Translational and therapeutic potential of oxytocin as an anti-obesity strategy: Insights from rodents, nonhuman primates and humans

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Abstract

The fact that more than 78 million adults in the US are considered overweight or obese highlights the need to develop new, effective strategies to treat obesity and its associated complications, including type 2 diabetes, kidney disease and cardiovascular disease. While the neurohypophyseal peptide oxytocin (OT) is well recognized for its peripheral effects to stimulate uterine contraction during parturition and milk ejection during lactation, release of OT within the brain is implicated in prosocial behaviors and in the regulation of energy balance. Previous findings indicate that chronic administration of OT decreases food intake and weight gain or elicits weight loss in diet-induced obese (DIO) mice and rats. Furthermore, chronic systemic treatment with OT largely reproduces the effects of central administration to reduce weight gain in DIO and genetically obese rodents at doses that do not appear to result in tolerance. These findings have now been recently extended to more translational models of obesity showing that chronic subcutaneous or intranasal OT treatment is sufficient to elicit body weight loss in DIO nonhuman primates and pre-diabetic obese humans. This review assesses the potential use of OT as a therapeutic strategy for treatment of obesity in rodents, nonhuman primates, and humans, and identifies potential mechanisms that mediate this effect.

Keywords

Obesity; Food intake; Energy expenditure; Oxytocin

1. Source and functions of oxytocin

The obesity epidemic and its associated complications [1–3] have become major health concerns [4]. Health care costs to treat obesity were projected to be nearly 147 billion dollars in 2008 [5]. Obesity affects approximately 78 million adults and 12.5 million

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children and adolescents in the US alone [6]. These estimates are attributed, in part, to increased dietary intake of high fructose corn syrup and sugar [7–9] which is linked with the development of metabolic abnormalities characteristic of metabolic syndrome (e.g. dyslipidemia, weight gain, and visceral fat) in humans [7–12] and diet-induced obese (DIO) nonhuman primates following long-term exposure to high fructose diet [13]. The resulting defects in the secretion of [14] and/or response [15–17] to peripheral satiety signals following prolonged maintenance on high fat or high fructose diets are hypothesized as underlying factors in the increased rise of obesity. However, current weight loss therapies are largely unsuccessful and there is an increased need for more effective treatments for this growing epidemic and associated complications.

While the neurohypophyseal peptide oxytocin (OT) is well recognized for its role in lactation [18], uterine contraction [19], osmoregulation [20], and prosocial behavior [21,22], it has attracted interest as a therapeutic strategy to treat schizophrenia [21,23], autism spectrum disorder [21,22,24,25], and obesity [26–35]. Currently, almost 400 completed, ongoing, or future funded investigations in humans list OT in pre-clinical trials to reduce caloric intake, gastric emptying, and obesity in addition to other conditions (ClinicalTrials.gov registry, National Institutes of Health). Taking into consideration the increased prevalence of obesity combined with the relatively modest effects of existing weight loss therapies, this review focuses on timely findings that assess efficacy of OT treatment for decreasing food intake and body weight in diet-induced [27,28,30–32] and genetically obese rodents [28,30,36,37] as well as in DIO nonhuman primates [26] and obese humans [33,34]. We also discuss the potential mechanisms involved in mediating these effects.

OT is synthesized predominantly by neuronal cell bodies that are located in the parvocellular division of the paraventricular nucleus (PVN) as well as the magnocellular neurons of both the PVN and the supraoptic nucleus (SON) in rodents [38–42], nonhuman primates [43–46] and humans [47–51] (for review see [52,53]). OT is also expressed to a lesser degree in a few other forebrain areas (e.g. bed nucleus of the stria terminalis medial preoptic area (MPA), anterior hypothalamus, medial amygdala, and subzona incerta) [54,55]. OT is released from somatodentrites within the SON and PVN, as well as distally at synaptic terminals on axons that originate from magnocellular PVN and SON projections to the neurohypophysis, as well as parvocellular PVN projections to CNS areas which include the arcuate nucleus (ARC) [56], ventral tegmental area (VTA) [57], nucleus of the solitary tract (NTS) [38,39], and spinal cord [39]. Recent evidence suggests that magnocellular PVN and SON OT neurons also project to the ARC [56] (see Fig. 1). OT is also synthesized in the periphery [58], including the gastrointestinal (GI) tract in rodents and humans [59,60]. Previous findings reveal that the GI tract [61] and nodose ganglion [60] in rodents as well as adipocytes in both rodents and humans [62–68] express oxytocin receptors (OTRs). The potential role(s) of OTR signaling through adipocytes, the GI tract, or vagal sensory afferent nerves in the control of energy balance is discussed in Sections 7 and 8.

2. OTR distribution in CNS areas linked to energy balance in rodents, nonhuman primates and humans

There is a wide distribution of OTRs in areas linked to the control of energy balance in rodents, including the basal ganglia (e.g. nucleus accumbens and central amygdala), hypothalamus [e.g. ARC, MPA, PVN, SON, and ventromedial hypothalamus (VMH)], midbrain (e.g. VTA), hindbrain [e.g. dorsal motor nucleus of the vagus (DMV), NTS or area postrema (AP)] [52,69–71], and spinal cord [72]. In contrast to rodents, there is a more restricted distribution of OTRs in areas linked to energy balance in nonhuman primates (e.g. nucleus accumbens, preoptic area, VMH, DMV, and spinal cord) [73–75] and humans (e.g. central amygdala, anterior hypothalamus, MPA, PVN, VMH, AP, NTS, and spinal cord) [76–78]. Limitations with respect to specificity of pharmacological tools and/or antibodies may preclude drawing definitive conclusions about species differences. However, the similarity in patterns of OTR expression implicates important roles of discrete nuclei within the basal ganglia, hypothalamus, hindbrain and spinal cord in regulating body weight that are well conserved across species.

3. Role of OT signaling in energy balance

Existing data indicate that OT plays a critical role in the control of energy homeostasis [26–28,30–32,34–36,56,62,79–89]. For example, global deficiencies in either OT [90] or OTRs [91] are associated with adult-onset obesity in mice. Furthermore, copy number variations linked with the OTR gene *(OXTR)* are associated with an extreme early-onset obesity phenotype in humans [92]. Moreover, DIO mice exhibit defects in OT release within the hypothalamic PVN [31] which may, in turn, contribute to the corresponding reductions in circulating OT displayed by these animals [31], Zucker rats [64], *db/db* mice [93]), as well as obese humans and individuals with type 2 diabetes [94]. However, the reductions in circulating OT are not necessarily observed across all rodent models of obesity, for reasons that are not entirely clear, as circulating levels in DIO rats and *ob/ob* mice are, in fact, not decreased relative to their respective lean counterparts [30,62]. In some cases, OT levels are increased in certain obese rat models [95–98] as well as in obese humans [99] but are reduced following chronic pair-feeding in rats [97] or gastric banding-associated weight loss in humans [99]. In addition, other apparent inconsistencies arise in certain pathological states of energy deficit in humans where it has been shown that nocturnal levels of OT are reduced in both anorexia nervosa [100] and amenorrhea [101]. Whether these are considered adaptive or contributing factors in the development of anorexia nervosa remains to be determined [100]. OT levels are, however, positively correlated with body weight, body fat, and resting energy expenditure in amenorrheic athletes which may implicate a potential role of OT in the regulation of energy expenditure in certain states of energy deficit [102]. However, the pathogenesis of Prader-Willi syndrome, a genetic disorder that afflicts up to 350,000–400,000 humans in the world [103] is characterized by hyperphagia and severe obesity and linked to a reduced number and size of PVN OT neurons [104], suggesting that a reduction in OT secretion within the CNS and/or periphery, in some circumstances, may be pathogenic and contribute to obesity. Existing data show that both acute administration and chronic administration of OT are sufficient to circumvent the effects of impaired or defective

leptin signaling to decrease body weight gain in DIO [27,28,30–32] and genetically obese rodent models [29,30,36,62,93,105] as well as in DIO nonhuman primates [26] and obese humans [33]. Collectively, these findings suggest that OT plays a principal role in energy balance, although the mechanisms contributing to these effects have not been fully established.

4. Intact response to OT despite impaired leptin signaling

OT-elicited decreases in food intake likely contribute to its effectiveness in reducing body weight (or attenuating weight gain) in rodents and nonhuman primates [26]. The finding that OT dose-dependently reduces food intake, whether administered systemically, intranasally or directly into the central nervous system (CNS), is well documented [27–30,36,56,62,79,80,83,84,86,88,105–109]. While many such investigations have targeted the lateral, third, and fourth ventricles, the data show that OT reduces food intake following administration directly into the ARC [56], VMH [108], VTA [107] and NTS [88]. All of these sites express OTRs and many also receive OT projections from the PVN or SON (see Fig. 1). Moreover, central and/or systemic administration of OT inhibits food intake in mice and rats with impaired (e.g. DIO models) [27,28,30–32] or defective leptin signaling (e.g. obese Zucker rat [29], Koletsky rat [30], *ob/ob* mice [62], and *db/db* mice [105]), as well as in obese mice with Sim1 haploinsufficiency [36]. Furthermore, central or systemic administration of OT reduces food intake without increasing pica consumption (marker of visceral illness) or eliciting a conditioned taste aversion in mice [31,105] or rats [108]. Collectively, these findings suggest that OT signaling is potentially an attractive therapeutic target in both DIO and genetic models of obesity.

In addition to suppressing consumption of low fat/high carbohydrate diets, including standard rodent [27–32,36,56,62,79,80,83,84,88,106,109,110] and monkey chow [26], acute or chronic central or systemic administration of OT also reduces consumption of sucrose [107], fructose-sweetened beverages [26], intraoral glucose [86], as well as high fat diets (HFDs) in mice, rats, or nonhuman primates [27,28,30–32]. These findings may also translate to humans as intranasal OT appears to reduce consumption of fat in a limited number of subjects although statistical significance was lost after adjusting for multiple comparisons [34]. It is worth noting that the HFDs used in some of these studies (D12331, D12451 or D12492; Research Diets Inc., New Brunswick, NJ or HFD32; CLEA Japan, Inc., Tokyo, Japan) contained between 6.7 and 17% kcal from sucrose [27–28,30–32], which may have contributed to the effectiveness of OT to reduce food consumption on the HFDs. Conflicting with previous pharmacological studies, however, is a report that incorporated the Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) technology in which Cre recombinase-dependent adeno-associated virus (AAV)-hM3Dq was administered bilaterally into the PVN of mice. These investigators administered clozapine-N-oxide (CNO) to activate PVN OT neurons in *oxytocin-Ires-Cre* mice [89], but this intervention failed to result in decreased consumption of chow relative to vehicle treatment. These findings raise important questions as to whether a) CNO-elicited activation of PVN OT neurons results in an anorexigenic response when administered during the light cycle at a time that coincides with the diurnal rhythmicity of circulating [32] or cerebrospinal fluid levels of OT [111] and

b) the response varies with respect to energy status (fasted vs. ad libitum fed), or diet (chow, high fat or high fat/high sucrose diet).

While PVN OT neurons are downstream targets of melanocortin 4 receptor (MC4R) signaling in rats [110,112] and mice [113], the extent to which MC4R signaling directly impacts PVN OT neurons controlling food intake is unclear. Optogenetic stimulation of PVN OT neurons suppresses the feeding response evoked by photostimulation of orexigenic agouti-related protein (AGRP) neurons, but photostimulation of PVN OT neurons alone fails to inhibit refeeding following a 24-h fast in mice [114]. While it will be important to determine if optogenetic activation of PVN OT neurons is sufficient to elicit release of OT from long axonal projections to the hindbrain [115,116], these findings are, however, consistent with what appears to be a relatively minor role of PVN OT neurons to suppress the refeeding response following a prolonged fast in rats [117]. Shah and colleagues demonstrated that reexpression of MC4Rs in PVN OT neurons in *oxytocin-Ires-Cre;Mc4R^{loxTB}/^{loxTB}* mice failed to attenuate the obesity phenotype in MC4R null MC4R^{loxTB}/^{loxTB} mice [118]. These findings suggest that direct MC4R signaling through PVN OT neurons may not be required to regulate body weight in mice. Alternatively, MC4R-expressing interneurons that in turn project to PVN OT neurons may be more important in regulating body weight in mice.

Impairments of OT signaling have been associated with increased consumption of carbohydrate-rich chow [31,32,36,79,80,82,106,119,120], sucrose [107,121–124], fructose [122], and glucose [86,122], as well as fat [31,32] in mice or rats, implicating a physiological role of endogenous OT to reduce intake of fat and sugar. While consistent with studies showing that ingestion of sucrose and intralipid stimulates Fos (marker of neuronal activation) in PVN OT neurons [123], disruptions in OT signaling, however, do not consistently lead to increased consumption of chow, sucrose, and HFDs. For example, OTR null mice and mice without OTRs in specific forebrain areas (e.g. lateral septum, ventral pallidum, and hippocampus) do not consume more sucrose relative to wild-type mice [125]. However, since the extent to which OTRs were deleted from CNS areas linked to the control of body weight (e.g. hypothalamus) was unknown, it is not clear whether compensatory up-regulation of OTRs in extra-hypothalamic areas such as the hindbrain and periphery may have contributed to these effects. It is also possible that these effects may be attributed to up-regulation of the structurally similar peptide, vasopressin, or vasopressin 1a receptor, both of which are linked to the control of body weight [126–129]. Furthermore, OTR and OT null mice fail to consume more chow relative to wild-type or littermate control mice [90,91,121]. Studies indicate that OTR null mice still consume larger meals during the dark cycle [130] despite showing no change in overall chow intake. In addition, removal of approximately 95% of PVN OT neurons following Cre-mediated diphtheria toxin administration in adult *oxytocin-Ires-Cre* mice failed to impact intake of chow or HFDs [87]. However, caution should be exercised when interpreting these latter findings as they could have been influenced by loss of other neurotransmitters or neuromodulators expressed by PVN OT neurons. Additional work needs to address the potential influence of gliosis in OT projection sites as contributing to these effects [131]. Moreover, variable experimental outcomes on food intake maybe related to different genetic strain backgrounds [123] or site specific developmental changes in OT [132] or OTR expression [52,132,133] that may be associated

with length of diet exposure [68] or age [52,68,132,133] in these mice at the time when potential impairment in PVN OT signaling was initiated.

5. Effects of OT on energy expenditure

In addition to suppressing food intake, OT may also elicit weight loss in rodents and nonhuman primates by stimulating energy expenditure and lipolysis. Indirect evidence from pair-feeding studies in mice and rats, where the amount of weight loss following OT exceeds that of pair-fed control animals [27,30,62], implicates increased energy expenditure and possibly lipolysis as contributing to negative energy balance and weight loss (see Fig. 1).

Decreases in OT signaling have been shown to be associated with obesity and reductions in energy expenditure [32,87,90,91,134], including defects in sympathetic nervous system activity, brown adipose tissue (BAT) thermogenesis [90,91,134], and oxygen consumption [32,87], in the absence of hyperphagia in mice [87,90,91,121,130]. In contrast, direct injections of OT into the CNS increased energy expenditure [31,32,108], body temperature [71], and heart rate [71,135] in mice or rats. In addition, chronic subcutaneous administration of OT increased energy expenditure in DIO nonhuman primates [26] but failed to stimulate energy expenditure when given acutely by intranasal administration into humans [34,35]. It may be that, in humans, acute administration of OT impacts food intake at doses subthreshold for eliciting changes in energy expenditure. Future studies should determine whether chronic intranasal administration of OT recapitulates the effects of chronic subcutaneous administration to stimulate energy expenditure in DIO nonhuman primates [26] and whether these effects translate to obese humans. Sutton and colleagues demonstrated that acute CNO-induced activation of PVN OT neurons in *oxytocin-Ires-Cre* mice increased Fos in thoracic sympathetic preganglionic neurons in the spinal cord [89]. OT also activated thoracic sympathetic preganglionic neurons in the cat [136] as well as the stellate ganglia in the dog [137]. The well-defined polysynaptic projections from the OT neurons in the PVN to interscapular BAT (IBAT) [138] and stellate ganglia [139] as well as both polysynaptic [138] and monosynaptic projections to spinal cord [39] in rats, strongly suggest the possibility that OT may have a physiological role in regulating sympathetic nervous system activity. In addition to a role of PVN OT neurons, it is likely that OT neurons located outside the PVN are important in stimulating BAT. OT is also expressed in the subzona incerta in Siberian hamsters [55], a CNS region with robust sympathetic innervation of IBAT [140]. It will be exciting to determine the extent to which stimulation of subzona incerta OT neurons increases BAT thermogenesis in a mouse model.

Thus, the ability of OT to stimulate energy expenditure appears to contribute to its effectiveness in eliciting weight loss and reductions in weight gain, although the location of OTR populations that mediate these effects remains to be determined. Acute CNO-elicited activation of PVN OT neurons in *oxytocin-Ires-Cre* mice increased energy expenditure as well as activity and also tended to increase IBAT temperature ($P = 0.13$) relative to vehicle [89], which may implicate OTR populations in the PVN, VTA, NTS, or spinal cord. OT injections into the median raphe increase both heart rate and body temperature [71] supporting a role of OTRs in this region in the regulation of energy expenditure. In addition, direct VMH injections of OT also stimulate energy expenditure in rats [108]. In addition,

adeno-associated viral expression of OTRs into the VMH/dorsomedial hypothalamus (DMH) of OTR null mice corrected defects in β3- and α2-adrenceptor mRNA expression in IBAT and rescued deficits in cold-induced thermogenesis [134], providing additional evidence that OTRs in the DMH/VMH are associated with the regulation of energy expenditure. In addition to potential functions in either the VMH or DMH, OT may also stimulate sympathetic nervous system activity via polysynaptic projections from OTR-expressing premotor NTS neurons to IBAT [39,138,139]. It will be important to address the extent to which ablation of OTR populations in the hypothalamus, midbrain, hindbrain, and spinal cord reduces energy expenditure and predisposes animals to diet-induced obesity.

Several reports have shown that persistent reductions in food intake and body weight result in reductions in energy expenditure in both animal models [141] and humans [142–144]. However, despite the persistent weight loss and reductions in food intake, chronic CNS [27] or systemic OT treatment [28,30] is not associated with a reduction in energy expenditure in DIO mice or rats, observations that we have confirmed. While a control group that lost a comparable amount of body weight to that of an OT-treated group was not examined in these studies in mice or rats [27,28,30], these findings raise the possibility that, in rodent models, sustained OT treatment may also prevent the reduction in energy expenditure associated with weight loss.

Existing data support a potential role of OT to stimulate the transformation of white adipose tissue (WAT) to the more metabolically active "brite" or "beige" adipose tissue, a process termed "browning" [145]. For example, chronic subcutaneous administration of OT appeared to increase the number of uncoupling protein-1 (+) cells in the subcutaneous and visceral fat of obese *db/db* mice [93]. However, the data were not quantified in this study and it is not clear to what extent these findings may translate to rodent models of DIO. In addition, Lawson and colleagues demonstrated that OT secretion in amenorrheic athletes is positively correlated with resting energy expenditure as well as fibroblast growth-factor 21 (FGF-21) and irisin [102], two factors that induce the conversion of WAT to the "brite" or "beige" adipose tissue [146–148]. OT could potentially elicit "browning" through a direct effect on adipocytes [65–67], where OTRs are expressed in both inguinal [63] and epididymal fat [62–65] as well as indirectly through outgoing polysynaptic sympathetic nervous system projections from the PVN to inguinal [149] and epididymal fat [149,150]. These findings support an important role for OT in regulating energy expenditure and raise the question as to what extent weight loss attributed to chronic increases in CNS OT is associated with "browning" of WAT.

6. Gender specific effects of OT on regulation of body weight?

The majority of published data has focused on the role of OT on energy homeostasis in male animal models. Thus, it is not clear if OT has gender specific effects on the regulation of body weight. OT reduces food intake and weight gain in obese female Sim1 haploinsufficient mice [36] and elicits weight loss in obese men and women [33]. There are also mixed results from the limited number of studies that have examined the impact of global loss of either OT or OTRs on body weight. Both male and female OT null mice develop obesity to a similar extent [90] whereas only male but not female OTR null mice

develop obesity [91]. Similarly, selective ablation of PVN OT neurons results in predisposition to HFD-elicited obesity in male but not female mice [87]. Thus far, existing data from genetic loss of function studies have done little to clarify potential gender specific effects of OT on regulation of energy homeostasis. If OT is to be considered for anti-obesity therapy, future studies should address the gender specific effects of chronic OT on weight loss in male and female animal models, including nonhuman primates and humans.

7. Effects of OT on lipolysis and impact on fat mass

OT increases free fatty acids and glycerol and/or reduces triglycerides in cultured 3T3-L1 adipocytes [27,68], rats [27] and DIO nonhuman primates [26]. These findings suggest that OT may reduce body weight by increasing lipolysis, perhaps through a direct action on adipocytes [65–67], which express OTRs [62–68], or from an indirect action via outgoing polysynaptic sympathetic nervous system circuits from the PVN to both inguinal WAT [149] and epididymal WAT [149,150]. OT also increases epididymal WAT expression of hormone sensitive lipase (an enzyme linked with lipolysis) [27,62] and reduces expression of fatty acid synthase (an enzyme linked to lipogenesis) in rats [62], the latter suggesting that OT may also inhibit lipogenesis. Triglycerides also appeared to be lower following chronic intranasal OT in a limited number of pre-diabetic obese humans but these effects were not statistically significant [33]. Furthermore, chronic OT central or systemic infusions *in vivo* result in decreases in fat mass in mice and rats [27,28,30,32,62,93], including the adipocyte area from mesenteric [28], epididymal [28,62,151], subcutaneous [93], perirenal [93] and epicardiac [93] fat depots. Importantly, chronic central or systemic administration of OT reduced fat mass in lean or DIO rats [27,30], DIO C57Bl/6 mice [32], *db/db* mice [93] and *ob/ob* mice [62] without reducing lean mass [27,32,62,93]. In contrast, one study reported that chronic systemic OT reduced lean mass in lean C57Bl6/J mice, although this was unexpected [62] and the mechanisms underlying these effects are unclear. Chronic central or systemic OT infusions are also associated with reductions in the respiratory quotient in DIO mice [28] and rats [27] relative to either vehicle treatment [27,28] or pair-fed control animals [27]. Recent findings indicate that intranasal OT also reduces respiratory quotient in lean and obese men [34]. Overall, these data suggest that OT treatment is also associated with increased lipolysis as well as lipid utilization or oxidation.

Consistent with a potential physiological role of OT to stimulate lipolysis, *in vivo* data from OT or OTR null mice report increases of abdominal fat deposition [90,91] and increases of perirenal, mesenteric, and epididymal fat depot weights in relation to wild-type littermate control mice [91]. Furthermore, selective lentiviral reduction of PVN OT mRNA [32] or ablation of PVN or SON OT neurons in mice [87] is associated with increases of body fat while not impacting lean mass. Interestingly, mice exposed to HFDs for 7 weeks [68], *ob/ob* mice [62] and obese Zucker rats [63,64] also showed increased OTR mRNA expression in epididymal [62–64,68], mesenteric [68], perirenal [68], or subcutaneous WAT [68], raising the possibility that reductions in endogenous OT signaling in WAT may impact lipolysis and fat mass in certain rodent models of obesity. These findings unveil potential mechanisms whereby OT could decrease body adiposity via separate or combined effects of attenuation of food intake, and stimulation of both lipolysis and energy expenditure.

8. Potential role of peripheral OTRs in the nodose ganglia or GI tract?

In addition to the presence of OTRs in adipocytes, the existence of OTRs elsewhere in the periphery, specifically the GI tract [59–61,152–154], the enteric nervous system [60,152], smooth muscle cells [61,152] and the vagus nerve [60], raises the possibility that circulating OT, in addition to actions at central OTRs [106,155,156], may also act in the periphery to reduce food intake. Systemic treatment with OTR antagonists that penetrate the blood brain barrier (BBB) increases food intake in mice and rats [32,123], effects that could possibly be mediated through both central and peripheral OTRs. Studies indicate that systemic administration of the non-penetrant antagonist L-371,257 stimulates food intake and weight gain in rats [106]. Furthermore, systemic administration of OT in mice reduces food intake and elicits Fos in the hindbrain, in part, through activation of vagal afferent nerves [105]. These findings are consistent with a potential physiological role of peripheral OTRs in the regulation of food intake and body weight.

The peripheral effects of circulating OT to reduce food intake may be attributed to a direct action of circulating OT to suppress gastric emptying. These data are mixed, however, as peripheral treatment with OT has been reported to have no effect on gastric emptying rate in humans [157] and rats [158] or a stimulatory effect on gastric motility in rabbits, possibly due to species differences [159]. However, systemic OT reduces gastric emptying in both mice [160] and rats [153,154]. Furthermore, these effects are also attenuated by pretreatment with an OTR antagonist, Atosiban [153,154], suggesting that these effects are mediated by OTRs.

The extent to which circulating OT enters the CNS is still controversial [106,155,156,161–163]. Flanagan, Rogers, and colleagues have shown that central administration of OT inhibits gastric motility [164,165] and these effects appear to be mediated by OTRs in the dorsal vagal complex [165]. While circulating OT may inhibit gastric motility through a central mechanism these effects may also be mediated through stimulation of OTRs that are expressed in the enteric nervous system [60,152], smooth muscle cells [61,152] or nodose ganglion [60].

OT may suppress gastric emptying through an indirect effect mediated through the release of the meal-related satiety peptide, cholecystokinin (CCK-8), and CCK-elicited activation stimulates the release of CCK-8 [153,154], both of which occur within the time period whereby peripheral administration of OT reduces food intake [106]. Furthermore, these effects of systemic OT to suppress gastric emptying are blocked by the CCK1 receptor antagonist, devazepide [153,154]. Iwasaki and colleagues demonstrated that both systemic OT and CCK-8 activate single vagal afferent neurons [105] raising the possibility of both a direct as well as an indirect action mediated through the release of CCK-8 [153]. Determining the impact of peripheral administration of OT to suppress feeding in rats with gastric cannulas that remain open (sham feeding; no gastric distension) or closed (real feeding) would help identify whether decreases in gastric emptying are required to elicit the anorexigenic response to OT.

Another potential mechanism whereby systemic OT may inhibit food intake is through the suppression of ghrelin. Previous findings indicate that systemic OT reduces circulating levels of ghrelin in men [166] within a time frame that coincides with the hypophagic effects of OT on rodents [106]. In contrast, intranasal administration of OT, at a dose that reduced total caloric intake [34] and cookie consumption [35] and increased circulating levels of OT in other studies [167,168], failed to reduce plasma ghrelin [34,35], suggesting that this mechanism is not likely to contribute to the anorexigenic response to circulating OT.

9. Does cholesterol contribute to OT's effects in the setting of HFDs?

Existing studies indicate that OT treatment appears to be more effective at reducing food intake [28,30] and weight gain [27,30,31] in DIO mice and rats maintained on the HFDs relative to low fat diets, including chow. Similarly, impairments of OT signaling result in increased weight gain and decreased energy expenditure in mice fed a HFD but not in chow-fed control mice [87]. This raises an intriguing question of whether higher levels of cholesterol, or sucrose (as previously discussed), may explain the more pronounced effects seen in animals maintained on the HFDs. While the amount of cholesterol in the HFDs used in many existing studies is variable, in some studies it was higher than levels found in rodent chow (« 60–200 mg/kg) and thus may have contributed to increased effectiveness of OT reported in this model.

OTRs are observed in two affinity states (both high and low), and cholesterol is required for high-affinity OT binding [52]. The presence of cholesterol in media that contain solubilized OTRs can potentially enhance high-affinity OT binding and stabilize the OTR in a high-affinity state [93,169]. The potential role of cholesterol levels is a possible complicating factor in interpreting the results of studies on the impact of OT on HFD-fed animals. Additional studies to examine the contributions of cholesterol to OTR binding in HFD-fed DIO animals relative to chow-fed control animals will be helpful in addressing the extent to which increased OTR binding may contribute to the enhanced sensitivity to OT.

10. What contributes to OT's prolonged effects to reduce body weight gain?

Chronic administration of OT into either the CNS or periphery over periods between 7 and 84 days is sufficient to decrease either body weight or body weight gain in DIO mice and rats [27,28,30–32] and genetically obese mice [62,93]. Interestingly, these effects of OT are maintained despite reports of reduced OTR binding in many areas of the CNS following chronic CNS infusions [170,171]. Moreover, in translational studies in DIO nonhuman primates, body weight loss was found to be less than that of vehicle-treated animals out to 7 weeks during the washout period. In addition, these animals did not begin to regain significant body weight until week 3 of the washout period. These sustained carryover effects appear to be mediated by decreases in food intake that continued for the initial 2 weeks into the washout phase [26] and are similar to other findings in obese nonhuman primates that received fibroblast growth factor-21 [172,173], adipotide [174], or a melanocortin 4 agonist, BIM-22493 [175]. Moreover, Maejima and colleagues showed that reductions in body weight gain persisted for 9 days following termination of OT treatment in

DIO mice [28]. Furthermore, the effects of OT on exploratory and anti-aggressive behavior continued for at least 1 week following the end of treatment in male rats [176]. Similarly, the effects of chronic intracerebroventricular (ICV) or subcutaneous administration of OT to reduce blood pressure persisted for nearly 10 days after OT treatment ended in male and female rats [177]. Acute systemic administration of OT is also capable of activating PVN OT neurons [178,179] and stimulating the release of OT in the PVN in a rodent model [32]. These self-stimulatory properties [27] in addition to its prolonged bioavailability of OT in the CNS are thought to contribute to its favorable effects on prosocial behavior [180] and may also explain its sustained effects on body weight loss following stoppage of treatment [28].

The extent to which chronic CNS OT suppresses key orexigenic and energy conservation mechanisms in the CNS to restore energy reserves following weight loss and leptin deficiency has not been examined. In addition, the degree to which any OT-elicited reductions in orexigenic gene expression persist following cessation of treatment is also unclear. In lean and DIO animals, chronic food restriction increases gene expression of orexigenic peptides neuropeptide Y (NPY) [171,181–183] and AGRP [183] in the ARC and decreases gene expression of the anorexigenic peptide precursor proopiomelanocortin (POMC) in the ARC [171,182]. However, no changes in mediobasal hypothalamic expression of NPY, AGRP or POMC were observed in wild-type or *ob/ob* mice following 14-day subcutaneous infusions of OT [62]. Future studies should include gene profiling and RNA sequencing at the beginning and end of the washout period in the mediobasal hypothalamus. In addition, it would be informative to determine the impact of chronic OT signaling on the expression of downstream targets in the hindbrain (e.g. glucagon-like peptide-1 [109], POMC [29], and catecholamines [106]) and other CNS areas linked to energy homeostasis.

11.   Does OT reduce inflammation in animal models of obesity or hyperlipidemia?

It is well established that obesity is associated with macrophage infiltration (reviewed in [184]) and increased inflammation in the vasculature as well as peripheral tissues, including liver, muscle and fat [185]. Previous findings indicate that inflammatory responses within the mediobasal hypothalamus, particularly in ARC POMC neurons [186], occur much sooner than in peripheral tissues and precede the majority of weight gain during the course of diet-induced obesity [185,186]. Emerging evidence suggests that systemic OT has anti-inflammatory properties in peripheral tissues across a variety of obese animal models. For example, chronic systemic OT reduces macrophage infiltration in epididymal WAT of *ob/ob* mice without impacting macrophage infiltration in wild-type mice [62]. In addition, chronic systemic OT also reduces the expression of pro-inflammatory markers, such as NF-κB, interleukin 1 beta (IL1-β), and interleukin 6 (IL-6) from heart tissue of *db/db* mice [93] as well as in rats following myocardial infarction [170]. Interestingly, chronic systemic OT also reduces IL-6 secretion from epididymal fat in hyperlipidemic apolipoprotein E (ApoE) deficient mice [187] and C-reactive protein in Watanabe Heritable Hyperlipidemic rabbits [188]. OTR deficient mice also display increased levels of IL1-β, IL-6 and tumor necrosis

factor alpha (TNF-α) mRNA expression in the colons following experimental colitis, findings that suggest a possible protective anti-inflammatory effect [160]. These findings support an anti-inflammatory role of OT in peripheral tissues in genetically obese and hyperlipidemic animals.

Despite these existing data it is still unclear if OT has similar anti-inflammatory properties in the brain as observed in peripheral tissues. Future research needs to address the questions of whether increased OT signaling is sufficient to prevent the mediobasal hypothalamic inflammatory responses that occur before notable weight gain in animals maintained on a HFD [186], and also whether this aids in the prevention of diet-induced obesity. Maejima and colleagues identified an OT projection from the PVN to the ARC in mice [56] (see Fig. 1) as well as the existence of OTRs in POMC neurons in the ARC of a reporter knock-in mouse line ($Oxtr^{Venus\ Neo/+}$) where the OTR gene was replaced with Venus cDNA (an enhanced yellow fluorescent protein) [71]. Moreover, OTRs are also expressed in hypothalamic astrocytes [189] and glial cells in the subfornical organ, cerebellar cortex, and organum vasculosum of the lamina terminalis [71], although it is uncertain if this is true in the ARC. In addition, both central administration and systemic administration of OT also induce Fos within the ARC in mice [28,56] where OT also acts to reduce chow intake [56]. These effects may also be mediated through a direct action of OT on POMC neurons in mice [56]. Together, these findings raise questions as to whether a) impairments in OT release and in the vicinity of ARC astrocytes or POMC neurons that express OTRs may contribute to the pro-inflammatory responses following consumption of HFDs and b) increased OT signaling within ARC astrocytes or POMC neurons may prevent or ameliorate the anti-inflammatory effects associated with exposure to HFDs.

12. Translational potential

One of the key challenges with regard to OT's use as a therapeutic strategy to effectively treat obesity and take advantage of actions at both central and peripheral OTRs (as discussed in Sections 6 and 7) will be how to circumvent its relatively short half-life in the circulation ($T_{1/2}$ = 6 min; [190]) relative to the CNS ($T_{1/2}$ = 19 min; [161]). Some studies have aimed at modifying its activity and plasma stability through refinements in the disulfide bond [191], which is essential for OT's biological activity [63,192,193]. Other studies report that several longer acting OT analogues have been engineered to extend its half-life. Limited studies thus far have shown promise of longer acting OT analogues in the regulation of body weight. One such example is carbetocin, an OT analogue which has a half-life of 17.2 min in horses [93] and 41 min in non-pregnant women [194]. Its increased stabilization is thought to be attributed to N-terminal desamination as well as replacement of the 1–6 disulfide bridge with a methylene group [195]. Altirriba and colleagues reported that carbetocin reduced body weight gain over 10 days in genetically obese *ob/ob* mice [62]. Zhang and colleagues also reported that twice daily 3V administration of the commercially available OT analogues, [Ser4, Ile8]-OT (isotocin) and [Asu1,6]-OT, improved glucose tolerance and reduced fasting blood insulin levels independent of changes in body weight in pre-diabetic C57B1/6J mice maintained on HFDs for 2 months as well as in mice with streptozotocin-elicited diabetes [33]. Furthermore, improvements in glucose tolerance independent of changes in body weight were also obtained following peripheral administration of [Ser4,

Ile8]-OT [33]. While these findings are consistent with other reports of OT improving glucose tolerance in lean mice [83], DIO mice [28,32], DIO rats [27], and possibly normal-weight [35] and obese humans [33], recent studies, however, indicate that chronic infusions of OT actually worsen glucose tolerance in *ob/ob* mice [62]. Thus, additional studies are needed to examine these parameters in pre-clinical trials in obese humans.

While it is evident that improvements continue to be made in engineering OT analogues, it is unclear if multiple injections/day or injections in the early part of the light cycle to coincide with diurnal peaks of circulating OT [32] will be required to maximize the ability of OT to reduce body weight in nonhuman primates [26] or humans [33]. Future investigations should examine if intermittent or pulsatile delivery [83,196–201] of OT will extend its effectiveness and circumvent reductions in OTR binding known to occur in the CNS following chronic CNS infusions [170,171]. In addition, studies should examine if inhibition of oxytocinase activity[64], PEGylation [202–204] or conjugation to albumin [205] in combination with oral delivery [206] will produce prolonged effects and eliminate the need for multiple injections.

Intranasal delivery enables relatively rapid uptake into the CSF of several neuropeptides, including the melanocyte-stimulating hormone/adrenocorticotrophic hormone (4–10), vasopressin, and insulin within 30 min in humans [207]. Intranasal delivery appears to effectively enable OT to enter the CNS in mice, rats, nonhuman primates and humans within 30–35 min post-treatment [162,208,209]. However, the extent to which this effect is due to elevations in exogenous or endogenous OT is being debated [162,210]. OT is one of the few hormones that is capable of stimulating its own release through magnocellular SON [211,212] and PVN [180] OT autoreceptors following a central or systemic treatment. Systemic OT is capable of activating vagal afferents [105] where OTRs are expressed [60], inducing Fos within PVN OT neurons [179,213] and eliciting release of OT within the CNS [32] and likely back into the peripheral circulation. In addition, central infusions of OT up-regulate hypothalamic OT mRNA and increase circulating OT levels [27]. Given that circulating levels of OT are elevated by 40 or 60 min following intranasal administration in nonhuman primates [214] and humans [167,168,215] it is possible that intranasal OT is entering the circulation directly or indirectly following the release of endogenous OT into the CNS and peripheral circulation. Future studies that examine CNS levels of radiolabelled OT following intranasal administration into OT deficient mice with intact or severed vagal afferent signaling to the hindbrain will be helpful in addressing the extent to which OT enters the CNS without impacting release of endogenous OT within the CNS.

Agents that stimulate the sympathetic nervous system, may adversely impact cardiac function in rodents [216,217] and in humans [218], which is of particular concern for the large proportion of overweight and obese individuals with hypertension [219]. Current data, however, suggest that the intranasal route of administration is not associated with unwanted side effects [220], including adverse effects on blood pressure or heart rate relative to vehicle treatment in rats [210], healthy adults [34,167,215] and pre-diabetic obese men and women [33]. In addition, chronic subcutaneous infusions of OT failed to impact systolic blood pressure [28] or heart rate [28,93] in DIO [28], *db/db* [28,93] or hyperlipidemic ApoE deficient mice [187]. In rats, chronic subcutaneous or ICV injections reduced blood pressure

without impacting heart rate [177]. In contrast, acute administration of OT into the CNS or periphery is associated with increases, decreases, or no changes in heart rate [71,210,221,222], blood pressure [177,210,223], and body temperature [71,221] in mice or rats (for review see [224,225]). Preliminary data in our laboratory indicate that subcutaneous administration of OT does not significantly alter heart rate, blood pressure or body temperature at 90-min post-treatment in a limited number of sedated nonhuman primates (unpublished observations). Given these variable outcomes on blood pressure and heart rate following acute vs. chronic delivery and various routes of administration of OT it will be important to monitor potential adverse cardiovascular effects throughout the course of treatment in future pre-clinical trials.

In an effort to avoid unwanted peripheral side effects, some investigations have administered OT intranasally by nebulizer to allow for more targeted entry into the CNS without increasing circulating levels [214], but the data are mixed [226]. Regardless, it is encouraging that the intranasal route of administration has yielded positive prosocial effects in nonhuman primates [208], male and female individuals with schizophrenia [227,228], and in men and women who experience social rejection [229]. Furthermore, chronic subcutaneous injections of OT at doses that reduced food intake and body weight and increased energy expenditure in DIO nonhuman primates were also not associated with nausea or diarrhea [26]. The added benefit of potentially ameliorating obesity and its related complications without eliciting adverse side effects only adds to the excitement surrounding OT as a potential therapeutic strategy in humans.

Given the demand for new successful and noninvasive therapeutic strategies to treat obesity it is somewhat perplexing why there has yet to be a single clinical study performed to systematically examine the ability of chronic OT treatment to elicit weight loss in obese humans. While one preliminary report by Zhang and colleagues found that chronic intranasal OT evoked weight loss over an 8-week period in prediabetic obese men and women [33], they did not identify whether these effects may be due to decreases in food intake as well as elevations in energy expenditure and/or lipolysis. Recent findings indicate that acute intranasal administration of OT reduced total caloric intake [34] and cookie consumption [35] in humans as well as chow intake in mice [83] suggesting that reductions in food intake may contribute to the anti-obesogenic effects following this route of administration. Recently we provided the first key evidence that chronic subcutaneous administration of OT is a potential treatment strategy to produce prolonged weight loss in DIO nonhuman primates by a mechanism of reducing energy intake and increasing both energy expenditure and lipolysis. While the percent weight loss achieved in this study was below that reported in longer term (1 year) trials in humans treated with FDA-approved drugs [e.g. Qsymia (phentermine + topiramate)], it was similar in magnitude to that achieved with either orlistat or lorcaserin [230,231]. These findings collectively provide key pre-clinical data to justify future more extensive investigations that determine the impact of chronic intranasal OT treatment on weight loss, preference towards macronutrients and suppression of CNS feeding reward circuitry in both male and female obese nonhuman primates and humans.

13. Conclusions

It is evident that impairments in OT signaling contribute to obese phenotypes potentially through increases in food intake as well as reductions in energy expenditure and possibly lipolysis. The extent to which reductions in OT signaling are essential to the etiology of altered energy homeostasis or of maintaining the obese phenotype in the case of diet-induced obesity is unclear. While there is much enthusiasm over the potential use of OT as a therapeutic strategy to treat eating disorders and obesity, we await the results of ongoing pre-clinical trials in obese humans for additional confirmation of its feasibility as a long-term weight loss strategy in the absence of adverse side effects. It remains to be determined if chronic systemic administration of OT is associated with unwanted peripheral side effects such as uterine cramping in women. However, pre-labor uterine sensitivity to OT stems from a more than 150-fold up-regulation in myometrial OTRs [232], and this increase in OTR expression appears to be primed by high estrogen levels just prior to term [233] suggesting that it is unlikely to elicit uterine cramping in non-pregnant women. One potential concern is whether chronic OT, at doses that elicit weight loss, may also interact with vasopressin 2 receptors (V_{2R}s) in sufficient concentrations to cause hyponatremia (serum sodium < 135 mmol/L) [234]. This complication is not likely, however, given that OT has nearly a 90-fold higher affinity for the OTRs than the V_{2R}s [235]. While combination therapies that include V_{2R} antagonists are effective in correcting hyponatremia in humans [236,237], further studies will be important to determine whether hyponatremia is a potential side effect during chronic OT treatment.

It is clear that there are several means by which OT, given centrally or peripherally, can influence body weight, namely through reductions in food intake as well as increases in energy expenditure and/or lipolysis. Based on the finding that circulating OT may act through central [106] or peripheral OTRs to reduce food intake [105,106] and the observation that peripheral administration can stimulate the release of CNS OT [32], further studies are needed to address the relevance of peripheral OTR signaling in the setting of diet-induced obesity [60,105,106,153,154,160] and whether activation of CNS OT circuits is, in fact, necessary in order to maximize its therapeutic potential when given systemically. While rodent and the small number of nonhuman primate and human studies are promising thus far, OTRs may alter the function of other G protein-coupled receptors, including the beta-2 adrenergic receptor [238]. Therefore, multi-drug treatments and/or intermittent delivery [83,196–199] may need to be utilized to achieve the greatest benefits of targeting the OT signaling pathway [239]. Caution should be exercised before administering to children and young adults as one study suggested that behavioral impairments occur following chronic intranasal treatment in developing prairie voles [240]. While no major deleterious effects on social behavior were reported following chronic intranasal administration of OT (at doses being used in clinical trials) in wild-type mice and a mouse model of autism spectrum disorder [241], additional studies should address the long-term neuroendocrine and behavioral effects following multiple doses of OT in developing animals and nonhuman primates [24,240].

Acknowledgments

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HIGHLIGHTS

- Release of oxytocin within the CNS is implicated in the control of energy balance.

- Oxytocin elicits weight loss in obese rodents, nonhuman primates and humans.

- We assess potential mechanisms that may contribute to its anti-obesity effects.
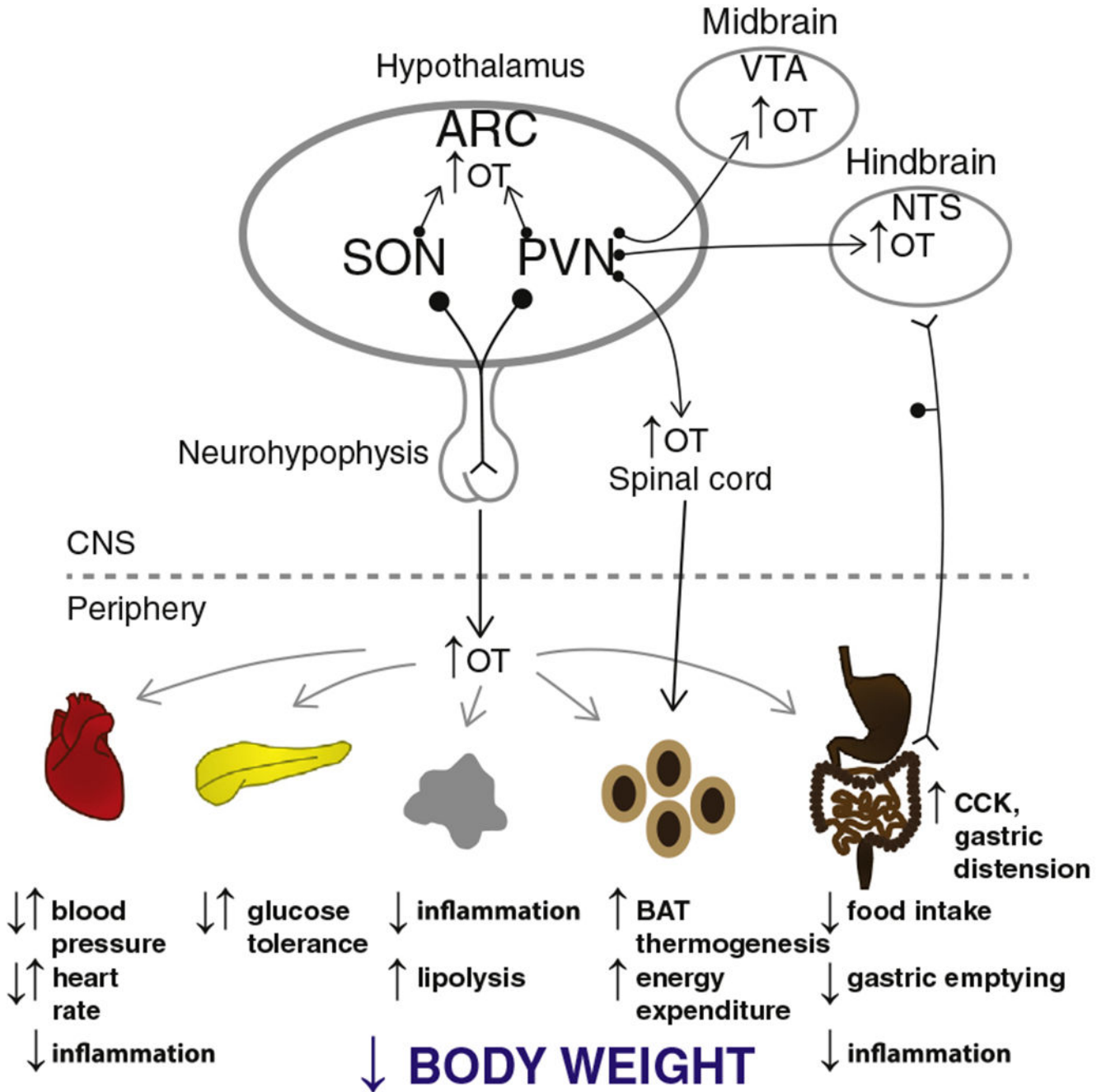
Fig. 1.

A schematic of circuitry that potentially contributes to the effectiveness of OT on energy homeostasis. OT release within the CNS, spinal cord, and from the neurohypophysis into the circulation (shown in black arrows) may impact metabolic processes (shown in gray) that result in the reduction of bodyweight. Dotted arrow represents implicated pathways from sympathetic preganglionic neurons in the spinal cord to WAT [149,150]. Reported opposing effects denoted by arrows pointed in opposite directions to one another. Abbreviation: ARC, arcuate nucleus; CCK, cholecystokinin; BAT, brown adipose tissue; NTS, nucleus of the

solitary tract; PVN, paraventricular nucleus; SON, supraoptic nucleus; and VTA, ventral tegmental area. This figure has been modified from a previous manuscript [*Endocrinology* Coming full circle: contributions of central and peripheral oxytocin actions to energy balance 154(2):589–96, 2013; http://www.ncbi.nlm.nih.gov/pubmed/23270805].