Chapter

Oxytocin as a Metabolic Modulator

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Abstract

Oxytocin (9-amino acid peptide) hormone is a member of the G-protein coupled receptor family. It regulates a range of physiologic actions in mammals other than assisting parturition and lactation functions. Evidence indicates that oxytocin alters lipids, protein, and sugar metabolism through various ways including modulation of appetite and satiety, enzyme activity, cellular signals, secretion of metabolic hormones, and energy consumption. Alterations in these processes have the potential to shift developmental trajectories and influence disease processes. Oxytocin can be a potential avenue for the treatment of endocrine disorders such as obesity, diabetes mellitus, and associated disorders. The chapter will include a comprehensive study about oxytocin and its physiological and pathological functions, which makes it a potential target for drug therapy.

Keywords: Oxytocin, metabolism, endocrine system, obesity, energy balance

1. Introduction

Oxytocin, which was long thought to be a hormone exclusively involved in social bonding, parturition, and lactation; now is extensively researched for its other possible implications. Evidence indicates that oxytocin alters lipid, protein, and sugar metabolism through various ways including modulation of appetite and satiety, enzyme activity, cellular signals, secretion of metabolic hormones, and energy consumption [1, 2].

1.1 Oxytocin synthesis and secretion

Oxytocin (Oxt) a nonapeptide hormone is a member of the G-protein coupled receptor family. It regulates a range of physiologic actions in mammals other than reproductive deeds [3]. The word oxytocin was taken from the Greek words (ω k ν ξ, τ o k ox ξ) meaning "quick birth". The uterine-contracting property of oxytocin was discovered by Dale [4], whereas the milk ejection property of oxytocin was revealed in the following years [5, 6].

Oxytocin is composed of nine amino acids (Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-GlyNH2) with a disulphide bridge between cysteine residues 1 and 6 [7, 8]. It is predominantly synthesized in magnocellular neurons of the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei of the brain. It is released into the blood circulation through the posterior pituitary gland where it is released to regulate parturition and lactation. In addition, oxytocin is produced and released outside the nervous system, such as the gastrointestinal tract [9] and bone marrow osteoblasts [10, 11] liver, placenta, amnion, heart [12], and subcutaneous adipose tissue. In adipose tissue, oxytocin has autocrine and paracrine effects via oxytocin

receptors [9, 10, 13]. A variety of stimuli such as parturition, suckling, and certain stresses are responsible for the release of oxytocin in the circulation.

Endogenous oxytocin does not readily cross the blood–brain barrier, but circulating oxytocin may directly enter the hindbrain or act on the vagus nerve [14–17]. Oxytocin can enter into the cerebrospinal fluid (CSF), as proved in an animal study [18]. A significant amount of oxytocin was found in cerebrospinal fluid when copious amounts of oxytocin were injected intravenously or intranasally in nonhuman primates [18]. Additionally, exogenous oxytocin administration may accelerate endogenous oxytocin secretion either directly through PVN oxytocin autoreceptors or indirectly through peripheral oxytocin receptors [19, 20]. Generally, oxytocin receptors are found throughout the central nervous system including the hypothalamus, basal ganglia, VTA, nucleus accumbens, frontal cortex, insula, NTS, and spinal cord. Oxytocin receptors are also present in peripheral regions (vagus nerve, anterior pituitary gland, adipocytes, gastrointestinal tract, and pancreas) that regulate food intake and metabolism [12, 21–25]. Infect, mRNA for oxytocin and its receptors throughout the entire human gastrointestinal (GI) tract was recently found. Such receptors are known as allosteric modulators [12] (**Figure 1**).

1.2 The therapeutic potential of oxytocin

The therapeutic potential of oxytocin has been studied extensively for the last few years. Use of oxytocin in the treatment of autism spectrum disorder (ASD) [26, 27], schizophrenia [26, 28], and obesity [20, 28–31] have been investigated and documented in leading journals. It has opened a new door for many more untouched aspects of oxytocin to be disclosed. Recently it was found that oxytocin could reverse the effects of beta-amyloid on mice hippocampal LTP in an *in vitro* study. ERK phosphorylation and Ca^{2+}-permeable AMPA receptors are involved in this effect of oxytocin [32]. Beta-amyloid is the main culprit of Alzheimer's disease, which gets deposited around the neurons of the brain and impaired cognitive functions.

1.3 Physiological role of oxytocin in feeding regulation

Oxytocin exerts a direct as well as an indirect effect on metabolism and energy balance. The direct effect is through anorexigenic activity with increased oxytocin secretion and/or signaling leading to decreased food intake via net effects on multiple different homeostatic and neurobehavioral pathways. Peripheral oxytocin induces anorexia was first demonstrated by Arletti et al. [33]. The indirect effect of oxytocin is explicitly on muscles potentiating the majority of the slow-twitch muscles.

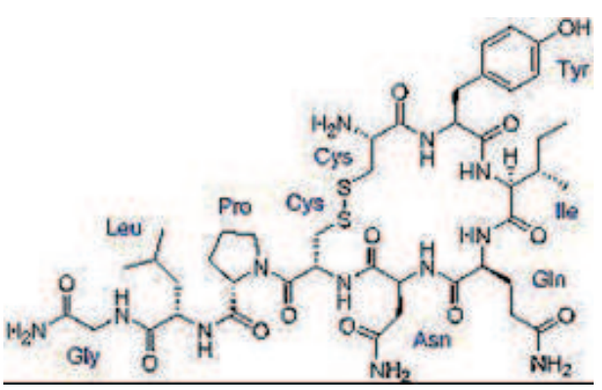

Figure 1.
Chemical structure of oxytocin [26].

Oxytocin not only affects food intake but also the choice of food that is consumed. Studies conducted with a variety of animal models, including rats, mice, and rhesus monkeys fed with standard chow with a substantial proportion of calories from carbohydrates. Such studies have shown that oxytocin reduced intake of sucrose [34–36], glucose, fructose-sweetened beverages), and HFDs sweetened with sucrose [19, 20, 30, 37–39], sucrose appears to activate a greater proportion of PVN oxytocin neurons relative to intake of fat (intralipid) [40]. Oxytocin has also been shown to suppress energy intake in animals fed HFDs without sucrose. Moreover, systemic administration of oxytocin antagonists (readily crosses the blood–brain barrier) [41] stimulates the intake of sucrose, but not chow or intralipid [42]. Conversely, impairments of oxytocin signaling is associated with increased consumption of carbohydrates, including sucrose [34, 43, 44], and glucose [44], as well as fat [38, 45], implicating a potential physiological role for oxytocin to limit consumption of both simple sugars and fat.

Oxytocin has a profound effect in termination of the food intake. The food intake is physiologically regulated by oxytocin neurons, responding to fasting and satiety conditions. It has been observed that food consumption activates oxytocin neurons [40, 46], whereas fasting is known to depress oxytocin neurons and recovery is possible with refeeding [29] or the leptin administration [47], conversely suppression of exocytosis of oxytocin, or genetic reduction of oxytocin expression increases food intake [29], and ablation of oxytocin neurons increase body weight gain by decreasing energy expenditure in male mice fed a high-fat diet (HFD) [48]. The ablation of the neurons that express oxytocin receptors, in the nucleus of the solitary tract (NTS) and arcuate nucleus induces hyperphagia [49, 50] and satiety [51]. Additionally, oxytocin also displays a circadian rhythmic pattern with a rise of circulating oxytocin level during the day and vice versa [52, 53].

1.4 The metabolic functions of oxytocin

Oxytocin is a potent regulator of caloric intake and metabolism. Metabolism is an exclusive attribute of living cells. Disturbance in metabolism can have a toll on both body and mind. Although, the epidemics of metabolic diseases have largely been attributed to genetic makeup, changes in diet, exercise and aging. However, other environmental factors may contribute to the rapid increase in the incidences.

Oxytocin has a direct effect on adipose tissue. It induces adipose tissue lipolysis [16, 20] and fat oxidation [20, 30, 54], subsequently leading to reduced body fat and weight gain [20] as well as glucose intolerance and insulin resistance. Moreover, oxytocin is believed to reduce visceral and liver fat deposition [30]. Such deposits are metabolically important and are known to increase the prognosis of metabolic syndrome and cardiovascular disease [55]. Sub chronic treatment of oxytocin extended improved adipocyte differentiation and increased gene expression of factors involved in adipogenesis in rats. This effect is related to an increased fatty acid-binding protein, peroxisome proliferator-activated receptor gamma, insulin-sensitive glucose transporter 4, leptin, and CD31 mRNA levels [56].

1.5 Energy balance

Energy balance is a complex physiological process that is regulated by multiple interactions between the gastrointestinal tract (GIT), adipose tissue, and the central nervous system (CNS). It requires both afferent signals from the periphery about the state of the energy stores as well as different signals that influence energy intake and expenditure [57] and is also influenced by behavioral, sensorial, autonomic, nutritional, and endocrine mechanisms [58]. Energy balance is quite essential in

daily life to be in shape physically as well as metabolically. Nevertheless, at times energy balance (intake and expenditure) may alter partially or completely, leading to consequent pathological changes in body weight. Adaptations to body weight changes include modifications at the level of circulating appetite-related hormones that, in turn, may profoundly interact with the homeostatic and hedonistic neural centers. The homeostatic control system makes it possible to maintain energy reserves through signals of hunger stimulation that are usually downregulated when the body receives an adequate caloric intake. However, this homeostatic system is asymmetrical, showing greater effectiveness in defending against energy deficit in the light of reduced efficiency in the defense against the energy excess. Furthermore, the homeostatic system is strongly influenced by hedonic signals, based on reward mechanisms, frequently causing food intake even in the absence of biological needs. This review will summarize the role of the main central and peripheral hormones involved in controlling energy balance.

2. Mechanisms underlying the effects of oxytocin on energy balance

The proposed mechanisms underlying the effects of oxytocin on calorie balance are discussed under the following topics.

2.1 Oxytocin may regulate appetite

Oxytocin may induce satiety by slowing gastric emptying [59–61]. Gastric emptying is a principal trait of postprandial glycemia. A lower rate of gastric emptying and a high-fat diet rationally enhances the glycemic index of carbohydrates. Moreover, slowing of gastric emptying by fat depends on the small intestine exposed to lipolytic products. Oxytocin is released in response to a fatty meal [62], which regulates gastric emptying [63, 64].

Conversely, systemic administration of oxytocin led to enhanced gastric emptying [63, 64] also oxytocin receptor antagonist atosiban delayed gastric emptying significantly [9]. Though the results from human studies are conflicting and only one human study on diabetic gastroparesis has reported prolonged gastric emptying time (40–80 mIU/min) [65]. The prokinetic effect of oxytocin on the gut has been assumed to be similar to the one in uterine myometrium and mammary myoepithelial cells; i.e., the intracellular release of **Ca2+** which leads to muscle contraction via myosin light kinase activity [12]. In normal subjects, oxytocin has been found in the gut where it is secreted after a meal [62] and stimulates colonic activity [66].

Oxytocin can influence other appetite-regulating hormones. Intravenous administration of oxytocin modulated levels of ghrelin (which is orexigenic) in human subjects [67], whereas 24 IU intranasal administration of oxytocin did not show any significant changes in fasting or postprandial levels of ghrelin [68, 69]. Ghrelin is a gastric hormone, which regulates hunger and food intake. Likewise, oxytocin administration can influence cholecystokinin concentration in circulation [60] but this change was not related to differences in caloric consumption between oxytocin and placebo conditions [35]. Oxytocin facilitates cholecystokinin elicited excitation of neurons within the nucleus of the solitary tract and reduces food intake [49].

2.2 Oxytocin and glucose homeostasis

Oxytocin influences glucose and insulin homeostasis, along with bodyweight balance. Numerous studies have shown that oxytocin encourages glucose uptake [70, 71] and stimulates insulin secretion [72–76] as well as pancreatic glucagon

secretion [75], which extends a hint about the involvement of oxytocin in the prognosis of diabetes. Intracerebroventricular oxytocin can improve insulin levels by activation of vagal cholinergic neurons innervating pancreatic beta-cells [76]. Conversely, insulin can modulate oxytocin levels in the hypothalamus by activating the insulin-regulated aminopeptidase as well [77, 78].

Studies have suggested that oxytocin has the capacity to reduce obesity-related diabetic changes, such as glucose intolerance, insulin resistance, and pancreatic islet hypertrophy [19, 20, 30, 38, 79, 80]. Two weeks of treatment with oxytocin decreased adiposity and food intake in obese mice lacking leptin, although, it worsens glucose metabolism, most likely due to an increase in corticosterone levels and enhanced hepatic glucose production. It could be suggested that the effect of oxytocin in decreasing fat mass is independent of leptin, while the beneficial impact on glucose metabolism requires the presence of leptin [81]. Whereas, oxytocin treatment for a longer period, notably reduced body fat accumulation, fasting blood glucose levels, and improved insulin sensitivity and glucose tolerance in leptin receptor-deficient mice [82]. The hypoglycemic stimulatory effect on insulin secretion and sensitivity, and improvement of pancreatic islet cells after oxytocin administration strongly suggested that oxytocin might be a therapeutic target for treating diabetes.

Oxytocin influences glucose metabolism in various ways. It may have a direct effect on glucose metabolism through the promotion of muscle cell differentiation. It has been found that a higher oxytocin concentration is linked with the anabolic effects of steroids in bovine and ovine skeletal muscle [83, 84]. A rapid increase in muscle regeneration was observed in old mice with a cardiotoxin muscle injury, when oxytocin was administered subcutaneously [79], though, the regenerative capacity of skeletal muscle and the levels of oxytocin receptor in muscle stem cells decrease with the age [79].

Further oxytocin-induced augmentation of muscle mass directly affects glucose uptake and insulin sensitivity. Oxytocin receptors are widely distributed in adipocytes of both humans and animals, especially in rats [12, 85, 86]. Oxytocin augments the transient increase in intracellular Ca^{2+} and stimulates PKC activity [87, 88], which in turn increases glucose uptake in mice adipocytes [88–90]. It has been noted that oxytocin stimulates glucose oxidation via enhancement of pyruvate dehydrogenase activity in mice adipocytes [90]. Oxytocin treatment induced a higher mRNA expression for gluconeogenesis and lowered glycaemia in lean control mice, probably because of the decreased liver glycogen content [82]. So, oxytocin treatment enhances net hepatic glucose oxidation, reduced glycogen synthase activity, and increased glycogen phosphorylase activity [91].

Oxytocin modulates pancreatic function centrally via vagal cholinergic neurons innervating β-cells [76] and peripherally by stimulating phosphoinositide turnover and activating PKC in pancreatic β-cells [92]. Insulin secretion (independent of glucose concentration) was found to be stimulated in isolated mouse pancreatic islets with oxytocin infusion [91]. Additionally, oxytocin increases insulin and glucagon secretion in both *in vivo* and in situ conditions and appears to have a greater effect on glucagon secretion than on insulin secretion (and to a much greater extent in insulin-deficient diabetic rats) [93–95]. Peripherally oxytocin regulates whole-body glucose metabolism. Studies have shown that oxytocin-deficient ($Oxt^{-/-}$) and high-fat diet-fed OTR-deficient ($Oxtr^{-/-}$) mice had decreased insulin sensitivity and impaired glucose tolerance [96, 97], and both insulin sensitivity, as well as glucose tolerance, were restored after oxytocin administration in obese diabetic (*db/db*) mice fed with standard and high-fat diets [20, 30, 82, 98]. Improvements in glucose tolerance, lowering of postprandial plasma glucose and insulin concentrations have been reported in subjects with normal weight and obesity who were

given oxytocin [33, 68, 69, 80, 99]. In contrast, increases in plasma glucose and hepatic glycogenolytic activity concurrent with an absence of effects on peripheral insulin sensitivity have also been reported [95].

2.3 The lipolytic effect of oxytocin

The lipolytic effect of oxytocin is well studied in animal models [16, 20] and human trials [100]. The intravenous administration of oxytocin (10 mIU/kg) increased plasma levels of non-esterified free fatty acids and reduced plasma levels of triglycerides in women with obese history [100]. Even the intranasal administration of oxytocin (24 IU before meals and at bedtime) in overweight or obese men and women for eight weeks resulted in improved lipid profile (lower levels of total cholesterol and LDL cholesterol), reduced waist circumference, and weight loss [80]. Oxytocin also acts as a homeostatic inhibitor of consumption, capable of mitigating multiple aspects of consumption behavior and energy metabolism [34]. Markedly, oxytocin reduces metabolically important fat for instance visceral and liver fat [30]. Such fat deposits are mostly responsible for the increased risk of metabolic syndrome and cardiovascular disease [55].

2.4 Energy expenditure

Despite the weight loss, it is believed that oxytocin contributed to the preservation of lean body mass, a key determinant of energy expenditure [54], activation of brown fat [97, 101, 102] and conversion of white adipose tissue to beige fat that is capable of thermogenesis [68, 82]. In young female athletes and non-athletes aged 14–21 years, fasting levels of oxytocin were positively associated with resting energy expenditure [68].

3. Conclusions

Metabolic disorders have reached to an explosive level and data projected by different government or non-government bodies are scary. Some alternative treatments should be adopted other than the conventional mode of treatment to coping such situations. Hormones are very powerful chemical substances and work precisely in the target organ. They mostly secrete far away from the site of action. Oxytocin is one such hormone that was long known for its reproductive involvement and is now being investigated for its multifunctional attributes. The therapeutic implications of oxytocin are gaining momentum. Studies have revealed that oxytocin alters metabolism in various ways including modulation of appetite and satiety, enzyme activity, cellular signals, secretion of hormones, and energy consumption. Despite the wealth of basic research showing broad anorexigenic effects of oxytocin, clinical studies on oxytocin's therapeutic potential in obesity, and associated disorders are still in their infancy and exhaustive research is needed. Future replicated and validated studies will help to characterize and better understand the underlying mechanisms for the regulation/dysregulation of metabolism and would be a good approach for treating the obese population, which is the need of the hour.

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Conflict of interest

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Other declarations

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Acronyms and abbreviations

AMP	Adenosine monophosphate
Ca	calcium
CD31	The cell adhesion molecule
CSF	Cerebrospinal fluid
CVD	Cardio vascular diseases
ERK	Extracellular signal-regulated kinase
HFDs	High fructose syrup
LDL	Low density lipoprotein
LTPL	Long term potentiation(hippocampus)
mRNA	Messenger RNA
NTS	Nucleus tractus solitarius
PKC	Protein kinase
PVN	paraventricular
VTA	Ventral tegmental area

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