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Review

The Basolateral Amygdala γ-Aminobutyric Acidergic System in Health and Disease

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The brain comprises an excitatory/inhibitory neuronal network that maintains a finely tuned balance of activity critical for normal functioning. Excitatory activity in the basolateral amygdala (BLA), a brain region that plays a central role in emotion and motivational processing, is tightly regulated by a relatively small population of γ-aminobutyric acid (GABA) inhibitory neurons. Disruption in GABAergic inhibition in the BLA can occur when there is a loss of local GABAergic interneurons, an alteration in $GABA_A$ receptor activation, or a dysregulation of mechanisms that modulate BLA GABAergic inhibition. Disruptions in GABAergic control of the BLA emerge during development, in aging populations, or after trauma, ultimately resulting in hyperexcitability. BLA hyperexcitability manifests behaviorally as an increase in anxiety, emotional dysregulation, or development of seizure activity. This Review discusses the anatomy, development, and physiology of the GABAergic system in the BLA and circuits that modulate GABAergic inhibition, including the dopaminergic, serotonergic, noradrenergic, and cholinergic systems. We highlight how alterations in various neurotransmitter receptors, including the acid-sensing ion channel 1a, cannabinoid receptor 1, and glutamate receptor subtypes, expressed on BLA interneurons, modulate GABAergic transmission and how defects of these systems affect inhibitory tonus within the BLA. Finally, we discuss alterations in the BLA GABAergic system in neurodevelopmental (autism/fragile X syndrome) and neurodegenerative (Alzheimer's disease) diseases and after the development of epilepsy, anxiety, and traumatic brain injury. A more complete understanding of the intrinsic excitatory/inhibitory circuit balance of the amygdala and how imbalances in inhibitory control contribute to excessive BLA excitability will guide the development of novel therapeutic approaches in neuropsychiatric diseases.

Key words: basolateral amygdala; GABA; autism; Alzheimer's disease; anxiety; epilepsy

The brain comprises a highly complex network of excitatory and inhibitory circuits that maintains exquisite balance in network activity. Hyperexcitability arises when there is an imbalance between excitation and inhibition

SIGNIFICANCE:

Deficits in the brain inhibitory systems can occur at any stage of life. The resulting hyperexcitability leads to the development of neurological and/or neuropsychiatric diseases. We assess how the loss of inhibitory synaptic transmission and mechanisms that modulate inhibition in the basolateral amygdala lead to increased anxiety. In addition, we examine how different diseases including autism/fragile X syndrome, Alzheimer's disease, traumatic brain injury, and epilepsy result in amygdalar hyperexcitability. By evaluating how deficiencies in inhibition within the amygdala contribute to these diseases, future research may be directed toward developing new therapies for reducing excitability that may alleviate the behavioral symptomology of neurologic diseases.

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(E/I), often as a result of deficiencies or disruption in γ-aminobutyric acid (GABA) inhibitory system control. Hyperexcitability of the amygdala, in particular, can be strongly associated with anxiety, hypervigilance, and an inability to regulate emotions. Acquired deficiencies in the GABAergic inhibitory system have been observed after traumatic brain injury (TBI; Reger et al., 2012; Almeida-Suhett et al., 2014; Depue et al., 2014; Guerriero et al., 2015) and status epilepticus (SE; Gean et al., 1989; Fritsch et al., 2009; Prager et al., 2014b). In addition, amygdala hyperexcitability resulting in anxiety has been observed in neuropsychiatric disorders, such as posttraumatic stress disorder (PTSD; Nuss, 2015; Truitt et al., 2009), as well as in neurodevelopmental disorders, including autism/fragile X syndrome (Olmos-Serrano et al., 2010; El-Ansary and Al-Ayadhi, 2014; Martin et al., 2014), and in neurodegenerative disorders, such as Alzheimer's disease (AD; Klein et al., 2014; Palop and Mucke, 2010).

Hyperexcitability of the basolateral nucleus of the amygdala (BLA) is associated with increased anxiety and often occurs in parallel with various neurodevelopmental, neurodegenerative, and neuropsychiatric disorders. The GABAergic inhibitory system is one target of therapeutic treatments to reduce anxiety and maintain homeostasis. For example, benzodiazepines, which allosterically enhance postsynaptic actions of GABA at the inhibitory type A GABA receptor ($GABA_A$ receptor), are one first-line treatment for anxiety (Farb and Ratner, 2014) and seizure disorders. However, in many cases, benzodiazepines are ineffective and/or exacerbate symptoms, as has been observed in seizure models when, for example, administration of diazepam initially suppresses seizures but leads to rebound seizures that are similar to or longer in duration than those of animals that do not receive the anticonvulsant (Apland et al., 2014). Thus, the efficacy of current treatments targeting the GABAergic system has been called into question, and new therapeutic targets merit preclinical investigation.

This Review discusses the BLA GABAergic system in health and disease, focusing on five diseases, autism/fragile X, AD, epilepsy, TBI, and anxiety and trauma- or stressor-related disorders (such as PTSD) because these disorders are prime examples of acquired amygdala dysfunctions that occur during development, during aging, or after injury. First, we review the anatomy and development of the GABAergic system in the BLA and the different ways in which GABAergic inhibitory synaptic transmission is modulated. Second, we review how local GABAergic inhibitory neurotransmission in the BLA is altered in disease. Through the study of how deficiencies in the GABAergic inhibitory system in the amygdala contribute to disease outcomes, future research may be directed at developing new therapies to reduce excitability or to increase inhibition.

THE GABAERGIC SYSTEM IN THE BLA

GABAergic Interneurons

The amygdala is located in the medial temporal lobe and is made up of 13 subnuclei (for a comprehensive review of the anatomical connections of the rat and human amygdala see Pitkanen, 2000; Sah et al., 2003; Whalen and Phelps, 2009). The BLA makes up a large component of this network, receiving input from cortical and subcortical structures. The BLA, which generally comprises the lateral and basal portions, contains two main types of neurons, glutamatergic (pyramidal) principal neurons and GABAergic interneurons (McDonald, 1992; Pare and Smith, 1998). Principal neurons constitute the majority of the neurons in the BLA (80–85%), whereas GABAergic interneurons form ~15–20% of the neuronal population (Sah et al., 2003; Spampanato et al., 2011). GABAergic interneurons can be subdivided into those that express calbindin (CB) or calretinin (CR) and can be further subdivided into groups by neuropeptide expression (i.e., vasoactive intestinal peptide [VIP] and/or cholecystokinin [CCK]) or by the expression of the calcium-binding protein parvalbumin (PV; Kemppainen and Pitkanen, 2000; McDonald and Mascagni, 2001a, 2002; Mascagni and McDonald, 2003; Davila et al., 2008; Table I). PV-immunopositive neurons make up about 40% of GABAergic interneurons and are the main source of the perisomatic innervation of principal cells, suggesting that their primary role is in feedback inhibition. CR interneurons make up about 25–30% of BLA GABAergic interneurons and innervate primarily other interneurons (McDonald and Mascagni, 2001a; Muller et al., 2003, 2006; Capogna, 2014).

$GABA_A$ Receptor Structure and Function

GABAergic inhibitory synaptic transmission plays a central role in the regulation of amygdala excitability. Pathological disruption of $GABA_A$ receptors causes a disruption of the E/I balance and has been increasingly implicated in neurological and neurodegenerative diseases (Deidda et al., 2014). Fast inhibitory synaptic transmission within the central nervous system is mediated by the $GABA_A$ receptor, a heteropentameric chloride-permeable, GABA-gated member of the cys-loop superfamily of ligand-gated ion channels. $GABA_A$ receptors are formed from limited combinations of subunits that have diverse structural and functional properties (α1–6, ß1–3, γ1–3, δ, ε, θ, and π; Olsen and Sieghart, 2009).

Proper maturation of the GABAergic system in the BLA is essential in neurodevelopment. Dysfunction in the development of the GABAergic inhibitory system within the BLA may be associated with neurodevelopmental diseases, such as autism or fragile X. In rat, the development of the mature GABAergic system in the BLA takes place between postnatal day (P) 14 and P30 with the emergence of PV interneurons (Berdel and Morys, 2000; Davila et al., 2008), an increase in the density of GABAergic fibers, and a decrease in the density of GABAergic cell bodies (Brummelte et al., 2007). Concurrently, $GABA_A$ receptor-mediated inhibitory postsynaptic currents (IPSCs) reach maturity between P21 and P28. Simultaneously, the reversal potential of $GABA_A$ receptors expressed in principal neurons shifts from –55 mV at P7 to –70 mV by P21. This increase in hyperpolarization

TABLE I. Summary of Systems Modulating BLA GABAergic Inhibition*

Immunohistochemistry				
General	Specific	Firing patterns	Innervation of GABAergic interneurons	Receptor subtypes and roles in modulating GABAergic transmission
CB	PV	Fast spiking, stuttering, nonadapting, adapting	~50% Cortical, < 1% thalamic to CB interneurons, VTA, SN, DRN, SI, VP of basal forebrain (cholinergic and GABAergic)	D1, ↑ firing, induces rhythmic oscillations; D2, ↓ presynaptic GABA release; 5-HT_{2A}, ↑ excitability; $GABA_B$, ↓ excitability
	CCK (VIP^-)	Nonadapting, burst adapting		5-HT_{3A}, ↑ excitability but rapidly desensitizing; α1 AR and α2 AR, ↑ AP firing and IPSCs; CB1, ↓ excitability; $GABA_B$, ↓ excitability
	SOM/NPY/NK_{1r}		DRN	5-HT_{1A} (NPY, NK_{1r}), ↓ presynaptic GABA release; 5-HT_{2C} (NPY), ↑ excitability; α1 AR and α2 AR, ↑ AP firing and IPSCs; $GABA_B$, ↓ excitability
CR	CCK (VIP^+)	Adapting	VTA and SN (<PV interneurons)	5-HT_{3A}, ↑ excitability but rapidly desensitizing; α1 AR and α2 AR, ↑ AP firing and IPSCs; $GABA_B$, ↓ excitability
Not localized to specific GABAergic interneuronal subpopulations			LC, NTS	M1 mAChR, ↑ excitability; M2 mAChR, ↓ excitability; α_7 and $\alpha_4ß_2$ nAChR, ↑ excitability; ASIC1A, ↑ excitability; AMPA lacking GluR2 and NMDA, ↑ excitability; GluK1, ↑ presynaptic GABA release (dose dependent)

*Note that no study has differentiated receptor localization to VIP^+ orVIP^-. Therefore, we have placed the receptor modulating VIP^+ or VIP^- in each category. For citations see text.

may be due, in part, to a switch from a greater expression of sodium-potassium-chloride cotransporter 1, which accumulates intracellular chloride and renders $GABA_A$ receptors excitatory, or to an increase in the potassium-chloride cotransporter 2, which extrudes chloride from the cell, rendering $GABA_A$ receptors inhibitory (Ben-Ari et al., 2012; Ehrlich et al., 2013). In addition, a decrease in rise-time and decay-time constant occurs because of a change in the $GABA_A$ receptor subunit composition (from primarily the α2 subunit to the α1 subunit; Ehrlich et al., 2013). This shift results in a GABAergic shunt that limits the extent of BLA activation (see below; Rainnie et al., 1991b).

The composition of $GABA_A$ receptors has been found to be quite diverse because their subunit assembly makes their roles significantly different, depending on the timing of activation and subcellular localization (Pouille and Scanziani, 2001; Marowsky et al., 2004). The BLA of mature animals contains α1 and α2 subunits of the $GABA_A$ receptor; α1 subunit-containing $GABA_A$ receptors are expressed primarily at the somal level of PV GABAergic interneurons but also exhibit coimmunoreactivity with the ß2/3 subunits (McDonald and Mascagni, 2004). Alternatively, $GABA_A$ receptors on principal neurons contain primarily the α2 subunit, which is predominantly responsible for the benzodiazepine allosteric potentiation of inhibitory currents (Marowsky et al., 2004). In addition, principal neurons in the BLA contain γ2 subunits, which likely contribute to the formation of α2ßxγ2 pentameric $GABA_A$ receptors, which contribute to fast inhibitory synaptic transmission (Esmaeili et al., 2009). Extrasynaptically, the $GABA_A$ receptor in the BLA is made up primarily of the α3 subunit, which strongly mediates tonic GABAergic currents (Marowsky et al., 2012). However, the α5 subunit, which is diazepam sensitive and shapes the decay phase of the inhibitory postsynaptic currents (Marowsky et al., 2004), and the δ subunit, both of which are hallmark subunits that contribute to tonic inhibition (Farrant and Nusser, 2005), are also expressed in the BLA, though not as strongly as the α3 subunit (Marowsky et al., 2012).

Temporal Dynamics and Intra-Amygdala Regulation of Excitatory Activity

GABAergic interneurons can be differentiated by their firing properties. PV interneurons fire primarily short duration, nonadapting action potentials (Rainnie et al., 2006; Woodruff and Sah, 2007b), whereas CB-

expressing GABAergic interneurons fire broad action potentials, display firing adaptation, and synapse primarily with somata (Jasnow et al., 2009; see Table I). Other interneurons expressing somatostatin (SOM), VIP, CR, and CCK also target dendrites or somata (Mascagni and McDonald, 2003; Muller et al., 2007a). Although GABAergic interneurons constitute only a fraction of the total neuronal population, they tightly regulate network excitability and lead to a low resting firing rate of principal neurons (Pare and Gaudreau, 1996; Lang and Pare, 1997; Woodruff and Sah, 2007a).

The regulation of excitatory activity by local GABAergic interneurons is influenced by the firing properties (Rainnie et al., 1991b; Lang and Pare, 1997). Most BLA GABAergic interneurons fire short-duration action potentials with small spike frequency adaptation in response to prolonged depolarization, although specific subpopulations of GABAergic interneurons have different firing patterns (see Table I). Principal neurons, by comparison, show spike frequency adaptation and prolonged afterhyperpolarization in response to prolonged depolarizing currents (Rainnie et al., 1991a,b; Pare et al., 1995; Sah et al., 2003). The axonal morphology of BLA GABAergic interneurons also allows for tight inhibitory control over principal neurons. GABAergic interneuron axons branch, on average, two to six times, forming relatively dense terminal and collateral fields with principal neurons (Millhouse and DeOlmos, 1983; Smith et al., 1998). BLA GABAergic projections participate in either feedback inhibition or transient disinhibition of principal neurons. Indeed, PV interneurons receiving strong excitatory local inputs from BLA projection neurons appear to be involved in feedback inhibition (Smith et al., 2000; Unal et al., 2014), whereas intercalated interneurons, which have recently been found to project to the BLA (Manko et al., 2011), appear to target PV- and CB-immunoreactive GABAergic interneurons and are likely to disinhibit principal cells transiently (Bienvenu et al., 2015).

The regulation of the firing rate by GABAergic interneurons controls the flow of information from the BLA, and evidence indicates that local inhibitory circuits in the amygdala mediate its functioning. Activation of the GABAergic system appears to play a central role in the synchronization of spiking activity. This synchronization can coordinate and enhance the effects of input signals, which precisely allows the activation of glutamatergic activity to drive behavioral responses (Courtin et al., 2014; Herry and Johansen, 2014). For example, the initiation and expression of fear requires synchronization of amygdala activity, among other regions (Stujenske et al., 2014). Ongoing research has revealed that the θ and the faster γ oscillations may be fundamental to circuits underlying sensory processing and cognitive functions and that changes in emotional states may be mediated by alterations in BLA γ coupling to θ frequency inputs (Fries, 2009; Stujenske et al., 2014). The activity of PV interneurons has been implicated in θ synchrony within the medial prefrontal cortex (PFC; Courtin et al., 2014) because suppression of PV interneuronal activity in the PFC is necessary to disinhibit prefrontal projection neurons to the BLA, thereby synchronizing their firing by resetting local θ oscillations. Although this work has not yet been confirmed in the amygdala it has been hypothesized that inhibiting PV interneurons in the BLA might also synchronize activity and enhance fear responses (Stujenske et al., 2014).

MODULATION OF $GABA_A$ RECEPTOR-MEDIATED INHIBITORY SYNAPTIC TRANSMISSION IN THE BLA

GABAergic inhibition in the BLA is modulated by afferents from both cortical and subcortical brain regions (Fig. 1A). In most cases, afferents from these regions project to both principal neurons and GABAergic interneurons. In some cases, it has been determined that projections are directed to particular subpopulations of neurons. This section reviews the afferent projections that modulate and facilitate GABAergic inhibitory synaptic transmission in the BLA. More specifically, we discuss how activation of different receptor types modulates the release of GABA from the presynaptic terminal or alters the excitation of GABAergic interneurons (Fig. 1B).

Cortical and Thalamic Regulation of BLA GABAergic Interneurons

The BLA receives extensive cortical and thalamic projections, which synapse onto both principal neurons and GABAergic interneurons. Stimulating afferents from either the cortical or the thalamic pathways have been found to monosynaptically activate BLA and lateral amygdala (LA) GABAergic interneurons, primarily in a feedforward manner (Rainnie et al., 1991b; Washburn and Moises, 1992; Lang and Pare, 1998; Szinyei et al., 2000). Recent studies have identified to which type of interneuron cortical and thalamic inputs project. Unal and colleagues (2014) found that BLA interneurons expressing CB receive about half of the cortical inputs to local-circuit cells of the BLA and constitute a major source of feedforward inhibition, whereas thalamic inputs form less than 1% of synapses on interneurons (Carlsen and Heimer, 1988; LeDoux et al., 1991). There appears to be a possible discrepancy in the regulation of GABAergic interneurons in the LA vs. the BLA. Cortical inputs to the BLA regulate primarily CB-expressing interneurons, whereas GABAergic interneurons in the LA respond equally to both cortical and thalamic pathways (Szinyei et al., 2000; Unal et al., 2014).

Dopaminergic Afferents

The BLA receives dense dopaminergic innervation from the ventral tegmental area (VTA) and the substantia nigra (SN; Fallon and Ciofi, 1992; Asan, 1997). VTA and SN projections synapse on BLA principal (projection) neurons and PV- and CR-immunopositive GABAergic interneurons (Brinley-Reed and McDonald, 1999; Pinard et al., 2008). However, compared with CR-immunopositive interneurons, PV interneurons appear to be the preferential

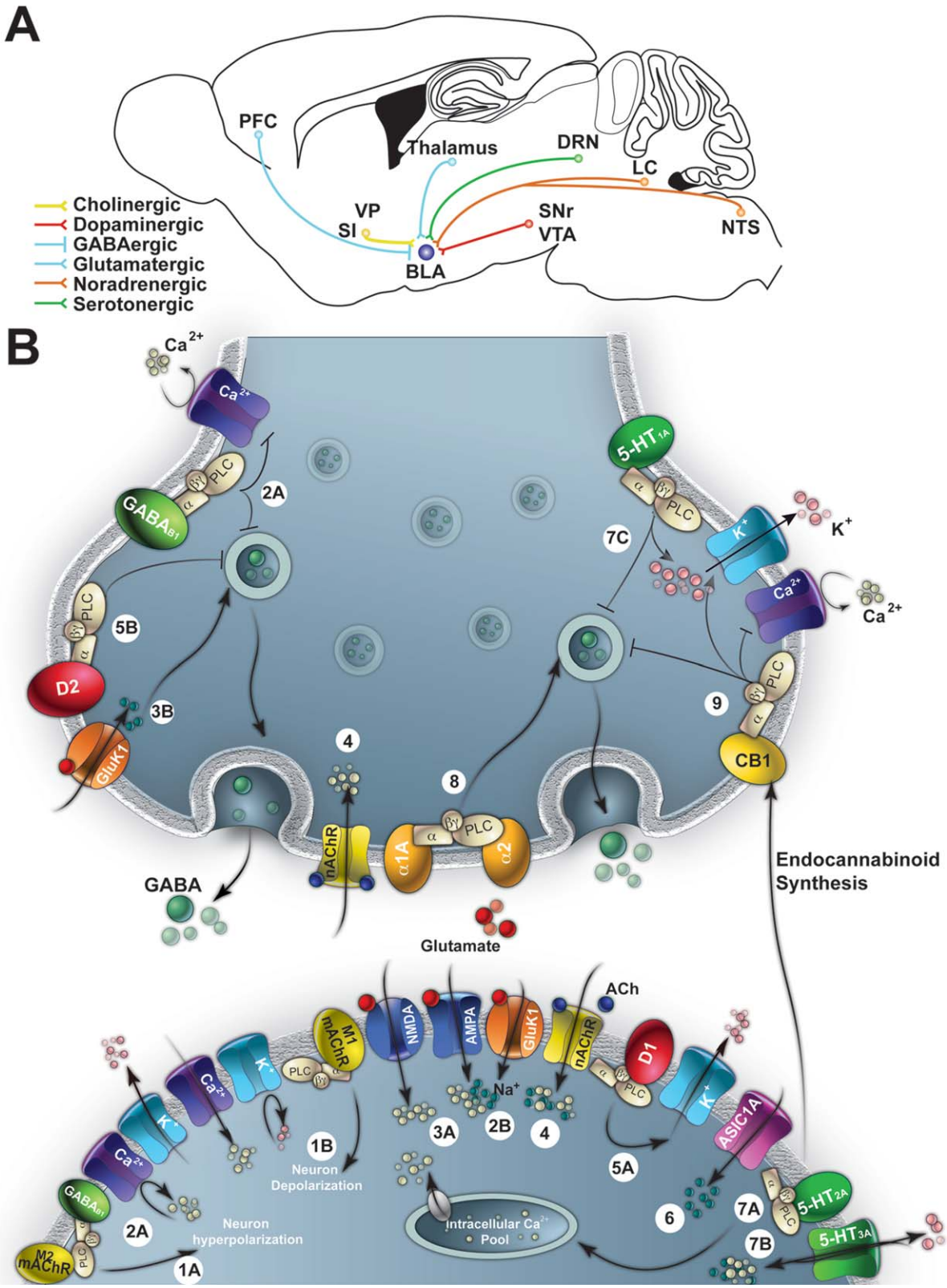
A
PFC
Thalamus
DRN
LC
VP
SI
SNr
VTA
NTS
BLA
Cholinergic
Dopaminergic
GABAergic
Glutamatergic
Noradrenergic
Serotonergic
B
Ca2+
5-HT1A
GABAB1
PLC
2A
7C
K+
5B
D2
3B
GluK1
4
8
9
CB1
nAChR
α1A
α2
GABA
Glutamate
Endocannabinoid
Synthesis
ACh
M1
mAChR
NMDA
AMPA
GluK1
nAChR
D1
Na+
3A
2B
1B
Neuron
Depolarization
5A
ASIC1A
6
7A
5-HT2A
7B
5-HT3A
Intracellular Ca2+
Pool
Neuron
hyperpolarization
M2
mAChR
1A

Fig. 1.

target of dopaminergic synapses in the BLA (Pinard et al., 2008). By projecting to principal neurons and GABAergic interneurons, dopamine (DA) influences the activity of both excitatory and inhibitory cell types within the BLA (Rosenkranz and Grace, 1999; Kroner et al., 2005). Via activation of D1 receptors, DA increases excitability and evoked firing of principal neurons by reducing slowly inactivating K^+ currents, whereas activation of D2 receptors increases input resistance. Moreover, D1 receptor activation increases evoked firing in fast-spiking BLA interneurons and the frequency of spontaneous IPSCs (sIPSCs; Kroner et al., 2005). Activation of DA receptors has also been found to induce rhythmic inhibitory oscillations (Loretan et al., 2004; Ohshiro et al., 2011), although increases in excitatory transmission are required to precede GABAergic interneuronal burst firing (Ohshiro et al., 2011). Although DA fibers synapse onto both GABAergic interneurons and principal neurons, there appears to be a net increase in excitatory activity within the BLA in response to DA application. This increase in excitatory activity may be the result of 1) reduced activation of GABAergic interneurons, which occurs when activation of D2 receptors on GABAergic interneurons causes a reduction in the probability of presynaptic quantal release (Seamans et al., 2001); 2) amygdala disinhibition and the subsequent increase in excitatory activity, which may occur when DA suppresses GABA release from PV interneurons onto principal neurons but not interneurons (Chu et al., 2012); or 3) DA increasing the excitatory drive onto disinhibitory interneurons, which would subsequently increase excitatory activity (Kemppainen and Pitkanen, 2000; Bissiere et al., 2003).

Serotonergic Afferents

Serotonergic projections originating from the dorsal raphé nucleus (DRN) innervate primarily BLA principal neurons, PV interneurons, and interneurons containing neuropeptide Y (NPY), a subgroup of CB and SOM interneurons (Ma et al., 1991; Muller et al., 2007b). Postsynaptically, serotonin (5-HT) neurotransmission leads to the activation of 5-HT receptors, which are grouped into seven families (5-$HT_{1–7}$). 5-HT_{1A} receptors, which are $G_{i/o}$ protein coupled, have been localized to principal neurons (Stein et al., 2000) and the presynaptic terminal of GABAergic interneurons within the BLA (Kishimoto et al., 2000). 5-HT_{1A} receptor activation inhibits the discharge rate of principal neurons by inducing hyperpolarization and reduces GABA release from presynaptic terminals by activating potassium channels (Kishimoto et al., 2000; Stein et al., 2000). Alternatively, 5-HT_2 receptors, and more specifically the 5-HT_{2A} and the 5-HT_{2C} receptors, are $G_{q/11}$-coupled membrane receptors that increase intracellular Ca^{2+} levels and increase interneuronal excitability (Jiang et al., 2009; Bonn et al., 2012). The 5-HT_{3A} receptor is a ligand-gated sodium, potassium, and calcium channel that also increases interneuronal excitability but leads to a rapidly desensitizing depolarization (Rainnie, 1999; Mascagni and McDonald, 2007; Gharedaghi et al., 2014).

Although all 5-HT receptors have been documented in the amygdala, most (~65–70%) GABA-immunoreactive neurons in the BLA exhibit 5-HT_{2A} immunoreactivity; fewer 5-HT_{2A} receptors are present on principal neurons (Bombardi, 2011). 5-HT_{2A} and 5-HT_{3A} receptors have been localized to specific interneuronal types in the BLA. 5-HT_{2A} receptors are found primarily on PV interneurons within the BLA (McDonald and Mascagni, 2007; Bombardi, 2011) and tightly control glutamatergic output by perisomatic inhibition (Muller et al., 2005; Holmes, 2008), whereas 5-HT_{3A} receptors are expressed primarily on the CCK interneuronal subpopulation (Mascagni and McDonald, 2007), which constitutes only a small proportion of GABAergic interneurons in the BLA (Mascagni and McDonald, 2003). In contrast, 5-HT_{1A}, which is expressed in low to moderate concentrations in the BLA (Asan et al., 2013), coexpresses with ~50% of NPY interneurons (Bonn et al., 2013) and about one-third of neurokinin-1 receptor (NK_{1r}) interneurons (Hafizi et al., 2012), whereas ~30–40% of NPY interneurons express the excitatory 5-HT_{2C} receptor subtype (Bonn et al., 2012, 2013). 5-HT_{1A} and 5-HT_3 receptors have been localized on

Fig. 1. Modulation of GABAergic inhibitory synaptic transmission in the BLA. **A**: Schematic representation of GABAergic projections from the PFC and glutamatergic projections from the thalamus. In addition, GABAergic interneurons in the BLA receive cholinergic projections from the SI and the VP, dopaminergic projections from the VTA and the SN, noradrenergic projections from the LC and the NTS, and serotonergic projections from the DRN. **B**: Schematic representation of receptors modulating GABAergic inhibitory synaptic transmission in the BLA. Postsynaptic M2 mAChRs (1A) and $GABA_B$ receptors (2A) hyperpolarize GABAergic interneurons by reducing voltage-gated Ca^{2+} channels and increasing K^+ channel conductance. M1 mAChRs (1B) increase excitability (though primarily expressed on principal neurons) by suppressing several K^+ currents and increasing voltage-gated Ca^{2+} conductance. Activation of presynaptic $GABA_B$ receptors (2B) inhibits neurotransmitter release on both excitatory and inhibitory synapses by inhibiting voltage-gated Ca^{2+} channels and, possibly, by interacting with vesicular release machinery. Activation of postsynaptic NMDARs or AMPARs (3A) on interneurons increases excitability. Activation of $GluK_1$-containing kainate receptors (3B) depolarizes interneurons by increasing the presynaptic release of GABA or increasing excitability via activation of postsynaptic $GluK_1$ receptors. Activation of α_7 nAChRs and/or $\alpha_4\beta_2$ nAChRs (4) presynaptically modulates GABA release or regulates neuronal activity by the position on interneurons. Dopaminergic projections (5A) activate postsynaptic D1 receptors, which increases excitability by reducing slowly inactivating K^+ currents, whereas D2 receptors (5B) reduce presynaptic release of GABA. Activation of ASIC1A receptors (6) increases interneuronal excitability. Postsynaptically, activation of 5-HT_2 (7A) and 5-HT_{3A} (7B) receptors increases interneuronal excitability via an increase in intracellular Ca^{2+} concentrations or increasing the interneuronal excitability, respectively. Activation of presynaptic 5-HT_{1A} receptors (7C) reduces quantal release and increases hyperpolarization. Activation of α1 and α2 receptors (8) depolarize interneurons, subsequently increasing action potential firing and enhancing inhibitory synaptic transmission. Activation of CB1 receptors (9) on CCK interneurons reduces presynaptic release by inhibiting voltage-gated Ca^{2+} channels and activating voltage-gated K^+ channels.

GABAergic nerve terminals in the BLA (Koyama et al., 1999, 2000), where activation of these receptors inhibits or facilitates miniature IPSC (mIPSC) frequency without effects on mIPSC amplitude, respectively (Koyama et al., 2002).

Noradrenergic Afferents

The BLA receives extensive noradrenergic (NA; norepinephrine) innervation from the locus coeruleus (LC) and nucleus of the solitary tract (NTS; Pitkanen, 2000; Williams et al., 2000), which synapse onto GABAergic interneurons (Li et al., 2002). NA released from LC terminals activates three distinct classes of adrenoreceptors (AR; α1, α2, and ß AR) that have multiple subtypes and appear to be more potent modulators of GABAergic inhibitory synaptic transmission than DA (Miyajima et al., 2010). Although no study has yet anatomically identified the type of interneuron to which the receptor subunits are localized in the BLA, electrophysiological evidence indicates that α1 and α2 AR activation depolarizes SOM- and CCK-positive interneurons, resulting in action potential firing and enhanced inhibitory synaptic transmission (Braga et al., 2004b; Buffalari and Grace, 2007; Kaneko et al., 2008). In addition to direct enhancement of inhibitory activity by LC afferents, NA enhancement of inhibitory activity in the BLA occurs indirectly. Indeed, activation of ß1 and ß3 ARs in lateral paracapsular (LPCS) interneurons, which are a distinct class of GABAergic interneurons bordering the BLA and external capsule and are thought to provide cortical feedforward inhibition to the BLA (Marowsky et al., 2005), enhances LPCS GABAergic inhibition of the BLA (Silberman et al., 2010, 2012).

Cholinergic Afferents

The BLA is extensively innervated by fibers from the substantia innominata (SI; nucleus basalis magnocellularis) and ventral pallidum (VP) of the basal forebrain (Emson et al., 1979; Woolf et al., 1984; Carlsen et al., 1985; Zaborszky et al., 1986). The extensive innervation leads to some of the highest levels of choline acetyltransferase, the synthesizing enzyme for acetylcholine (ACh), and acetylcholinesterase (AChE), the hydrolyzing enzyme for ACh, in the BLA compared with other brain regions (Ben-Ari et al., 1977; Prager et al., 2013). The basal forebrain projects both cholinergic and noncholinergic neurons to the BLA. Recent evidence indicates that ~10–15% of basal forebrain neurons projecting to the BLA are PV-immunopositive GABAergic interneurons (Mascagni and McDonald, 2009), which target primarily PV interneurons in the BLA but also target principal neurons (McDonald et al., 2011). In comparison, ~75–80% of the basal forebrain projection neurons are cholinergic (Carlsen et al., 1985; Zaborszky et al., 1986; Mascagni and McDonald, 2009), project primarily to dendritic shafts and spines of BLA principal neurons, and innervate PV GABAergic interneurons to a small extent (~7% of postsynaptic targets; Muller et al., 2011).

Stimulation of afferents from basal forebrain cholinergic neurons leads to the release of ACh, which extensively regulates neuronal excitability by acting on muscarinic (mAChR) and nicotinic (nAChR) acetylcholine receptors, both of which are abundant in the BLA (Mash and Potter, 1986; Swanson et al., 1987; Hill et al., 1993; Zhu et al., 2005; Pidoplichko et al., 2013). mAChRs are G-protein-coupled receptors that have five subtypes, designated M1–5. M1, M3, and M5 receptors couple preferentially to $G_{q/11}$ proteins, which subsequently initiate signaling cascades that mobilize intracellular Ca^{2+}, whereas M2 and M4 receptors couple to $G_{i/o}$ proteins, which subsequently hyperpolarize neurons or inhibit neurotransmitter release (for review see Alger et al., 2014). Although the BLA expresses M1–M4 mAChRs (Mash and Potter, 1986; Cortes et al., 1987; McDonald and Mascagni, 2010), M1 mAChR appears to be the predominant mAChR subtype in the amygdala. M1 mAChRs are localized primarily to principal neurons and appear to increase excitability of BLA principal cells resulting from the suppression of several potassium currents, whereas M1 immunoreactivity has been observed at low levels on GABAergic interneurons (McDonald and Mascagni, 2010; Muller et al., 2013). In contrast, M2 mAChRs are expressed on interneurons within the BLA and lead predominantly to hyperpolarization of GABAergic interneurons (McDonald and Mascagni, 2011).

In the brain, nAChRs are ligand-gated ion channels permeable to cations, including Ca^{2+}, that produce membrane depolarization and postsynaptic excitation or stimulation of neurotransmitter release (Dani and Bertrand, 2007). nAChRs comprise nine different subunits (α_{2-7} and $ß_{2-4}$) that combine as either homomeric or heteromeric pentameric receptors (Dani and Bertrand, 2007; Yakel, 2013). The homomeric α_7 and the heteromeric $\alpha_4ß_2$ are the two major subtypes of nAChRs found in the mammalian brain (Gotti et al., 2009); they have previously been found to be expressed in the BLA (Hill et al., 1993; Seguela et al., 1993) and appear to regulate neuronal excitability by presynaptically modulating neurotransmitter release or directly regulating neuronal activity by their position on somatodendritic sites of interneurons or principal neurons (Klein and Yakel, 2006; Pidoplichko et al., 2013). In addition, $\alpha_3ß_4$ nAChRs are also present on GABAergic interneurons and enhance GABAergic inhibitory synaptic transmission (Zhu et al., 2005).

The functional activity and subsequent modulation of either inhibition or excitation by mAChRs and nAChRs in the BLA appear to diverge from anatomical evidence. Indeed, although α_7 nAChRs are present on GABAergic interneurons and principal neurons and enhance both excitatory and inhibitory synaptic transmission, their activation powerfully modulates GABAergic inhibition, resulting in a net reduction in BLA excitability (Pidoplichko et al., 2013). Moreover, optogenetic activation of basal forebrain inputs to the BLA during periods of neuronal quiescence does not trigger excitatory responses; rather, muscarinic activation increases the inhibitory response, which may be a result of the contrasting

spatiotemporal profile of cholinergic receptor activation (Unal et al., 2015). Light-induced activation of basal forebrain inputs transiently silences cells, which is followed by a longer-duration inhibitory postsynaptic potential (IPSP; Unal et al., 2015). This suggests that the early IPSP is due to activation of nicotinic receptors and, from the results of Pidoplichko and colleagues (2013), presumptively α_7 nAChR activation, although the subunit configuration was not tested by Unal and colleagues (2015). In contrast, the late IPSP was mediated by M1 and not by M2 mAChR activation. It is important to emphasize that this inhibitory effect occurred only in quiescent principal neurons. During periods of strong activation, mAChR inhibition appeared to be overwhelmed, and M1-mediated excitation predominated (Unal et al., 2015).

Glutamate Receptors

GABAergic interneuronal excitability in the BLA is regulated, in part, by principal neurons within the BLA. Glutamatergic inputs make dual-component synapses with both fast α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and slower N-methyl-D-aspartate receptors (NMDARs), which are present on the postsynaptic membrane of interneurons and principal neurons (McDonald, 1992; Mahanty and Sah, 1998; Smith et al., 1998; Weisskopf and LeDoux, 1999; Sah et al., 2003). Glutamatergic inputs to interneurons express AMPARs that have rapid kinetics and strong inward rectification, indicating calcium permeability and a lack of the GluA2 subunit (Mahanty and Sah, 1998; Polepalli et al., 2010). Interneurons also express a heterogeneous population of NMDARs. These cells can be separated into groups that lack NR2B NMDAR subunits (Mahanty and Sah, 1998; Polepalli et al., 2010), express NMDARs that contain mostly NR2B subunits, and have fast decay kinetics (Williams, 1993; Polepalli et al., 2010) or express NMDARs that have slow kinetics and contain mostly GluN1/GluN2B heterodimers (Szinyei et al., 2003; Polepalli et al., 2010; Spampanato et al., 2011).

The heterogeneity of the subunits of AMPARs and NMDARs within specific populations of interneurons is essential for the regulation of feedforward inhibition to principal cells. Polepalli and colleagues (2010) demonstrated, for example, that long-term potentiation to interneurons is restricted to interneurons that contain GluR2-lacking AMPAR at the postsynaptic membrane. Only these neurons provided feedforward inhibition to principal cells, and, although this has not been specifically tested, it is likely that the CB-immunopositive interneurons are the subpopulation of interneurons that provides the feedforward inhibition to principal cells (Unal et al., 2014).

In addition to AMPARs and NMDARs, kainate receptors represent a distinct class of ionotropic glutamate receptors that are preferentially activated by kainic acid. Kainate receptors consist of five different subunits, $GluK_{1–3}$ and $KA_{1–2}$ (Chittajallu et al., 1999). $GluK_{1–3}$ subunits form functional homomeric and heteromeric channels, whereas the KA subunits generate only functional receptors with distinct physiological properties when combined with the $GluK_{1–3}$ subunits (Herb et al., 1992; Schiffer et al., 1997). Although kainate receptors are not widely distributed in the brain, the BLA has a markedly high expression of $GluK_1R$ subunit (Braga et al., 2003). Kainate receptors, and in particular the $GluK_1$ subunit-containing kainate receptor, have been found to enhance excitatory synaptic transmission in the BLA (Li and Rogawski, 1998) by modulating pre- and postsynaptic release of glutamate (Jiang et al., 2001; Braga et al., 2004a). Moreover, presynaptic $GluK_1$-containing kainate receptors have also been found to modulate GABA release in the BLA in a bidirectional manner. At low concentrations, activation of high-affinity $GluK_1$-containing kainate receptors depolarizes both principal neurons and GABAergic interneurons, which leads to a substantial increase in GABA release. However, high concentrations of agonists activate low-affinity presynaptic $GluK_1$-containing kainate receptors, which again depolarize both GABAergic interneurons and principal neurons but suppress evoked GABA release, leading to an enhancement in BLA network excitability (Braga et al., 2003; Aroniadou-Anderjaska et al., 2007, 2012).

$GABA_B$ Receptors

The late or slow component of inhibitory synaptic transmission is mediated by activation of $GABA_B$ receptors, which comprise the $GABA_{B1}$ and $GABA_{B2}$ subunits (Craig and McBain, 2014). Both $GABA_{B1}$ and $GABA_{B2}$ mRNA are expressed in the BLA (Bischoff et al., 1999; Durkin et al., 1999; Clark et al., 2000). Postsynaptically, the $G_{i/o}$-protein-coupled $GABA_B$ receptors (primarily the $GABA_{B1B}$ isoform) mediate hyperpolarization of postsynaptic membranes by inhibiting voltage-gated Ca^{2+} activation and activating inwardly rectifying potassium channels (Rainnie et al., 1991b; Sugita et al., 1993; Couve et al., 2000). Presynaptic $GABA_B$ receptors, primarily the $GABA_{B1A}$ isoform, on the other hand, have been found to inhibit neurotransmitter release on both excitatory and inhibitory synapses by inhibiting voltage-gated Ca^{2+} channels and, possibly, by interacting with vesicular release machinery (Yamada et al., 1999; Szinyei et al., 2000; Gassmann and Bettler, 2012).

Anatomically, $GABA_{B1}$ receptors are found in many amygdala nuclei. However, in the BLA, $GABA_B$ receptor immunoreactivity is found primarily on GABAergic interneurons; very few principal neuronal somata in the BLA exhibit immunoreactivity for $GABA_{B1}$ receptors (McDonald et al., 2004). However, the light staining found in the neuropil likely is due to the staining of dendritic shafts and spines belonging to pyramidal cells (McDonald et al., 2004). Among the subpopulations of GABAergic interneurons, $GABA_{B1}$ receptor immunoreactivity is found primarily on large CCK^+ neurons but is also found to a lesser extent on small CCK^+ interneurons. In addition, $GABA_{B1}$ receptor immunoreactivity is found on the remaining subpopulations of GABAergic interneurons in the BLA (e.g., SOM, PV, and VIP neurons;

TABLE II. Summary of Alterations in the BLA GABAergic System in Disease*

	Anxiety/trauma	Autism/fragile X	Alzheimer's disease	Epilepsy	TBI
Behavioral symptoms	Anxiety, hypervigilance, stress, fear	Impaired social interaction, language/communication deficits, repetitive/restricted interest, aggression, anxiety, epilepsy	Memory impairment, impaired fear conditioning, anxiety, epilepsy	Seizures, status epilepticus	Cognitive and emotional deficits, posttraumatic epilepsy (PTE), anxiety, increased fear conditioning, PTSD
GABA interneurons	↓ SOM/NK_{1r}	↓ Synaptic number but no interneuronal loss	↓ Total number of interneurons	↓ Total number of interneurons; ↓ density of SOM interneurons	↓ Total number of interneurons
GAD/GABA	↓ Tonic/phasic IPSC; ↓ GABA release	↓ GABA metabolism; ↓ GAD65/67; ↓ tonic/phasic IPSC	No change in IPSC of 1- or 7-month-old apoE4 mice (in LA); ↑ IPSC in 18–20-month-old apoE4 mice (in LA) but < ↑ in EPSC	↓ sIPSC frequency and amplitude; ↓ mIPSC amplitude	↓ sIPSC frequency and amplitude; ↓ mIPSC frequency and amplitude
$GABA_A$ receptors	↑ α2 in highly anxious rats	Delayed maturation of α1 and α2; ↓ α5, δ		↑ α1	↓ α1, ß2, γ2

*For citations see text.

McDonald et al., 2004). More recently, $GABA_{B1}$ immunoreactivity has been examined at the synapse in the LA. Evidence indicates that $GABA_{B1}$ receptors are localized to the extrasynaptic terminal of both interneurons and principal neurons. Although most receptors are found in the sensory afferent terminals of principal neurons (Pan et al., 2009), where they act to reduce glutamate release, $GABA_B$ receptors are also present on inhibitory inputs to principal neurons, where they act as autoreceptors (Szinyei et al., 2000).

Alterations in the modulation of inhibitory and excitatory synaptic transmission during development might be due, in part, to the activation of $GABA_B$ receptors, which are functionally expressed early in development (Bosch and Ehrlich, 2015). Indeed, the $GABA_B$ receptor, which mediates paired-pulse depression (PPD) of sensory evoked IPSCs (Szinyei et al., 2000), is differentially regulated during development; intra-BLA inhibitory synapses show pronounced PPD in the first 2 weeks of development, but this is reduced by the third week (Ehrlich et al., 2013). In other words, the contribution of PPD by $GABA_B$ receptors may be due primarily to activation of $GABA_B$ receptors in infancy, whereas PPD in older animals is only partially controlled by $GABA_B$ receptors. Moreover, Bosch and Ehrlich (2015) found that presynaptic $GABA_B$ receptors, which are present on sensory inputs to LA principal neurons, are activated as early as P8. Finally, tonic presynaptic control of IPSCs and excitatory postsynaptic currents (EPSCs) in the LA appears to be mediated by $GABA_B$ receptors and is likely permitted by ambient GABA that also emerge in adolescence (Bosch and Ehrlich, 2015).

Acid-Sensing Ion Channels

Acid-sensing ion channels (ASICs), in particular the ASIC1a splice variant, are highly expressed in the BLA (Waldmann et al., 1997; Biagini et al., 2001). ASICs are heterotrimeric or homotrimeric proton-gated channels activated by extracellular acidosis, intracellular pH, and other factors (Wemmie et al., 2013). Until recently, the precise role of ASIC1a activation in the BLA remained unknown. ASIC1a was thought to promote hyperexcitability because it was found to reduce fear and to have antidepressant and anxiolytic effects (Coryell et al., 2007, 2009; Dwyer et al., 2009; Ziemann et al., 2009). Indeed, electrophysiological evidence indicates that ASIC1a channels are present on principal neurons within the BLA and are activated by ammonium or by lowering extracellular pH, which increases glutamatergic activity (Pidoplichko et al., 2014). However, ASIC1a is also found on GABAergic interneurons within the BLA, and its activation increases GABAergic activity. The increase in $GABA_A$ receptor-mediated inhibitory synaptic transmission seems to predominate, suppressing overall excitability (Pidoplichko et al., 2014), which may be a result of the intrinsic organization of the BLA. Much of the excitatory input within the BLA is directed onto interneurons,

which subsequently project back onto principal cells (Lang and Pare, 1997; Smith et al., 1998).

Cannabinoid Receptors

Cannabinoids exert their effects by the activation of two known cannabinoid receptor subtypes, the cannabinoid type 1 (CB1) receptor and the cannabinoid type 2 receptor (CB2). The CB1 receptor, which is expressed primarily presynaptically and is activated by retrograde transmission of endogenous cannabinoids, is coupled to $G_{i/o}$ proteins. Activation of CB1 receptors decreases excitability of the presynaptic terminal by closing calcium (n and P/Q type) channels, increasing G-protein-coupled inwardly rectifying potassium channels, and decreasing cyclic adenosine monophosphate-dependent sodium conductance (Pertwee, 1997; Schlicker and Kathmann, 2001). The CB2 receptor is also coupled to $G_{i/o}$ proteins, but its expression is restricted primarily to immunological tissues peripherally, and is implicated in immunological functions (Schatz et al., 1997).

CB1 receptors are widely distributed in the brain but are present in relatively high concentrations in the BLA and, in particular, are present on the presynaptic terminal of CCK interneurons (Katona et al., 2001; McDonald and Mascagni, 2001b), which densely innervate principal neurons (McDonald and Pearson, 1989). Activation of the presynaptic CB1 receptors on CCK GABAergic interneurons reduces the amplitude of sIPSCs but does not affect mIPSCs (Katona et al., 2001) because CB1 receptors reduce GABA release via blockade of presynaptic N-type Ca^{2+} channels (Wilson et al., 2001). Activation of CB1 receptors has also been found to reduce excitatory synaptic transmission in the LA and decrease basal synaptic transmission, indicating that, in the LA, CB1 modulation of neuronal activity is determined by CB1 receptors expressed on principal neurons (Azad et al., 2003). In addition to regulating GABA release, CB1 receptor activation appears to be essential for the expression of postsynaptic $GABA_A$ receptors. Expression of $\alpha 1$ and $\alpha 2$ subunits of the $GABA_A$ receptor is reduced in the amygdala of $CB1^{-/-}$ mice. This reduction in subunit expression may be the result of a developmental neuroadaptation that compensates for the overstimulation of postsynaptic receptors resulting from the lack of inhibitory presynaptic activity exerted by CB1 receptors (Diana and Bregestovski, 2005; Uriguen et al., 2011).

GABAERGIC CIRCUIT DYSFUNCTION WITHIN THE BLA

A functional BLA GABAergic system is essential throughout one's life. Deficiencies in GABAergic inhibitory synaptic transmission are associated with neurodevelopmental diseases, such as autism or fragile X syndrome, and also appear in neurodegenerative diseases, such as Alzheimer's disease. In addition, deficiencies in the GABAergic system can appear as a result of brain trauma, such as after TBI, or may be acquired after SE. In this section, we first provide an overview with respect to how a reduction in GABAergic inhibitory synaptic transmission within the BLA is associated with the development of anxiety. We then provide an example of a neurodevelopmental and neurodegenerative disorder that results in deficiencies in the GABAergic system within the BLA (see Table II). In addition, we provide two examples of acquired GABAergic deficiencies. It must be noted that genetic variations may be an underlying factor in deficiencies of GABAergic inhibitory synaptic transmission. Unless genetic variations are directly involved in changing GABAergic function within the amygdala, we do not address these variations.

Anxiety and PTSD

Anxiety and stress-related disorders, such as PTSD, develop when individuals are exposed to situations eliciting extreme stress or fear (Heim and Nemeroff, 2001; van der Kolk, 2003). These disorders are commonly associated with amygdala hyperactivity (Terburg et al., 2012; Nuss, 2015) and are often treated by administering benzodiazepines, which mediate their actions via $GABA_A$ receptors (Smith, 2001). However, in many cases, the treatment of anxiety disorders with benzodiazepine-like compounds may be ineffective, potentially because of deficits in GABA release, GABAergic interneuronal loss in the BLA, or alterations in $GABA_A$ receptor functionality (Farb and Ratner, 2014).

The loss of GABAergic interneurons or reductions in glutamate decarboxylase (GAD), an enzyme that catalyzes the decarboxylation of glutamate into GABA, may lead to deficits in the presynaptic release of GABA and contribute to increased anxiety and associated BLA hyperexcitability. Indeed, excess reductions in GAD, such as occur when knocking out one of the GAD isoforms (GAD65), lead to reduced phasic and tonic inhibition and subsequently result in BLA hyperexcitability, increased anxiety, and pathological fear memory reminiscent of PTSD (Walls et al., 2010; Lange et al., 2014; Muller et al., 2015).

Selectively targeting GABAergic interneurons in the BLA has recently been investigated for the development of anxiety-like behavior as well as fear learning. Lesions to GABAergic interneurons that contain NK_{1r}, which colocalize with interneurons containing NPY, SOM, and CB, have been found to increase anxiety-like behaviors in rats (Truitt et al., 2007, 2009). It is notable that NK_{1r}-containing interneurons account for only ~3% of the total population of GABAergic interneurons in the BLA. The loss of NK_{1r}-containing interneurons does not result in a significant reduction in the total number of interneurons (Truitt et al., 2009). However, selective ablation of these interneurons and in particular the SOM GABAergic interneurons, which include approximately half of the NK_{1r}-immunoreactive interneurons, likely disinhibits the synchronizing activity of projection neurons and may impair feedforward inhibition (Truitt et al., 2009). By comparison, increasing the number of GABAergic interneurons in the BLA will reduce anxiety, and animals that had increased inhibitory neurons were

less sensitive to unlearned fear, although they could still acquire conditioned fear responses (Cunningham et al., 2009). Although anxiety appears to be regulated in part by NK_{1r}-containing interneurons, PV and SOM GABAergic interneurons bidirectionally regulate the acquisition of a fear memory through two distinct mechanisms. During an auditory cue, PV interneurons are excited through direct sensory input from the auditory thalamus and cortex and indirectly disinhibit principal neurons via inhibition of SOM neurons. However, during an aversive footshock, both PV and SOM interneurons are inhibited, most likely via the activation of other interneuron subtypes that contact both PV and SOM interneurons, suggesting that the interneurons exhibit distinct temporal dynamics that correlate with specific behavioral differences (Wolff et al., 2014).

Impaired GABA release, disinhibition of GABAergic interneurons, or deficiences in the activation of postsynaptic GABAA receptors may result in anxiety-like behavior and increased fear responses. Pharmacological alterations of $GABA_A$ receptor activity by microinjection of $GABA_A$ receptor agonists or antagonists induce anxiolytic or anxiogenic-like effects, respectively (Da Cunha et al., 1992; Sanders and Shekhar, 1995; Zangrossi et al., 1999; Barbalho et al., 2009). Moreover, highly anxious rats exhibit an increase in the expression of the $\alpha 2$ subunit of the $GABA_A$ receptor in the BLA (Lehner et al., 2010; Skorzewska et al., 2014). However, it remains unknown whether alterations in the expression of other $GABA_A$ subunits also contribute to increased anxiety. In all, these results indicate that deficiencies in GABAergic inhibitory synaptic transmission within the BLA contribute to BLA hyperexcitability and the subsequent development of anxiety- and trauma-related disorders.

Autism Spectrum Disorders and Fragile X Syndrome

Autism spectrum disorders (ASDs), which include fragile X syndrome, are a group of neurodevelopmental syndromes that are often associated with aggression, anxiety, and epilepsy (Parikh et al., 2008; Tuchman and Cuccaro, 2011). Emerging evidence indicates a glutamatergic/GABAergic imbalance in multiple brain regions, including the amygdala, with greater levels of glutamatergic and reduced GABAergic activity, which results in the manifestation of symptoms associated with ASD (Coghlan et al., 2012; El-Ansary and Al-Ayadhi, 2014). The amygdala has recently been implicated in ASD, including fragile X (Suvrathan and Chattarji, 2011), because increased activation of the left amygdala has been reported in functional magnetic resonance imaging studies of fragile X patients (Watson et al., 2008).

Environmental models of autism or fragile X knockout (KO) mice revealed deficiencies in the GABAergic system within the BLA. The reduced GABAergic inhibition appears to be a result of deficits in synaptic transmission and GABA metabolism and not the result of a loss of GABAergic interneurons (Kim et al., 2014). Indeed, in a fragile X mental retardation 1 (*FMR1*) gene KO model of fragile X syndrome, the total number of neurons, including GABA-immunopositive interneurons in the BLA, was unaffected. Similarly, human studies of autistic children have shown little morphological alterations in the BLA compared with developmentally typical children (for review see Blatt, 2012). However, there appears to be a significant decrease in the total number of BLA inhibitory synaptic connections, indicating aberrant circuit development (Olmos-Serrano et al., 2010). Moreover, in the BLA of *FMR1* KO mice, reductions in GAD1 mRNA and protein expression for GAD65/67 were observed and were associated with reduced presynaptic GABA release (Olmos-Serrano et al., 2010).

Although the overall number of amygdala GABAergic interneurons remains stable, mechanisms that modulate the activation of GABAergic interneurons may be impaired in ASD and fragile X models. For example, *FMR1* KO mice have reduced activation of SOM-expressing low-threshold spiking interneurons in layers II and III of the somatosensory cortex, causing reduced spike synchronization of BLA principal neurons (Paluszkiewicz et al., 2011b); reductions in spike synchronization from the cortex could subsequently impair neuronal activity in the BLA required in the expression of fear (Courtin et al., 2014) and also lead to hyperresponsivity within the amygdala (Rauch et al., 2006). In addition, in a rat model of ASD, reductions in dendritic morphology, including spine density, or distal connectivity between the PFC and the BLA may lead to impaired cortical BLA regulation (Bringas et al., 2013).

Deficits in GABAergic inhibitory synaptic transmission in ASD and fragile X appear to be also a result of genetic variations in genes coding for particular subunits of the $GABA_A$ receptor, as has been documented throughout multiple brain regions in ASD (Fatemi et al., 2010; Coghlan et al., 2012) and in fragile X (Deidda et al., 2014). In the amygdala of ASD and fragile X models, delays in the maturation of postsynaptic $GABA_A$ receptors (Vislay et al., 2013) may lead to reductions in phasic and tonic GABAergic inhibitory synaptic transmission (D'Hulst et al., 2006; Olmos-Serrano et al., 2010). In the fragile X model, the timing of the developmental expression of the $\alpha 1$ and the $\alpha 2$ $GABA_A$ receptor subunits was delayed, which in turn may have impaired the switch in GABA polarity (He et al., 2014) and proper neuronal connections in wiring of local neuron networks in the BLA (Cossart, 2011; Paluszkiewicz et al., 2011a).

In addition to the deficits in phasic (synaptic) inhibition, tonic inhibition, which is mediated by extrasynaptic $GABA_A$ receptors containing either the $\alpha 5$ or the δ subunit, is also compromised in the BLA of *FMR1* KO mice (Martin et al., 2014) and in related ASDs (Zhang et al., 2008). Tonic inhibition, maintained by low levels of ambient GABA in the extrasynaptic space (Farrant and Nusser, 2005), provides a persistent inhibitory conductance that regulates the E/I balance (Semyanov et al., 2004). The reduction in the expression of the $\alpha 5$ subunit of the $GABA_A$ receptor narrows the integration window

necessary for feedforward inhibition. Moreover, because of the reduced GABA release, more synchronized afferent inputs must be generated to result in an action potential and to modulate the integration of postsynaptic excitatory and inhibitory potentials (Pouille and Scanziani, 2001; Gabernet et al., 2005).

Alzheimer's Disease

AD is associated with severe neuronal loss, with a predilection for brain regions within the medial temporal lobe, including the amygdala (Arnold et al., 1991; Braak and Braak, 1991). Recent studies have shown that, in symptomatic AD patients, the basomedial and lateral nuclei of the amygdala, display between 14% and 60% volumetric loss compared with controls as well as nonuniform shape changes (Cavedo et al., 2011, 2014; Poulin et al., 2011; Miller et al., 2015). In addition, postmortem studies have revealed that, although there is damage throughout the amygdala, the degree of atrophy and neurofibrillary tangles of amygdala nuclei is greater in the corticomedial group than in the BLA, suggesting that perhaps there is a selective loss of neurons that contributes to the loss in amygdala volume (Tsuchiya and Kosaka, 1990).

Although the overall loss of neurons, contributing to volumetric changes, has been observed in the amygdala, it remains unknown whether GABAergic interneuronal subpopulations or specific subunits of the $GABA_A$ receptor are targeted in the BLA and contribute to the observed deficits in fear learning and increased anxiety. Indeed, a loss of GABAergic interneurons or alterations in the expression of $GABA_A$ receptor subunits in the amygdala is possible, given that it has been observed that in the canine PFC PV- or CR-immunoreactive interneurons are resistant to neuronal death, whereas CB-positive interneurons are depleted (Pugliese et al., 2004); in the mouse dentate gyrus, significantly fewer SOM-immunopositive neurons are observed, whereas in the cornus ammonis 1 hippocampal region there is a significant loss of PV and SOM interneurons (Levenga et al., 2013). In addition, as observed in the hippocampus (see Mizukami et al., 1998; Armstrong et al., 2003; Iwakiri et al., 2009), $GABA_A$ receptor subunit expression might also be reduced in the BLA, which could contribute to amygdala hyperactivity.

Although it may be hypothesized that there are alterations to the expression of $GABA_A$ receptors and the interneuronal population in the BLA, only one study has examined alterations to the E/I balance in an AD model and focused this examination on the LA. In a study using the apolipoprotein E4 (apoE4)-targeted replacement mouse to model AD (Wang et al., 2005), 1- or 7-month-old mice expressing apoE4 displayed reduced excitatory synaptic transmission in the LA but no changes in inhibitory synaptic transmission (Klein et al., 2010). However, aged (18–20 months) apoE4 animals displayed significant increases in both inhibitory and excitatory synaptic transmission and an increased seizure phenotype (Hunter et al., 2012; Klein et al., 2014), suggesting that increased excitatory synaptic transmission predominates. The results indicate that it is unlikely that, in the LA, there are alterations in the subunit composition of the $GABA_A$ receptor; rather, increased excitatory transmission may be the result of alterations in the presynaptic release of GABA. Although it remains unknown why animals display increased excitatory activity in addition to the increased inhibitory activity, one hypothesis is that the increased excitatory activity seen in apoE4 mice may be the result of a loss of inhibition from extrinsic afferent cortical inputs (Swanson and Petrovich, 1998; Klein et al., 2014) or deficiencies in neuromodulatory mechanisms such as the loss of GABAergic interneurons but not cholinergic neurons in the basal forebrain (Loreth et al., 2012).

Epilepsy and Seizures

As a principal circuit projecting to many brain regions, hyperexcitability within the amygdala may be one source of seizure generation (Prager et al., 2013). For instance, spontaneous bursting activity has been found to appear first in the BLA of kindled animals (White and Price, 1993; Smith and Dudek, 1997), and seizure generation after a nerve agent exposure occurs only if AChE activity is significantly impaired in the amygdala compared with other seizurogenic brain regions (McDonough et al., 1987; Prager et al., 2013). The amygdala receives monosynaptic inputs from many frontal and temporal cortical areas that are known to generate and propagate seizure activity (Pitkanen et al., 1998). The convergence of input onto specific nuclei can then recruit a large number of neurons from interdivisional network connections, which may contribute to ictal-like activity within different amygdala nuclei. Efferents from amygdala nuclei may subsequently provide routes by which the amygdala can recruit other brain regions and lead to seizure propagation (Hirsch et al., 1997; Pitkanen et al., 1998; Pitkanen, 2000).

The loss of neurons in the amygdala and subsequent reductions in amygdalar volume further indicate the amygdala's role in the generation and propagation of seizures. The amygdala has previously been found to be severely damaged in patients with temporal lobe epilepsy and in both adults and children who experience SE (Pitkanen et al., 1998). Although often occurring in combination with hippocampal damage, neuronal loss has been observed in the amygdala without any apparent damage to the hippocampus (Hudson et al., 1993; Miller et al., 1994; Pitkanen et al., 1998). The loss of neurons in the amygdala has also been observed in animal models, the BLA being among the most damaged nuclei (Tuunanen et al., 1996; Apland et al., 2010; Figueiredo et al., 2011; Prager et al., 2013, 2014a). The loss of GABAergic interneurons in the amygdala in different seizure models has also been examined. Seizures or SE causes between 37% and 64% of GABAergic interneurons in the BLA to die, irrespective of the seizure model, although the loss of GABAergic interneurons was delayed by 7 days in animals

that developed SE after a nerve agent exposure (Callahan et al., 1991; Figueiredo et al., 2011; Prager et al., 2014a). Tunnanen and colleagues (1997) found a 35% decrease in the density of SOM-immunoreactive neurons in a kindling model.

Kindling- or nerve agent-induced SE causes long-lasting changes in synaptic transmission in the BLA, including impaired feedforward GABAergic inhibition and disinhibition of excitatory circuits (Rainnie et al., 1991a, 1992) and network reorganization resulting in BLA hyperexcitability (Smith and Dudek, 1997; Prager et al., 2014a). The loss of feedforward inhibition has been observed indirectly as a significant increase in paired-pulse facilitation beginning 24 hr after SE and continuing up to 30 days after nerve agent exposure (Zinebi et al., 2001; Prager et al., 2014a) and directly as a prolonged reduction in $GABA_A$ receptor-mediated inhibitory synaptic transmission, which likely was due to the loss of GABAergic interneurons in the BLA (Prager et al., 2014b). The loss of inhibitory synaptic transmission has been found to cause a concomitant increase in excitatory synaptic transmission (Prager et al., 2014b), which is associated with an increase in both NMDAR- and non-NMDAR-mediated glutamatergic transmission (Gean et al., 1989; Rainnie et al., 1992; Shoji et al., 1998).

Although alterations in GABAergic synaptic transmission have been observed in the amygdala after nerve agent-induced SE, reductions in $GABA_A$ receptor-mediated IPSCs appear to be model specific. After nerve agent-induced SE, there was a significant reduction in the frequency but not the amplitude of $GABA_A$ receptor-mediated mIPSCs (Prager et al., 2014b), indicating that the deficits in inhibitory synaptic transmission resulted from the loss of GABAergic interneurons. However, 7–10 days after kainate acid-induced SE, there was an increase in $\alpha 1$ subunit and GAD expression but a reduction in tonic inhibition (Fritsch et al., 2009). Although few studies have addressed how the stoichiometry of $GABA_A$ receptor subunits changes in the BLA after prolonged SE, it is well known that the expression of $GABA_A$ subunits is altered in other brain regions, such as the hippocampus (Mohler, 2006; Ferando and Mody, 2012). Thus, perhaps in some cases of epilepsy, alterations in the stoichiometry of $GABA_A$ receptor subunits may contribute to impaired inhibition in the BLA, whereas in other cases the loss of GABAergic inhibition may be the result of the death of interneurons.

Traumatic Brain Injury

Similarly to many other disorders, TBI can affect many brain regions, including the amygdala, and the disruption in neuronal excitability in surrounding regions may ultimately alter the homeostasis of the amygdala. The disruption in the E/I balance stems from an initial rise in glutamate release, which is responsible for excitotoxicity, and also from a delayed disruption of excitatory glutamate circuits, which may underlie the cognitive and motor deficits observed after TBI (Guerriero et al., 2015). Alterations in both glutamatergic and GABAergic synaptic transmission and the expression of their corresponding receptors have been observed after TBI in many brain regions, including the BLA (Almeida-Suhett et al., 2014; Guerriero et al., 2015), although this work is in its infant stages. An increase in the NR1 subunit of the NMDAR has been observed in the amygdala 2 weeks after injury (Reger et al., 2012), and reductions in the $\alpha 1$, ß2, and $\gamma 2$ subunits of the $GABA_A$ receptor were observed 7 days after a mild TBI (Almeida-Suhett et al., 2014). Moreover, even when there is no overt neuronal death in the BLA, a delayed loss of GABAergic interneurons is observed after a mild TBI, which may contribute to increased anxiety-like behavior (Almeida-Suhett et al., 2014) and enhanced fear conditioning (Reger et al., 2012).

CONCLUSIONS AND FUTURE DIRECTIONS

Although alterations in GABAergic inhibitory synaptic transmission in different diseases have been reviewed separately, it cannot go unstated that, in many cases, comorbidity occurs within many of these diseases. For example, estimates of comorbidity between PTSD and some types of TBI, including combat-related TBI, are as high as 73% (Hoge et al., 2008; Taylor et al., 2012). Moreover, epilepsy is often found to occur with diseases, including autism/fragile X (Berry-Kravis et al., 2010; Khetrapal, 2010), schizophrenia (Kandratavicius et al., 2012), AD (Palop et al., 2007; Chan et al., 2015), and anxiety disorders (Trimble and Van Elst, 2003; Vazquez and Devinsky, 2003). Indeed, many of these disorders have comorbidities, and often these comorbidities involve deficiencies within the BLA GABAergic system.

We are not arguing in this Review that amygdala hyperactivity results in the development of symptoms associated with the diseases discussed above. Rather, this Review seeks to provide evidence that reduced GABAergic inhibition and alterations in the mechanisms that modulate GABAergic inhibition contribute, in part, to amygdalar hyperexcitability; BLA hyperexcitability is common among these disorders and may lead to comorbid behavioral deficits. The extensive innervation of the amygdala by multiple brain regions has revealed that specific pathways modulate GABAergic inhibitory synaptic transmission and that these pathways may be disrupted in different diseases.

GABAergic activity in the BLA is modulated by dopaminergic, serotonergic, noradrenergic, and cholinergic activation as well as by the activation of various glutamate receptor subtypes and the CB1 and ASIC1a receptors. For the diseases discussed, deficiencies in the release of monoamines or ACh or alterations in glutamatergic receptor activity can lead to reduced modulation of GABAergic inhibition and, more locally, greater excitation via deficiencies in either feedforward or feedback inhibitory mechanisms. Moreover, because many of these systems are interconnected, deficiencies in one system may result in a cascading effect, which could contribute to disinhibition of excitatory neurons in the BLA and,

subsequently, increased anxiety-like behavior or increased seizure activity. However, the data in many cases are not conclusive. Much remains unknown with respect to how alterations in neurotransmitter release, receptor activation, and stoichiometry contribute to the behavioral deficits and increased anxiety often associated with these disorders.

E/I balance in the amygdala is dependent on functional neuromodulatory mechanisms and local interneuronal regulation. Neuromodulation is ineffective when there is a substantial loss of GABAergic interneurons, as has been observed in the amygdala in various neurological and neuropsychiatric disorders. In some cases, it is known that a specific class of interneurons is differentially affected, but in most cases it remains unknown what type of interneuron is most susceptible to cell death. Moreover, the loss of GABAergic interneurons may be delayed compared with the death of principal neurons. The immediate death may be due to the excitotoxic effects that occur with glutamatergic excitotoxicity (Zhou et al., 2013); however, one hypothesis is that the delayed loss of GABAergic interneurons is due to an upregulation of D-serine, an endogenous coagonist for NMDARs (Liu et al., 2009). Alternatively, even if there is no interneuronal degeneration, deficits in GAD may reduce the synthesis of GABA, which could subsequently reduce the concentration of GABA released in the synapse and impair inhibitory synaptic transmission. Alternatively, in many of the diseases discussed, alterations in expression of $GABA_A$ receptor subunits have been observed in the BLA. Although it is unknown whether these changes are transient or permanent, it can be assumed that alterations in the subunit stoichiometry may lead to reduced tonic and phasic inhibitory synaptic transmission.

This Review has two major themes. First, we have summarized the neuromodulatory systems that modulate $GABA_A$ receptor-mediated inhibitory synaptic transmission. Second, we have discussed how reduced GABAergic inhibition in the BLA throughout the life span can contribute to the behavioral manifestation of symptoms associated with autism and fragile X, AD, epilepsy, TBI, and anxiety- or stress-related disorders. In each case, results indicate that BLA hyperexcitability is associated with deficits in mechanisms that modulate GABAergic inhibitory synaptic transmission, loss of GABAergic interneurons, or alterations in $GABA_A$ receptor subunit expression. However, in many of the diseases discussed above, much remains unknown with respect to why the amygdala is hyperexcitable. By understanding how the GABAergic system is impaired, future research can target the functional aspects of the $GABA_A$ receptor for potential therapeutic options. Future research might also develop new therapies that induce the growth of interneurons in specific brain regions or target and reduce excitation of the glutamatergic system. The latter option has been implemented after a nerve agent-induced seizure, for example, in which administering a $GluK_1$ antagonist prevented neurodegeneration and associated increases in anxiety or seizure activity (Figueiredo et al., 2011; Prager et al., 2015). Overall, identifying the alterations to the inhibitory system and the mechanisms that modulate inhibitory synaptic transmission is a fundamental prerequisite for the design of effective and well-tolerated therapeutic treatments for these and other neurological and neuropsychiatric disorders.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests

ROLE OF AUTHORS

All authors take responsibility for the integrity and accuracy of this article. Drafting of the manuscript and critical revisions of the article: EMP, HCB, GHW, MFMB

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