. GMAP inhibits the growth of the major human fungal pathogen *C. albicans* and other *Candida* species (Rauch et al., 2007; Holub et al., 2011) and interferes with hyphal development, whereas alarin is only effective against the Gram-negative bacteria *E. coli*, inducing bacterial membrane blebbing (Wada et al., 2013; see section IX.B).

Interestingly, infection of human colonic T84 cells with pathogenic *E. coli* upregulated GAL_1 expression, possibly via nuclear factor-κB activation, which led to increased chloride ion secretion in response to galanin in these cells in vitro (Hecht et al., 1999). Increased GAL_1 mRNA levels have also been observed in mouse bladder in the early phase of acute cystitis induced by LPS (Zvarova and Vizzard, 2006). The importance of GAL_1 activation as part of an innate intestinal epithelial defense mechanism has been confirmed in the mouse colon after infection with *E. coli* (Hecht et al., 1999) or other bacterial pathogens such as *Shigella* and Salmonella (Matkowskyj et al., 2000), as well as with Rhesus rotavirus (Hempson et al., 2010a).

GAL_3 might also be important in the regulation of innate immune responses, because it is highly expressed in murine neutrophil, monocyte, and macrophage immune cell subsets (Chiu et al., 2013). Data on galanin levels in peripheral tissues in the early phases after bacterial infection are scarce. In the rabbit intestine, galanin levels were not altered 8 and 16 hours after experimental *Shigella* infection (Svensson et al., 2004).

Galanin also interacts with the major proinflammatory cytokines of the innate immune system. Incubation of cultured primary bovine chromaffin cells with TNF-α or IL-1 led to increased *GAL* mRNA levels in a time- and dose-dependent manner (Ait-Ali et al., 2004). This could represent a negative regulatory feedback mechanism abrogating the inflammatory response, because galanin inhibited TNF-α production in the BV2 murine microglia cell line stimulated with LPS by a posttranscriptional mechanism (Su et al., 2003) and decreased *TNF-α* and *IL-1β* mRNA levels in an injured mouse calvaria (McDonald et al., 2007). Furthermore, galanin suppressed TNF-α release of murine macrophages in vitro in response to *Staphylococcus aureus* stimulation (Chiu et al., 2013). On the other hand, galanin induced upregulation of *IL-1α*, *TNF-α*, and *IL-8* mRNA expression in cultured human keratinocytes (Dallos et al., 2006a), suggesting a proinflammatory role of galanin. Similarly, intracerebroventricular injection of GALP into Sprague-Dawley rats stimulated production of IL-1α and IL-1β in macrophages and/or microglia in some brain areas (Man and Lawrence, 2008). The BV2 mouse microglia cell line and cultured rat microglial cells solely express GAL_2 (Su et al., 2003; Ifuku et al., 2011), which mediates galanin-induced cell migration and upregulation of class II major histocompatibility complex expression in these innate immune brain cells (Ifuku et al., 2011). Microglial cells also participate in the events leading to multiple sclerosis (Weissert, 2013), and a recent study detected a marked upregulation of galanin expression in microglia associated with multiple sclerosis lesions in postmortem brain tissue from chronic multiple sclerosis patients (Wraith et al., 2009).

B. Acute Pancreatitis

Acute pancreatitis (AP) is a disease with a complex pathophysiology (Yadav and Lowenfels, 2013), which undoubtedly involves inflammation (Gukovsky et al., 2013), and in recent years, evidence has accumulated that galanin participates in the pathogenesis of experimental AP. Galanin-KO mice display reduced myeloperoxidase (MPO) activity and a lower acinar cell necrosis score than their WT littermates in a mouse model of cerulein-induced AP (Bhandari et al., 2010b). After galanin administration, MPO activity and the acinar cell necrosis score returned to normal levels in the galanin-KO mice, (Bhandari et al., 2010b). However, the reduction in neutrophil accumulation, reflected by reduced MPO activity, in galanin-KO mice is not exclusively restricted to AP and seems to be a more general phenomenon of inflammation, because it has also been observed with inflammatory skin responses (Schmidhuber et al., 2008).

In a mouse model of cerulein-induced AP, galanin receptor antagonists significantly reduced MPO activity and the acinar cell necrosis score and also reduced AP-induced plasma amylase and lipase activities (Bhandari et al., 2010a,b). The ameliorating effect of the galanin antagonist galantide on MPO activity was inhibited by coadministration of the somatostatin analog octreotide, although octreotide alone also significantly reduced AP-induced MPO activity (Barreto et al., 2010). Although all three galanin receptors are expressed in mouse pancreas, a recent study suggests a major role for GAL_3 in mediating the effects of galanin in AP, because the GAL_3-specific antagonist SNAP-37889 reduced pancreatic MPO activity, damage to pancreatic acinar cells, and hyperamylasemia in cerulein-induced AP in mice (Barreto et al., 2011).

Similar to the skin microvasculature, where galanin has vasoconstrictor activity (Schmidhuber et al., 2007), galanin is also thought to reduce blood flow through the pancreas, which is a contributing factor in pancreatic necrosis in AP (Brooke-Smith et al., 2008). It has been proposed that GAL_3 is responsible for the effects of galanin on the dermal microvasculature (Schmidhuber et al., 2009), and it seems likely this also occurs in the pancreatic microvasculature. Therefore, galanin and its receptors are potential therapeutic targets for the treatment of AP and other inflammatory disorders if the pleiotropic actions of galanin at different levels in inflammation can be accounted for and harnessed successfully.

XI. Final Considerations

Following the 30th anniversary of the discovery of galanin, this review, along with other recent articles cited, will, we hope, provide a useful summary of both early research and recent progress in the field, and in doing so, provide a valuable reference for scientists and students interested in galanin biology. The galanin peptide family plays key roles in the regulation of numerous physiologic and pathophysiologic functions via actions in the CNS and PNS and in various peripheral organs. Galanin is by far the most extensively investigated family member. Although much attention has been focused on its modulatory role in the nervous system, in particular in relation to a number of diseases, it is now clear that the galanin peptide family also participates in a number of nonneuronal actions, including inflammation, oncology, and skin physiology. New and intriguing data emerge on a regular basis, for example, a notable recent report identified additional peptides that may represent endogenous ligands for galanin receptors. The novel neuropeptides known as spexins (SPX), which are currently of unknown function, were shown to interact with galanin receptors (Kim et al., 2014). These studies identified that the *SPX* gene and a second SPX gene (*SPX2*), present in vertebrate genomes, reside in the near vicinity of the galanin and kisspeptin family genes on their chromosomes. Alignment of peptide sequences reveals some sequence similarity among the three peptide groups, with SPX more closely related to galanin, and ligand-receptor interaction studies revealed that SPXs activate human $GAL_{2/3}$ but not GAL_1, suggesting they may be natural ligands for $GAL_{2/3}$. Furthermore, SPXs exhibited higher potency at GAL_3 than galanin (Kim et al., 2014), suggesting a possible role in endogenous regulation of GAL_3 signaling that should prompt further experimentation, particularly in relation to reproduction (e.g., Porteous et al., 2011; Kalló et al., 2012).

The application of cutting-edge mouse molecular genetics is allowing the generation of transgenic strains with galanin receptors tagged with a fluorescent protein or with neurons expressing a receptor gene specifically within the cell body (cytoplasm) and proximal and/or distal processes of the neurons (Table 1). This will allow better "phenotyping" of galanin receptor-expressing cells in brain circuits and in other target tissues. Similarly, powerful Cre/Lox technology (Brault et al., 2007; Wang, 2009), including mice in which galanin- or galanin receptor-expressing neurons express both Cre-recombinase and "floxed" genes, could be used along with viral-based methods for conditional gene deletion, and state-of-the-art methods, such as optogenetics and designer receptors exclusively activated by designer drugs, could be used for tracing and activating specific galanin-responsive neural circuits (e.g., Alexander et al., 2009; Zhang et al., 2010; Yizhar et al., 2011). In fact, such an approach taking advantage of a *GAL*-Cre mouse line was published recently, revealing the importance of galanin-containing neurons in the anterior hypothalamus in the control of parental behavior (Wu et al., 2014). It is anticipated that further such insights will be obtained in the future using similar techniques.

In addition, future research on galanin pathophysiology will be best advanced by the application of novel experimental tools and approaches. For example, the development of antibodies and small-molecule drugs that are CNS penetrant (Robertson et al., 2010; Zhang et al., 2012) and specific for the different galanin receptors will help provide more detailed information on the distribution and function of each receptor. Finally, with many preclinical studies indicating that the galanin system is of particular importance in a range of pathologies, the hope is that both current and new information will be translated through to clinical studies, resulting in novel pharmacological therapeutic strategies for a number of diseases.

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Author Contributions

Wrote or contributed to the writing of the manuscript: Lang, Gundlach, Holmes, Hobson, Wynick, Hökfelt, Kofler.

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