Role of oxytocin signaling in the regulation of body weight

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Abstract Obesity and its associated metabolic disorders are growing health concerns in the US and worldwide. In the US alone, more than two-thirds of the adult population is classified as either overweight or obese [1], highlighting the need to develop new, effective treatments for these conditions. Whereas the hormone oxytocin is well known for its peripheral effects on uterine contraction during parturition and milk ejection during lactation, release of oxytocin from somatodendrites and axonal terminals within the central nervous system (CNS) is implicated in both the formation of prosocial behaviors and in the control of energy balance. Recent findings demonstrate that chronic administration of oxytocin reduces food intake and body weight in diet-induced obese (DIO) and genetically obese rodents with impaired or defective leptin signaling. Importantly, chronic systemic administration of oxytocin out to 6 weeks recapitulates the effects of central administration on body weight loss in DIO rodents at doses that do not result in the development of tolerance. Furthermore, these effects are coupled with induction of Fos (a marker of neuronal activation) in hindbrain areas (e.g. dorsal vagal complex (DVC)) linked to the control of meal size and forebrain areas (e.g. hypothalamus, amygdala) linked to the regulation of food intake and body weight. This review assesses the potential central and peripheral targets by which oxytocin may inhibit body weight gain, its regulation by anorexigenic and orexigenic signals, and its potential use as a therapy that can circumvent leptin resistance and reverse the behavioral and metabolic abnormalities associated with DIO and genetically obese models.

Keywords Satiety · Meal size · Oxytocin · Hindbrain

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1 Introduction

While the nonapeptide oxytocin is historically recognized for its role in parturition [2], lactation [3], and osmoregulation [4], it has gained more recent attention for its effects on prosocial behavior [5, 6] and therapeutic potential in the treatment of autism spectrum disorder (ASD) [5, 6], schizophrenia [5, 7] and obesity [8–14]. In fact, 225 completed, ongoing or future investigations in humans list oxytocin in studies on caloric intake, gastric emptying, or obesity (ClinicalTrials.gov registry, National Institutes of Health). In light of the growing obesity epidemic, which impacted over 78 million adults and 12.5 million children and adolescents in the U.S. in 2009–2010 [15], combined with the relative ineffectiveness of existing weight loss strategies, this review will focus on timely findings that assess oxytocin's ability to reduce food intake and body weight in diet-induced obese (DIO) [8, 10, 12–14] and genetically obese rodent models [9, 11, 12], highlight potential downstream CNS and peripheral mechanisms that could potentially elicit these effects, and discuss its regulation by anorexigenic and orexigenic signals.

1.1 Oxytocin production and release

Oxytocin is produced primarily from parvocellular paraventricular nucleus (pPVN) and magnocellular neurons in both

the PVN and the supraoptic nucleus (SON) whereas more limited amounts are produced in the anterior hypothalamus, bed nucleus of the stria terminalis (BNST), medial preoptic area, medial amygdala and in the periphery [16–18]. Its release occurs locally in the SON and PVN via somatodendrites and distally via terminals that originate from magnocellular PVN and SON projections to the posterior pituitary and pPVN projections to sites that include the ventral tegmental area (VTA) [19], nucleus of the solitary tract (NTS) [20, 21] and spinal cord [21]. Several studies suggest that the major source of circulating oxytocin derives from the posterior pituitary, as oxytocin concentrations in the extracellular space of the SON are nearly 100-fold higher than circulating levels [22], oxytocin levels in the rat hypothalamus are 3-fold higher compared to heart and uterus [16], and oxytocin levels in pituitary extracts are over 250-fold higher than in heart per-fusate [16]. Whereas recent findings point to the nodose ganglion [23] and gastrointestinal (GI) tract [24] as sites of oxytocin receptor (OXTR) expression and the GI tract as a site of synthesis [25], the extent to which OXTR signaling within the GI tract or vagal sensory afferent nerves contributes to energy homeostasis is unknown.

1.2 OXTR signaling and distribution

To date only one subtype of the OXTR has been identified. The majority of research has focused on the association between OXTR variants or polymorphisms and ASD and schizophrenia, but recent developments point to a link between rare OXTR variants and severe early-onset obesity in humans [26]. The extent to which these OXTR variants are causally related to variation in energy regulation in humans awaits further investigation. Nonetheless, the importance of oxytocin signaling to energy balance is clearly reflected in the wide distribution of OXTRs in relevant areas of the CNS such as the basal ganglia (nucleus accumbens (NAc), central amygdala), hypothalamus (PVN, SON, ventromedial hypothalamus (VMH)), and hindbrain (NTS, area postrema (AP)) [27–30], as well as in several peripheral tissues, including adipocytes [31–33] and GI tract [25].

The second messenger systems coupled to OXTRs in the CNS have only been recently identified [29, 34]. The classical uterine OXTR is a G protein-coupled receptor (GPCR) that signals through two G proteins, $G_{q/11}$ and $G_{i/0}$. It signals primarily through phospholipase C-β via G_q-binding proteins, stimulating production of inositol trisphosphate and 1,2-dia-cylglycerol that leads to the release of intracellular Ca^{2+} and phosphorylation of target proteins [28]. In contrast to GPCR signaling in uterine OXTRs, neuronal G_q is inhibitory and G_i stimulates an inward rectifying current [35] thereby eliciting changes in neuronal activation.

2 Effects of oxytocin on reductions in food intake and body weight

2.1 Role of oxytocin as an anorexigenic agent

Oxytocin was first reported to inhibit food intake following systemic administration in rodents by Arletti and colleagues in 1989 [36, 37]. Subsequent studies showed these effects could be reproduced following administration of much lower doses when given directly into the CNS [8, 9, 12–14, 38–40] and these effects were completely blocked by pretreatment of an oxytocin antagonist [36, 37, 39]. This ability to reduce food intake appears to be through a specific effect of oxytocin to reduce meal size [18, 38, 41] and increase latency to the first meal [37]. Meal-related stimuli are associated with activation of PVN and SON oxytocin neurons, release of oxytocin into the circulation, and activation of hindbrain neurons that regulate meal size. These stimuli include food intake [41–45], refeeding following a 24-[18] or 48-h fast [43, 45], the satiety signal cholecystokinin (CCK-8) [46, 47], gastric distension [47–49], activation of gastric vagal afferents [50, 51] and changes in osmolality following food intake [43]. Although circulating levels of oxytocin were not measured in these studies, the dietary signals associated with activation of PVN oxytocin neurons include branched-chain amino acids (e.g. leucine [41]), the dietary fat-derived signal, oleoylethanolamide (OEA) [52], and sucrose [44]. Peak circulating levels in the dark cycle generally correspond to typical patterns of food intake in mice [14]. Not surprisingly, energy deficits induced by prolonged fasting are associated with reductions in oxytocin mRNA when samples are restricted to the pPVN [53] or include the entire PVN [9, 54], and this effect is restored by refeeding [9]. Together, these studies suggest that nutrient excess is linked with increased hypothalamic oxytocin signaling while energy deficits are coupled with reductions in hypothalamic oxytocin signaling.

2.2 Physiological relevance of oxytocin in the control of food intake

Several lines of evidence have established a link between oxytocin signaling and food intake. For example, oxytocin antagonists stimulate intake of chow [9, 13, 14, 39, 41, 55], glucose [38], and sucrose [44] through a specific increase in meal size [38, 41]. Recent findings in OXTR null mice show increases in meal size during the dark cycle [18] despite no change in daily food intake [18, 56]. However, increases in daily food intake are observed in mice with reductions in mature hypothalamic oxytocin levels [57] (MAGED1 deficient mice). Interestingly, MAGED1 is a member of MAGE gene family associated in patients with Prader-Willi Syndrome, characterized by hyperphagia and reductions in number and size of PVN oxytocin neurons [58]. Likewise, rodent

mutations of the single-minded 1 gene, SIM1 (e.g. Sim1 haploinsufficient mice) are also associated with hyperphagia and reductions in PVN oxytocin expression. These deficits in food intake in Sim1 haploinsufficient mice can be restored with oxytocin treatment [9]. Consistent with these findings, lentiviral knockdown of PVN oxytocin mRNA expression in adult mice results in increased intake of both low and high fat diets (HFD) [13]. In contrast, a recent finding showed that ablation of nearly 95 % of PVN oxytocin neurons via Cre-mediated diphtheria toxin treatment in adult oxytocin-Ires-Cre mice has no effect on chow or HFD intake [59]. However, caution must be used in interpreting these latter results as they may be due, in part, to ablation of other neuropeptides or neurotransmitters expressed in PVN oxytocin neurons. Further studies will also need to take into account the potential impact of gliosis in projection sites [60], background strain [44] as well as site specific developmental changes in OXTR expression [28, 61] that may be related to age [28, 61] or diet exposure in these mice at the time the loss in PVN oxytocin signaling occurred to determine the extent to which these factors may play a role in these differential effects.

2.3 Does oxytocin inhibit food intake by reducing gastric emptying and gastrointestinal transit?

Historical studies have shown that injections of small quantities of oxytocin into the DVC inhibit gastric motility in rats [62] and that oxytocin excites both NTS and dorsal motor nucleus of the vagus (DMV) cells that are activated in response to gastric distension [63]. Verbalis and colleagues speculated that oxytocin elicited suppression of gastric motility results from the effects of oxytocin to excite NTS neurons which, in turn, inhibit DMN neurons that stimulate gastric motility, resulting in an inhibition of gastric motility [4]. While previous findings show that systemic administration of oxytocin has either no effect on gastric emptying rate in humans [64] and rats [65] or a stimulatory effect on gastric motility in rabbits ([66]; attributed to species differences), recent findings show that systemic administration of oxytocin reduces gastric emptying in rats [67, 68] consistent with the presence of oxytocin receptors along the GI tract [24]. These effects are blocked by an oxytocin antagonist [67, 68]. They also appear to be dependent on CCK release and CCK1R signaling as these effects are blocked by the CCK1R antagonists, devazepide [67, 68] and lorglumide [67, 68], but not by the CCK2R antagonist, L-365,260 [67, 68]. These findings raise the question as to whether the effects of systemic oxytocin to inhibit gastric emptying require activation of hindbrain NTS OXTRs and whether the ability of peripheral oxytocin to reduce food intake also requires reductions in gastric emptying. Testing the effects of both central and systemic administration of oxytocin to reduce food intake in rats with gastric cannulas that remain open (sham feeding; absence of gastric distension) or closed (real feeding) would be helpful in determining the extent to which reductions in gastric emptying contribute to the anorexigenic response to oxytocin.

2.4 Does oxytocin reduce food intake by suppressing feeding reward circuitry?

Existing studies implicate an important role of endogenous oxytocin to reduce intake of highly palatable foods, such as sucrose [44, 69, 70] and HFD [8, 10, 12–14]. While exogenous administration of oxytocin reduces intake of HFD [8, 10, 12–14] and sucrose [71], it appears that endogenous oxytocin may preferentially inhibit intake of carbohydrates. Although PVN oxytocin neurons are activated towards the end of a meal consisting of HFD or sucrose, sucrose appears to activate a greater proportion of PVN oxytocin neurons relative to intake of fat (intralipid) [44]. Moreover, systemic administration of an oxytocin antagonist that readily crosses the blood brain barrier (L-368,799) [72] stimulates intake of sucrose, but not chow or intralipid [44]. Similarly, oxytocin knockout mice exhibit increased intake of sucrose [69], but not chow [69]. Work from Olszewski and colleagues provide a mechanism whereby opioids inhibit oxytocin signaling when a diet high in sugar is administered [73], and this may explain why the ability of sucrose to activate PVN and SON oxytocin neurons is impaired following long-term exposure to sucrose [74]. Furthermore, the ability of oxytocin to stimulate CCK-8 release in the SON is inhibited by morphine [75] although it is not clear the extent to which morphine also impacts the ability of oxytocin to enhance the hindbrain satiety and neuronal response to CCK-8. Together, these findings suggest that oxytocin signaling is sufficient to limit intake of rewarding foods high in sucrose, but chronic exposure to sucrose leads to impaired regulation and overconsumption.

The CNS pathways that potentially contribute to the effects of oxytocin to suppress intake of palatable food are not fully understood. Recent findings suggest that oxytocin may suppress food intake, in part, through a mechanism that involves inhibition of feeding reward circuitry in the NAc. Systemic oxytocin reduces drug reward behavior such as methamphetamine (METH) elicited self-administration [76] and METH-seeking behavior, which coincides with a suppression of METH-elicited neuronal activation in the NAc [76, 77]. These findings are consistent with studies that show central administration of oxytocin reduces METH-elicited hyperactivity, dopamine release in the striatum and NAc [78] and conditioned place preference [78]. Whether these effects require activation of OXTRs in the NAc or NTS with subsequent activation of ascending NTS-NAc projections remains to be determined.

As reviewed by Paul Kenny [27] signaling via glucagon-like peptide-1 (GLP-1) and noradrenergic (NA) neuronal projections as well as NTS proopiomelanocortin (POMC) neurons may represent shared components that underlie feeding and

drug reward circuitry within the NTS (see 6.1; Fig. 1). DIO is associated with both a reduction in the hindbrain satiety [79] and NTS neuronal response to CCK-8 [80]. These impairments may be driven by reductions in hindbrain oxytocin signaling in DIO animals, leading to an inability of CCK-8 to activate NTS neurons that express GLP-1 [81], NA (including prolactin releasing peptide (PrRP)) [82–85] and POMC [86, 87] and thus elicit satiety [88–91]. NTS GLP-1 and NA neurons project to feeding reward areas in the limbic system such as the VTA [92, 93] and NAc [92, 94–96]. GLP-1 also inhibits food intake following administration into the VTA [92] and NAc [92, 97], the latter of which occurs at doses that do not elicit a conditioned taste aversion (CTA). Furthermore, GLP-1 administration into the NAc core appears to preferentially inhibit intake of sucrose and HFD relative to chow [92]. Reductions in CNS GLP-1 signaling in adult rats also result in a predisposition to DIO [98]. Opiate administration into the NTS inhibits POMC neurons [86] whose overexpression in the NTS prevents DIO [99] and reduces adult-onset obesity [100]. Although the outgoing NTS POMC neuronal circuits that contribute to these effects are unknown (Fig. 1), fourth ventricular (4 V) administration of MTII inhibits sucrose intake, and supports a potential role of melanocortin 4 receptors (MC4R) in the NTS

in the suppression of highly palatable food [101]. Although current data support potential roles of NTS GLP-1 and POMC neurons in suppressing intake of palatable food, the role of NTS NA neurons is less clear. While there is reduced sensitivity of NTS noradrenergic neurons to lipids in DIO or genetically obese mice [102, 103], the existing data favor an interpretation that the drug reward is enhanced by increased NA signaling in the NTS. For example, the reward associated with morphine is eliminated in dopamine-B-hydroxylase (DBH; enzymatic precursor to noradrenaline) null mice but restored following viral reexpression of DBH into the NTS [104]. Together, these findings indicate that, while NA neurons in the NTS may not be essential to drug reward, the nature of GLP-1, NA, and POMC neuronal signaling in the NTS in feeding reward has not been fully elucidated [27].

3 Physiological relevance of oxytocin in the control of body weight

Although both central [8, 12–14] and peripheral [10, 12, 14] administration of oxytocin reduces body weight the best
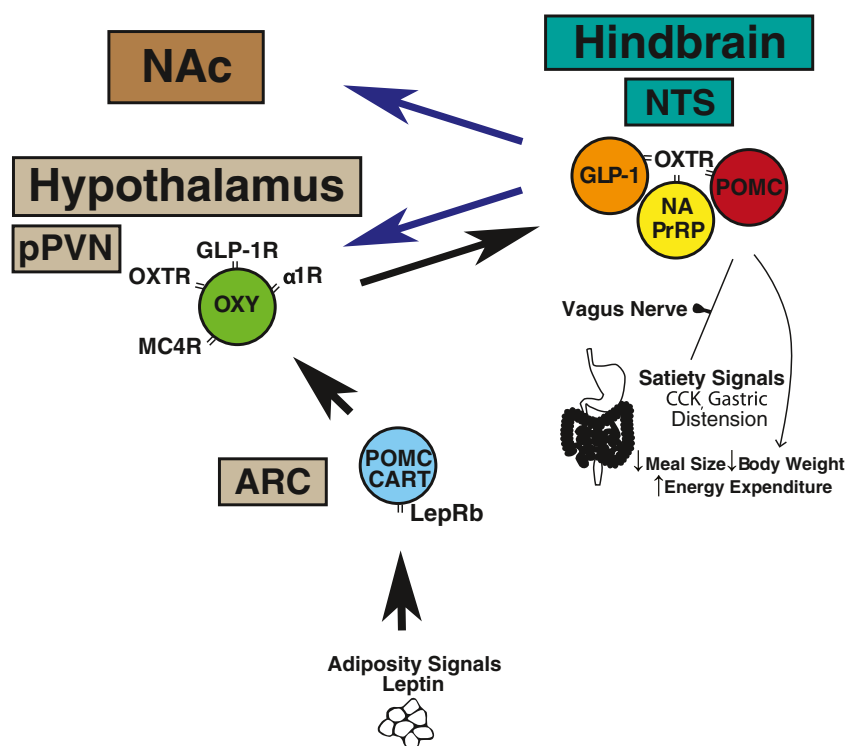
Fig. 1 A schematic of proposed CNS circuitry involved in oxytocin regulation of energy balance. Leptin activates pPVN oxytocin neurons through a MC4R-dependent mechanism resulting in the release of oxytocin in the hindbrain. Oxytocin is proposed to activate ascending cNTS NA and GLP-1 neuronal projections to the PVN and NAc (denoted by purple arrows to PVN and NAc) as well as POMC neurons. These combined effects are proposed to reduce body weight by reducing food intake and increasing energy expenditure. Abbreviations: α-1R Alpha-1 adrenoceptor, *ARC* Arcuate nucleus, *CART* Cocaine-amphetamine-regulated transcript, *CCK* Cholecystokinin, *GLP-1* Glucagon-like peptide-1, *GLP-1R* Glucagon-like peptide-1 receptor, *LepRb* Long form of the Leptin receptor, *MC4R* Melanocortin 4 receptor, *NA* Noradrenergic, *NAc* Nucleus accumbens, *NTS* Nucleus of the solitary tract, *OXY* Oxytocin, *OXTR* Oxytocin receptor, *PrRP* Prolactin releasing peptide, *PVN* Paraventricular nucleus, *POMC* Proopiomelanocortin

evidence for the role of endogenous oxytocin signaling in the control of body weight stems from pharmacological and genetic loss of function studies. Oxytocin antagonists increase body weight gain [13, 14] and mice with global loss in oxytocin and OXTRs develop adult-onset obesity [56, 105]. Moreover, anatomically selective loss of oxytocin in the PVN in adult mice is associated with increased body weight gain on both low and HFD [13]. Similarly, recent reports show that ablation of PVN oxytocin neurons following diphtheria toxin treatment results in increased body weight gain on a HFD [59]. Mice with reductions in MAGED1 and reductions in mature hypothalamic oxytocin are also associated with adult-onset obesity and reduced activity. Reductions in the number and size of PVN oxytocin neurons are observed in patients with Prader-Willi syndrome that are characterized by hyperphagia and obesity [58]. Likewise, humans with mutations of SIM1 are associated with severe obesity in humans [106, 107] and Sim1 haploinsufficient mice are characterized by hyperphagia, obesity and reductions in PVN oxytocin expression. These deficits in relation to the body weight gain observed in Sim1 haploinsufficient mice can be restored with oxytocin treatment [9]. DIO mice are also associated with impairments in oxytocin release within the PVN and reductions in serum oxytocin [13]. These findings in DIO mice are attributed to increased PVN expression of synaptotagmin-4 (SYT4), a negative regulator of oxytocin release both in the PVN and in periphery [13]. Consistent with a link between increased oxytocin signaling and reductions in body weight is the finding that SYT4 null mice are lean and resistant to the development of DIO [13].

3.1 Weight loss associated with oxytocin treatment is not fully explained by reductions in food intake: Effects on energy expenditure

The effects of oxytocin to increase energy expenditure appear to be a principal driving force behind its ability to reduce body weight. Oxytocin produces reductions in body weight at doses that are ineffective at reducing food intake when administered chronically [8]. In cases where chronic oxytocin treatment inhibits both food intake and body weight gain its ability to reduce body weight is maintained even after treatment has ended [10] or food intake has returned to control values [10]. These findings are consistent with data which show that body weight loss attributed to oxytocin exceeds that from pair-fed control animals [8, 12]. Additionally, oxytocin and OXTR null mice develop adult-onset obesity, yet have no impairments in daily food intake [18, 56, 69, 105]. OXTR null mice also exhibit impairments in cold induced thermogenesis [56] and oxytocin null mice have reduced urinary adrenaline consistent with impairments in the sympathetic nervous system [105]. Oxytocin activates sympathetic preganglionic neurons [108], including the stellate ganglia [109]. With well

characterized polysynaptic projections to brown adipose tissue [110], stellate ganglia [111], and spinal cord [21], these findings suggest that oxytocin plays an important role in regulating sympathetic nervous system activity. Consistent with this are findings that oxytocin increases heart rate [30, 112], body temperature [30] and oxygen consumption in mice [13, 14] and prevents the decrease in energy expenditure associated with reductions in body weight [12]. In addition, transgenic mouse models with reductions in PVN oxytocin signaling, such as Sim1 haploinsufficient mice [113] and SYT4 null mice [13] are characterized, in part, by reduced energy expenditure. Recent reports show that ablation of PVN oxytocin neurons following diphtheria toxin treatment results in increased body weight gain and reductions in energy expenditure in the absence of any changes in food intake in animals maintained on a HFD [59] confirming a role for PVN oxytocin neurons in the regulation of energy expenditure. In contrast, there are no changes in food intake, obesity and energy expenditure in lean mice [59]. These findings implicate an enhanced sensitivity to changes in oxytocin signaling in DIO relative to lean animals. While additional studies need to confirm the extent to which the metabolic phenotype following complete ablation of PVN oxytocin neurons could be attributed to nonspecific effects independent of a mechanism mediated by oxytocin signaling, these findings are consistent with the enhanced sensitivity to changes in oxytocin signaling in DIO [10, 12, 13] and genetically obese rodent models [9]. In contrast to the work from Wu and colleagues [59], other studies indicate that selective lentiviral knockdown of PVN oxytocin mRNA in adult mice increases food intake and body weight gain in animals fed either a low or HFD [13]. Together, these studies raise awareness for the need to examine energy expenditure following selective ablation of OXTRs in distinct forebrain and hindbrain sites that are linked to the regulation of energy expenditure, including those that receive projections from the pPVN (e.g. NTS and spinal cord) that may be impacted by gliosis and astrocytic infiltration that accompany ablation of neurons in response to diphtheria toxin administration [60]. It would also help extend the field by using the recently described OXTR-Venus knock-in mice (OXTR $^{Venus\ \Delta\ Neo/+}$) [30] to assess downstream targets that could potentially underlie these effects on energy expenditure. One such downstream target which could contribute to the effects of oxytocin on energy expenditure is GLP-1 [114], and evidence in support of GLP-1 being a downstream target of oxytocin action is discussed later in this review.

3.2 Weight loss associated with oxytocin treatment is not fully explained by reductions in food intake: Effects on lipolysis

Oxytocin may also reduce body weight due, in part, to its ability to increase lipolysis through a direct effect on adipocytes [31–33, 115] or an indirect mechanism involving

polysynaptic projections from the PVN to white adipose tissue [116, 117]. OXTRs are expressed on primary and cultured adipocytes [31–33] and oxytocin elicits direct effects on these cells [115]. *In vitro* data from 3 T3-L1 adipocytes show that oxytocin increases enzymes associated with lipolysis [8] and results in increased glycerol release [8]. In addition, chronic oxytocin treatment *in vivo* results in reductions in fat mass [8, 10, 14], particularly adipocyte area from both mesenteric and epididymal fat [10]. Consistent with these findings, *in vivo* data from animals with global loss in oxytocin signaling show increases in abdominal fat [56, 105] and increases in perirenal, mesenteric, and epididymal fat pad weights relative to littermate controls [56]. Similarly, selective ablation of oxytocin neurons in the PVN and SON [59] and postnatal ablation of PVN Sim1 neurons (resulting in a 50 % drop in hypothalamic oxytocin mRNA expression) [113] are associated with increases in body fat. These findings corroborate those from pair-feeding studies [8, 12], studies that report oxytocin to be effective at reducing body weight at doses ineffective at reducing food intake [8], and studies that show reductions in body weight persist well beyond the normalization of food intake and cessation of treatment [10]. Together, these recent studies unveil potential mechanisms whereby oxytocin reduces body fat through separate or combined effects to promote lipolysis and increase energy expenditure.

3.3 Evidence to support role of descending oxytocin pPVN-NTS projections in regulation of body weight

Several lines of evidence support the hypothesis that a neural pathway from the pPVN to the NTS (Fig. 1) is a critical component of CNS circuits that regulate the long-term control of body adiposity [55, 89, 118–120]. Decerebrate animals (all connections between hypothalamus and hindbrain severed) are unable to mount a normal compensatory response to energy deficits by increasing food intake, despite intact feeding responses to many short-term, meal-related stimuli [121]. The NTS not only integrates descending information originating from the hypothalamus, but it receives ascending information from the GI tract through its extensive innervation by vagal afferent projections that originate from the gut [122]. Substances may also access the NTS through the nearby AP, a region that lacks a blood brain barrier and is thus capable of directly responding to nutrient and blood-borne factors released during the course of a meal. It is well established that the meal-related satiety signals, CCK-8 and gastric distension, activate neurons in the AP and NTS [82, 123]. Lesions of both the AP and NTS eliminate the ability of CCK-8 to inhibit food intake [124]. Together, these studies reveal the importance of these areas in integrating information pertaining to meal-related satiety signals (CCK-8, gastric distension) to control feeding [122, 123, 125, 126].

Further understanding of the role of caudal brainstem neurons in the regulation of regulation of food intake has been facilitated by identifying the neuronal circuits involved in this pPVN-NTS pathway. Oxytocin fibers comprise 11–16 % of pPVN projections to the medulla and spinal cord [127] of which nearly 6 % project directly to the DVC [46], specifically the NTS and DMV. Previous data show that oxytocin fibers in the NTS arise solely from the pPVN [20] and are in close anatomical proximity to areas in the NTS that respond to CCK-8 [89]. PVN lesions are also associated with an attenuated satiety response to CCK [128] and destruction of either PVN neurons [129] or this hindbrain projection results in hyperphagia and obesity [130].

3.4 Role of descending pPVN-NTS oxytocin projections in contributing to leptin signaling

Descending pPVN-NTS oxytocin projections are hypothesized to contribute to the ability of leptin to enhance the hindbrain neuronal and satiety response to CCK-8 [55, 90]. Leptin activates pPVN oxytocin neurons [55, 131, 132], some of which project to the caudal NTS [55] [132], and prevents the drop in PVN oxytocin mRNA expression associated with long-term fasting [54, 132]. Blockade of OXTR signaling attenuates leptin's ability to inhibit food intake [55, 59] and body weight [132]. Moreover, blockade of endogenous oxytocin signaling attenuates the ability of leptin to enhance the hindbrain neuronal response to CCK-8 [55], and reduces the effectiveness of CCK-8 to inhibit food intake [88, 89]. Together, these findings suggest that endogenous oxytocin contributes to the ability of leptin to reduce food intake through a mechanism that involves enhancing the hindbrain response to satiety signals such as CCK.

Evidence to date suggests that leptin activates pPVN oxytocin neurons through both a direct and an indirect melanocortin-dependent mechanism. One recent study in rats provides evidence in support of a direct effect by showing that leptin elicits phosphorylation of signal transducer and activator of transcription-3 (pSTAT3) signaling in pPVN oxytocin neurons that project to the NTS [132]. However, the majority of evidence in both rats and mice supports an indirect mechanism of leptin to activate pPVN oxytocin neurons. For example, leptin elicits little pSTAT3 signaling in pPVN [133] consistent with low levels of expression of leptin receptors [134]. In addition, the ability of leptin to induce Fos in PVN neurons and inhibit food intake is completely blocked by pretreatment with the melanocortin 3/4 receptor (MC3/ MC4R) antagonist, SHU9119 [135]. Furthermore, CNS administration of the MC3/MC4R agonist, alpha-melanocyte-stimulating hormone or a selective MC4R agonist (cyclo(β-Ala-His-D-Phe-Arg-Trp-Glu)-NH2), activates PVN oxytocin

neurons [9, 136], which express MC4R [137]. pPVN neurons that project to the NTS also express MC4R [138] and PVN administration of alpha-MSH induces Fos in both PVN and NTS neurons [45]. Importantly, blockade of endogenous oxytocin also blocks the effects of MTII to reduce food intake [139]. Together, these findings support both a direct action as well as an indirect effect of leptin to activate downstream pathways that secrete alpha-MSH from POMC neurons onto pPVN MC4R/oxytocin neurons that project to the NTS, resulting in activation of CCK-sensing neurons in the hindbrain and an enhanced satiety response to CCK.

3.5 Proposed impact of leptin resistance on activation of downstream descending oxytocin pPVN-NTS projections

The use of leptin as therapeutic agent to treat obesity was initially an exciting concept, but has since been disappointing due to the development of "leptin resistance", characterized by an impaired ability of leptin to activate both intracellular signals in the ARC and downstream signaling pathways in rodents and in all likelihood humans [140]. These impairments result in the failure of leptin to reduce food intake [141] and body weight [142], despite elevated levels of leptin in the circulation [141]. Leptin resistance is selective in the ARC [133], and impairments in leptin signaling occur within one week of exposure to a HFD in rodents [133]. Although the causes of leptin resistance are not well understood, many factors are thought to contribute to leptin resistance, including defective transport of leptin across the blood brain barrier [141, 143], hyperleptinemia [144], defects in leptin intracellular signaling in the ARC through upregulation of suppressor of cytokine signaling 3 (SOCS-3) [145], leptin promoter DNA methylation [146], hypothalamic inflammation [147], and increased levels of hypothalamic protein-tyrosine phosphatase 1B [148, 149]. One predicted outcome of leptin resistance is a failure of leptin to activate downstream pathways that secrete alpha-MSH from POMC neurons onto pPVN MC4R/oxytocin neurons that project to the NTS, resulting in a defect in both the activation of CCK-sensing neurons in the hindbrain and the satiety response to CCK, both of which occur in animals fed a HFD [79, 80]. Recent studies illustrate that mice deficient in SOCS-3 in the mediobasal hypothalamus (MBH) have restored leptin sensitivity, reductions in food intake and body weight gain, and increased hindbrain responsiveness to satiety signals [90]. In addition, blockade of endogenous oxytocin attenuates the response to satiety signaling in these animals [90]. Moreover, leptin resistant animals have reductions in oxytocin content in the DVC relative to leptin sensitive MBH SOCS-3 null mice. Together, these findings suggest that leptin resistance is associated with downstream impairments in oxytocin release within the NTS [90]. The extent to which this impairment is important in causing or maintaining the metabolic and behavioral abnormalities in DIO remains to be determined.

3.6 What is the potential role of forebrain OXTRs in the regulation of body weight?

Few studies have examined the impact of neuroanatomically specific knockdown or overexpression of OXTRs on the control of food intake and body weight. Surprisingly, one study found a lean phenotype is associated with postnatal loss of OXTRs in the lateral septum, hippocampus and ventral pallidum [150]. However, the extent to which OXTRs were ablated in other forebrain areas linked to the regulation of energy expenditure (e.g. PVN, VMH) was not discussed nor was the possibility that developmental upregulation of OXTRs in extrahypothalamic areas or in the periphery could contribute to these effects. As indicated earlier, lentiviral reduction in PVN oxytocin mRNA expression is associated with a clear phenotype on food intake and body weight [13], but it is unclear whether this phenotype resulted from loss in PVN oxytocin autoreceptors and/or loss in outgoing oxytocin projections to NTS, spinal cord, sympathetic ganglia or brown adipose tissue. Although much work has been done to elucidate the role of PVN oxytocin neurons, examining the impact of selective loss in OXTRs in the PVN and VMH would better help delineate the role of forebrain OXTR signaling in the regulation of energy balance.

3.7 Does systemic administration of oxytocin inhibit body weight through a mechanism that requires OXTRs in the CNS?

While there is a lot of excitement regarding the therapeutic potential of systemic oxytocin to reduce food intake and body weight following systemic administration, it is not clear the extent to which this route of administration reduces food intake through receptors in the brain vs. periphery. Systemic oxytocin increases Fos induction in PVN oxytocin neurons [77, 151] and increases the release of oxytocin within the PVN [14]. Oxytocin may, in turn, activate PVN oxytocin neurons via autoreceptors making it hard to differentiate a central from peripheral mechanism. The evidence supporting the notion that circulating oxytocin enters the brain is mixed as studies report that only 0.01 to 0.002 % enters the brain following intravenous administration [152, 153] but does so within only 10 min postinjection [152]. Furthermore, recent findings in rats and mice show increases in oxytocin levels in both the hippocampus and amygdala within 30-min of an intraperitoneal injection [154]. In addition, peripheral administration of oxytocin recapitulates the effects of CNS administration on food intake [12, 14], body weight [12, 14], and Fos induction in hindbrain areas [10, 12, 14, 40, 123, 151, 155] that express OXTRs [28–30]. Access to OXTRs in the AP and NTS could be achieved through leaks in the blood brain barrier [156], tanycytes [156] or other transporters [157, 158]. Since such small doses of oxytocin are required to inhibit food intake following CNS administration little would actually need to be transported into the brain in order

to elicit an effect which may explain why large acute systemic doses are required to inhibit food intake [10, 12, 14, 36, 37]. Consistent with oxytocin being able to cross the blood brain barrier [152, 153] recent findings show that the anxiolytic activity following systemic administration of oxytocin is blocked by intracerebroventricular (ICV) administration of a nonpenetrant oxytocin antagonist [159]. Future efforts should examine the effectiveness of systemic administration of oxytocin to reduce food intake and body weight in animals with timed and localized ablation of OXTR in the hindbrain.

4 Oxytocin is a common downstream effector of anorexigenic signals

4.1 Stimulation of oxytocin neurons by anorexigenic signals

Cocaine-amphetamine-regulated transcript (CART) Earlier we discussed reports that show PVN oxytocin neurons are activated by both leptin and MC3/MC4R ligands and appear to be critical components of both leptin and melanocortin signaling. The extent to which oxytocin contributes to the anorexigenic response to CART, a downstream target of leptin and expressed on ARC POMC neurons, is unknown. CART activates magnocellular and pPVN oxytocin neurons and increases serum levels of oxytocin [160]. Future studies could address the extent to which CART [161] inhibits food intake in animals pretreated with selective oxytocin antagonists or in animals with global or site specific ablation in either OXTRs or oxytocin.

Fat mass and obesity associated gene (FTO) Recent data show that *FTO*, a gene linked to the regulation of food intake and body weight, has a high degree of colocalization with magnocellular and pPVN oxytocin neurons [162], and increases the expression of oxytocin *in vitro* [163]. The exact role of *FTO* remains unclear as overexpression leads to increased food intake and obesity [164] yet global loss [165] and mutations in *FTO* [166] lead to increased food intake, reduced body weight and increased energy expenditure. It remains to be determined if overexpression or absence of *FTO* produces the predicted changes in oxytocin signaling *in vivo*.

Leucine The branched chain amino acid, leucine, inhibits meal size, in part, by activating ARC POMC neurons, PVN oxytocin neurons, and OXTRs in the NTS [41]. Administration of an oxytocin antagonist into the 4 V blocks the effects of MBH application of leucine to inhibit food intake, suggesting that endogenous oxytocin in the NTS contributes to the ability of MBH leucine to inhibit food intake [41]. Recent studies show that this is not the only mechanism by which leucine inhibits food intake as sites within the caudal hindbrain also contribute to the anorexigenic response to leucine [167].

Nesfatin-1 Nesfatin-1, a peptide derived from the precursor nucleobindin-2 (NUCB2), is expressed in the CNS, including the hypothalamus and hindbrain, and colocalizes with PVN oxytocin neurons [11]. It activates magnocellular and pPVN oxytocin neurons [11], increases the release of PVN oxytocin [11] and inhibits food intake through an oxytocin dependent mechanism [139]. Recent studies show that, similar to oxytocin, it inhibits food intake through a central [11, 139] and peripheral route of administration [168]. It remains to be determined if nesfatin-1, like oxytocin, is also capable of activating PVN oxytocin neurons when given by a peripheral route of administration.

OEA OEA, which is produced in small-intestinal enterocytes following dietary fat absorption, inhibits feeding via peroxisome proliferator-activated receptor-alpha (PPAR-alpha) and the release of oxytocin [52]. OEA increases Fos mRNA in the PVN, increases oxytocin mRNA in both PVN and SON, and increases plasma oxytocin [52]. While these studies suggest that oxytocin is downstream of PPAR-alpha, recent studies indicate that a single dose of oxytocin fails to inhibit food intake in PPAR-alpha KO mice [8]. Together, these studies suggest that PPAR-alpha and oxytocin may reciprocally regulate one another, but additional dose–response studies would be helpful to confirm these findings.

PPAR-gamma coactivator (PGC)-1 alpha Mice that lack the transcriptional coactivator, PGC-1 alpha, develop adult-onset obesity [169], similar to what is observed in OXTR [56], oxytocin null mice [105], and MAGED1 deficient mice [57]. PGC-1 alpha is coexpressed with oxytocin in the zebrafish hypothalamus [170] and forms a complex that contains PGC1-alpha and the oxytocin promoter [170] in fed, but not fasted zebrafish [170]. Moreover, PGC-1alpha overexpression increases the expression of oxytocin in muscles and neurons [170] and reductions in PGC-1 alpha also decrease oxytocin mRNA [170] suggesting that PGC1-alpha contributes to oxytocin synthesis.

5 Oxytocin as a downstream target of orexigenic signals

5.1 Inhibition of oxytocin neurons by orexigenic signals

Agouti-related protein (AGRP) Recent advances in optogenetics and electrophysiology have determined that AGRP fibers appear to contact PVN oxytocin neurons [171] and that AGRP stimulates food intake by inhibiting these neurons [171]. This can be reversed with bilateral cophotostimulation of PVN oxytocin neurons and ARC-PVN AGRP axonal projections [171].

Opioids Previous studies have shown that opioid receptors are expressed on PVN and SON oxytocin neurons [172] and that opioid agonists can inhibit further activation of PVN oxytocin towards the end of a meal [73]. The ability of oxytocin to stimulate CCK-8 release in the SON is inhibited by morphine [75]. The effectiveness of LiCl to induce Fos in PVN and SON oxytocin neurons is also inhibited by opioids [173]. Olszewski and colleagues also show that opioid-induced inhibition of oxytocin signaling is particularly evident when a diet high in sugar is administered [73]. Interestingly, others have also shown this to occur during periods of hyperphagia in mid to late pregnancy [174, 175], but sex steroids (e.g. progesterone) may play a more predominant role in the inhibition of oxytocin neurons during pregnancy [22].

SYT4 Work from Zhang and colleagues demonstrate that lentiviral expression of SYT4 into the PVN of SYT4 null mice results in impaired release of oxytocin within the PVN, increased HFD intake and body weight gain in DIO animals [13]. While these findings reveal another important negative regulator of oxytocin regulation in the control of food intake and body weight, remaining issues to address are whether SYT4 is expressed on pPVN neurons that project to the NTS and the extent to which SYT4 is regulated by leptin and MTII. In addition to alterations in oxytocin signaling being an important downstream effector of both anorexigenic and orexigenic signals, recent studies have identified potential downstream intracellular signals and CNS targets that underlie the effects of oxytocin.

6 Potential downstream NTS targets that contribute to the effects of oxytocin on food intake and body weight

It is well appreciated that endogenous oxytocin acts, in part, through OXTRs in the NTS to inhibit food intake through a reduction in meal size [8, 10, 11, 40, 41, 55, 88, 89, 130, 176]. Some of the outstanding questions in the field are as follows: What are the potential signals and downstream targets that contribute to these effects? To what extent does activation of OXTRs in forebrain areas contribute to the inhibition of food intake? To what extent does systemic administration of oxytocin inhibit food intake through a mechanism that requires OXTRs in the CNS?

6.1 Potential OXTR signaling mechanism (s) in NTS

NTS receptors Recent electrophysiological data show oxytocin excites NTS neurons through both a postsynaptic [177] as well as a presynaptic mechanism involving release of glutamate and subsequent activation of NTS neurons through 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid receptors (AMPA) [177]. These findings extend

immunocytochemical data that show central [40, 123, 155] and peripheral [10, 12, 14, 77, 151] administration of oxytocin induces Fos largely in the caudal NTS (cNTS) where OXTRs are expressed [28–30].

Potential intracellular signals in NTS Stimulation of PVN OXTRs leads to transactivation of the epidermal growth factor receptor and activation of a MEK-extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAP kinase) pathway [34]. Ingestion of food increases Erk1/2 phosphorylation in PVN oxytocin neurons [41]. Although it remains to be determined if ERK signaling in the NTS mediates the effects of oxytocin to reduce food intake, ERK signaling in this site contributes to the ability of CCK-8 to inhibit food intake [178]. Further studies are required to determine if ERK signaling also contributes to the ability of oxytocin to enhance the satiety response to CCK [88, 89].

6.2 cNTS A2 NA neurons

cNTS NA neurons are activated by visceral afferents [82], gastric distension [126], PYY(3–36) [179], nicotine [180], high protein meals [181], CCK-8 [82, 182], and oxytocin [183–185]. Oxytocin fibers that originate from the pPVN are found in anatomical proximity to NTS NA neurons [186]. Previous findings indicate that oxytocin contributes to the satiety response to CCK-8 [89, 91] and to the ability of leptin to enhance the hindbrain neuronal response to CCK-8 [55]. Previous data that show a) CCK-8 activates NTS NA neurons [82, 182] via a presynaptic mechanism involving release of glutamate [82]; b) the satiety response to CCK-8 is attenuated in rats with cNTS NA lesions [83]; c) cNTS NA neurons are potential downstream targets of leptin and CCK-8 [187], and d) CCK-8 increases ERK1/2 expression in cNTS NA neurons [188]. Together, these findings raise an intriguing possibility that cNTS NA neuronal signaling through ERK1/2 contributes to the ability of oxytocin to inhibit food intake. Interestingly, in mice, cNTS NA neurons do not appear to be a direct target of leptin action [189], which may represent a species difference with respect to downstream targets of leptin action or that NTS NA neurons are indirect targets of leptin action in both species. Regardless, these findings raise the possibility that NTS NA neurons contribute to the ability of oxytocin to inhibit food intake by enhancing the satiety response to CCK-8.

6.3 Do NA projections from the cNTS to PVN contribute to oxytocin-elicited anorexia?

Both CCK-8 and oxytocin induce Fos in PVN oxytocin neurons. CCK-8-elicited activation of PVN oxytocin neurons appears to occur through ascending NA innervation of the PVN from the A2 region of the cNTS [95, 127] (Fig. 1) as lesions of cNTS NA neurons blunt the ability of CCK-8 to

activate PVN oxytocin neurons [83]. Furthermore alpha-1 adrenoceptor activation in the PVN is associated with reductions in food intake [190, 191] and alpha-1 adrenoceptor 1D mRNA is expressed on PVN oxytocin and corticotrophin-releasing hormone (CRH) neurons [192]. Further studies need to address whether oxytocin activates PVN neurons that express alpha-1 adrenoceptor 1D subunits and determine the extent to which reductions in alpha-1 adrenoceptor signaling in the PVN contribute to the effects of oxytocin to inhibit food intake.

6.4 cNTS PrRP

The majority of cNTS NA neurons express PrRP [193] (reviewed in [85]), a peptide found to suppress food intake [84, 194]. Recent findings show that PrRP receptors are expressed on both magnocellular and pPVN oxytocin neurons [18]. In addition, the ability of refeeding (following a 24-h fast) and CCK-8 to activate PVN oxytocin neurons and increase circulating oxytocin is suppressed in PrRP-deficient mice [18]. Furthermore, the effects of leptin [195] and CCK-8 [84] to reduce food intake are impaired in PrRp-deficient mice, which likely contributes to PrRp-deficient mice having increased meal size [195]. Similar to OXTR [56], oxytocin null mice [105], and MAGED1 deficient mice [57] both PrRp [195] and PrRP receptor deficient mice [196, 197] develop late onset-obesity. Further studies need to determine the extent to which reductions in PrRP receptor signaling in the PVN impair the ability of oxytocin to inhibit food intake.

6.5 cNTS GLP-1 neurons

CNS GLP-1 derives predominantly from posttranslational processing of preproglucagon (PPG) in the NTS. NTS GLP-1 neurons, which are distinct from NA (and PrRP) neurons [198–200], are activated by vagal afferents [201], leptin [201], gastric distension [202], CCK-8, noradrenaline, adrenaline [81], and oxytocin [40]. NTS oxytocin fibers are found in anatomical proximity to NTS GLP-1 neurons [40], and central administration of oxytocin induces Fos in NTS GLP-1 neurons [40]. Furthermore, ICV administration of the GLP-1 receptor (GLP-1R) antagonist (des His1 Glu9-exendin 4) attenuates the ability of oxytocin to reduce food intake [40]-findings which raise the possibility that local release of GLP-1 in the NTS or via ascending projections to the forebrain may contribute to these effects.

6.6 Which GLP-1 neuronal projections potentially contribute to oxytocin-elicited anorexia?

NTS GLP-1 neurons provide a source of GLP-1 within the cNTS [201, 203], but they also project to numerous sites in the forebrain, all of which express OXTRs, including the ARC [203], dorsomedial hypothalamus (DMH) [203], PVN [203]

(Fig. 1), VTA [92] and NAc [92, 94] (Fig. 1; see 2.4). Of these possibilities it appears that activation of GLP-1Rs in the PVN or NTS most likely to contribute to oxytocin elicited anorexia. For instance, GLP-1 inhibits food intake following administration into the PVN [204], where GLP-1Rs are expressed on PVN oxytocin neurons [205]. Furthermore, GLP-1 fibers are also in anatomical proximity to PVN oxytocin neurons [198] and CNS administration of GLP-1 [206] recapitulates the effects of oxytocin to induce Fos in PVN oxytocin neurons [77, 151] although this effect may also occur through a direct action of oxytocin on autoreceptors on PVN oxytocin neurons [207]. Within the NTS, GLP-1R agonists and antagonists inhibit and stimulate food intake, respectively [97]. As discussed earlier, ICV administration of oxytocin elicits Fos in NTS GLP-1 neurons [40]. Although the ARC receives GLP-1 projections [203] and expresses Fos in response to oxytocin [10], GLP-1Rs in the ARC appear to be principally involved with regulation of glucose homeostasis [208], as GLP-1R agonists fail to reduce food intake following administration in this area [208]. GLP-1 also inhibits food intake following administration into the DMH [209], which receives GLP-1 projections [203], but oxytocin fails to elicit Fos in this area [10]. Further studies need to address whether a) oxytocin activates GLP-1R in the PVN; b) reductions in GLP-1R signaling in the PVN and NTS impair the ability of oxytocin to reduce food intake, and c) oxytocin inhibits food intake in transgenic mice with specific ablation of OXTRs in NTS GLP-1 neurons [210].

6.7 cNTS POMC neurons

NTS oxytocin terminals are in anatomical proximity to NTS POMC neurons, oxytocin evokes the release of intracellular Ca^{2+} from NTS POMC neurons, and third ventricular (3 V) administration of SHU9119 blocks the effects of oxytocin to inhibit feeding [11]. Both hindbrain melanocortin [87] and oxytocin signaling [88, 89] contributes to the ability of CCK-8 to reduce food intake. Furthermore, CCK-8 increases ERK1/2 expression in NTS POMC neurons [188], and this effect is abolished following hindbrain MC3/MC4R blockade [211]. While it still remains to be determined whether activation of ERK1/2 signaling through NTS POMC neurons is required to mediate the effects of OXTR signaling in the NTS, ERK is a downstream intracellular signal induced by ingestion of food in PVN oxytocin neurons [41]. Together, these findings suggest that activation of ERK1/2 in NTS POMC neurons may contribute to the effects of oxytocin to suppress food intake.

7 Oxytocin as a potential therapeutic target?

Given the uncertainties to the extent to which systemic oxytocin targets OXTRs in the CNS, one of the benefits to the use

of oxytocin as a potential therapeutic agent is that oxytocin is one of the few hormones that can stimulate its own [77, 151, 212, 213] release via autoreceptors in the magnocellular SON [212, 213] and PVN [207] following a central or peripheral route of administration. CNS administration of oxytocin upregulates PVN oxytocin mRNA expression [8] and systemic administration of oxytocin activates PVN oxytocin neurons [77, 151] and stimulates release of oxytocin in the PVN [14]. Long-term changes in function [214] may be linked to this mechanism of stimulation [215, 216]. During parturition, oxytocin concentrations in the CSF are as high as levels in the periphery and likely remain high as a result of the reduced clearance in brain ($T_{1/2}$=19 min; [152]) vs. periphery ($T_{1/2}$= 6 min; [217]). The prolonged bioavailability of CNS oxytocin in combination with its self-stimulatory properties are thought to contribute, in part, to its positive effects on prosocial behavior [207] and may contribute to its prolonged effects on body weight loss following cessation of treatment [10] .

The fact that oxytocin inhibits food intake in DIO rats with impaired leptin signaling [8, 10, 12–14] and in animal models with defective leptin signaling, such as the obese Zucker [11] and Koletsky rats [12], as well as obese animals with Sim1 haploinsufficiency [9] make it an attractive therapeutic target in both DIO and genetic models of obesity. To date only one paper reports tolerance in the effectiveness of ICV administration of a potent oxytocin agonist [e-L- β-MePhe^2]oxytocin to reduce food intake over 3 days [39]. Importantly, these effects do not appear to interfere with its ability to reduce body weight as chronic administration of oxytocin over 14–17 days produces sustained reductions in body weight [8, 10] raising the question as to how long this weight loss could be maintained. Recent findings in DIO mice show that chronic administration of oxytocin produced a sustained loss in body weight loss over a 6-week period [14]. This is particularly exciting given that other substances, such as exendin-4, typically fail to maintain body weight loss after 17 days [218]. Of obvious clinical significance are findings that indicate oxytocin reduces anxiety [219], blood pressure [220], the size of cardiac infarcts [221], and is not causally related to the development of a CTA [222] in rats. Moreover, CNS [13] administration of oxytocin fails to elicit a CTA at doses that suppress food intake and body weight in rodents [12, 14, 36].

While it remains to be determined whether chronic systemic administration of oxytocin reduces body weight in the absence of unwanted peripheral side effects in women (e.g. uterine cramping), the intranasal route of administration appears to effectively allow oxytocin to access the CNS in mice, rats, nonhuman primates and humans within 30–35 min after administration [154, 223, 224] without causing unwanted side effects [225]. In humans, intranasal administration of vasopressin (structurally similar to oxytocin) reaches the CSF within 10 min and levels are maintained for at least 80 min

following administration [226]. One uncertainty is the extent to which these levels reflect exogenous oxytocin and/or endogenous oxytocin release following stimulation of hypothalamic oxytocin neurons that project within the CNS. Another uncertainty is whether intranasal delivery restricts oxytocin to the CNS as the increase in plasma oxytocin levels could result from either direct entry of intranasal oxytocin into the circulation or oxytocin-elicited autostimulation of hypothalamic oxytocin neurons that project to the posterior pituitary. One means to circumvent direct entry of drugs into the circulation without altering concentrations in the CSF is to include a vasoconstrictor such as phenylephrine in the intranasal treatment [227]. Regardless, this route of administration has yielded positive prosocial effects in nonhuman primates [223], male and female schizophrenics [228, 229], and in men and women who experience social rejection [230]. The added benefit of potentially ameliorating obesity and its related complications only adds to the excitement surrounding oxytocin as a potential therapeutic strategy in humans. While rodent and limited nonhuman primate and human studies are encouraging thus far, OXTRs have the capacity to interact with and modulate other GPCRs such as the β2 adrenergic receptor [231], and multi-drug therapies may need to be considered to maximize the benefits of targeting the oxytocin signaling pathway [232]. Caution should be used prior to administration in children and young adults as some studies suggest that behavioral deficits occur in response to chronic administration in developing prairie voles [233]. Additional studies should continue to address the long-term neuroendocrine and behavioral effects following multiple doses in developing animals [233, 234].

8 Conclusions

It is clear that disruptions in oxytocin signaling contribute to obese phenotypes through what appear to be impairments in both food intake and energy expenditure. It remains to be determined whether such disruptions in oxytocin signaling are critical to causing and/or maintaining the obese phenotype in DIO. While there is tremendous excitement over the potential use of oxytocin as a therapeutic agent, we await the results of ongoing human trials for further confirmation of its effectiveness as a weight loss strategy in the absence of unwanted side effects. It is clear that there are several means by which oxytocin, given centrally or peripherally, can influence body weight, namely through reductions in food intake, increases in energy expenditure, and lipolysis. In light of the finding that oxytocin is synthesized in the GI tract, and the observation that peripheral administration can stimulate the release of CNS oxytocin, additional studies are required to address the relevance of peripheral stores of oxytocin on energy balance and whether activation of CNS

oxytocin circuitry is, in fact, required to maximize its therapeutic potential when given systemically.

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