Physiology & Behavior 176 (2017) 31–39

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Review

Current findings on the role of oxytocin in the regulation of food intake

Maartje S. Spetter [a,b,*], Manfred Hallschmid [b,c,d]

[a] School of Psychology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
[b] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Otfried-Müller-Str. 26, 72076 Tübingen, Germany
[c] German Center for Diabetes Research (DZD), 72076 Tübingen, Germany
[d] Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, 72076 Tübingen, Germany

HIGHLIGHTS

- The hypothalamic neuropeptide oxytocin acts as an anorexigenic signal.
- Intranasal oxytocin delivery curbs food intake in healthy and obese individuals.
- Possible links to oxytocin's psychosocial function are discussed.
- Does oxytocin hold some clinical potential as an appetite-reducing drug?

ARTICLE INFO

Article history:
Received 1 December 2016
Received in revised form 17 February 2017
Accepted 6 March 2017
Available online 8 March 2017

Keywords:
Oxytocin
Intranasal administration
Central nervous system
Brain
Metabolism
Food intake
Eating behavior
Glucose homeostasis
Cognitive processes
Psychosocial function
Obesity

ABSTRACT

In the face of the alarming prevalence of obesity and its associated metabolic impairments, it is of high basic and clinical interest to reach a complete understanding of the central nervous pathways that establish metabolic control. In recent years, the hypothalamic neuropeptide oxytocin, which is primarily known for its involvement in psychosocial processes and reproductive behavior, has received increasing attention as a modulator of metabolic function. Oxytocin administration to the brain of normal-weight animals, but also animals with diet-induced or genetically engineered obesity reduces food intake and body weight, and can also increase energy expenditure. Up to now, only a handful of studies in humans have investigated oxytocin's contribution to the regulation of eating behavior. Relying on the intranasal pathway of oxytocin administration, which is a non-invasive strategy to target central nervous oxytocin receptors, these experiments have yielded some promising first results. In normal-weight and obese individuals, intranasal oxytocin acutely limits meal intake and the consumption of palatable snacks. It is still unclear to which extent – or if at all – such metabolic effects of oxytocin in humans are conveyed or modulated by oxytocin's impact on cognitive processes, in particular on psychosocial function. We shortly summarize the current literature on oxytocin's involvement in food intake and metabolic control, ponder potential links to social and cognitive processes, and address future perspectives as well as limitations of oxytocin administration in experimental and clinical contexts.

Contents

* Corresponding author.
E-mail address: M.S.Spetter@bham.ac.uk (M.S. Spetter).

http://dx.doi.org/10.1016/j.physbeh.2017.03.007
0031-9384/

1. Introduction

The hypothalamic neuropeptide oxytocin, besides its physiological function in parturition and lactation, is primarily known for its role in psychosocial and affective processing, e.g., in bonding behavior, emotion regulation, and sexual function [1–4]. Oxytocin is released into the circulation by axonal terminals in the posterior pituitary and, in addition, acts directly on central nervous receptors. Interestingly, oxytocin is produced in hypothalamic regions that also regulate appetite and metabolism and are targets of appetite-regulating hormones like leptin, cholecystokinin (CCK) and ghrelin [5,6]. Important insights into the role of oxytocin in the central nervous regulation of metabolic functions have been obtained in animal experiments (e.g., [7–9]; for review see [10,11]) which indicate that oxytocin contributes to the control of food intake, energy expenditure and glucose homeostasis [12,13]. In recent years, first experiments to investigate respective effects in the human organism have been performed, primarily relying on the intranasal pathway of neuropeptide delivery to the brain. Intranasal administration of oxytocin in humans has been repeatedly shown to inhibit eating behavior driven by hunger due to energy depletion as well as by more reward-related, 'hedonic' factors associated with food intake [14–16]. This short review summarizes the effects of oxytocin on ingestive behavior in healthy humans and subjects with obesity or eating disorders, with the aim of providing an update on current research and future directions, and looks at possible links between oxytocin's eating-related function and its role in psychosocial regulation (see Fig. 1 for an overview of oxytocin effects).

2. The neuropeptide oxytocin

Oxytocin is a nine-amino acid neuropeptide hormone that is predominantly produced in two hypothalamic regions, the paraventricular nucleus (PVN) and the supraoptic nucleus [17]. PVN oxytocin neurons project to the pituitary gland (about 40%) and a number of brain areas including the brainstem. Around 10% of PVN neurons project to three core areas of the brainstem that play an important role in the regulation of food intake: nucleus tractus solitarius, dorsal motor nucleus of the vagus nerve (DMNV), and area postrema [18,19]. Oxytocin in addition is active in brain areas of relevance for reward- and eating-related behavior such as the ventral tegmental area (VTA), nucleus accumbens (NAcc), and nucleus stria terminalis [20]. It is assumed that only a small ratio of oxytocin released into the periphery via the posterior pituitary passes the blood-brain barrier to re-enter the brain [21], which might explain why oxytocin concentrations are up to 1000 times higher in the brain than in the blood. In conjunction with the observation that the half-life of the peptide in the central nervous system (CNS) is over three times longer than in the periphery (19 vs. 6 min) [22,23], this pattern furthermore points to the specific relevance of the hormone for central nervous functions [24].

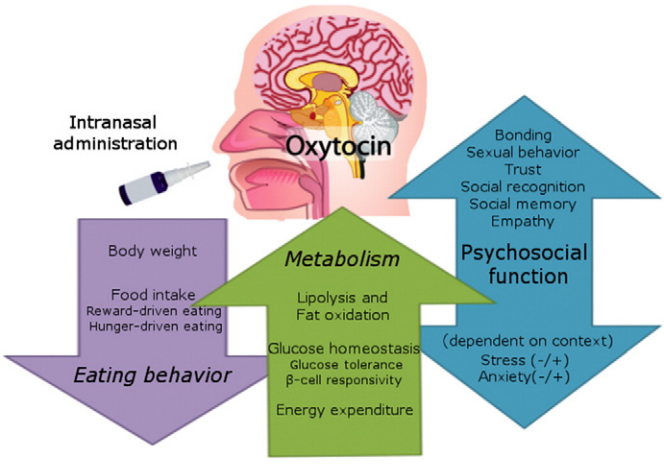

Fig. 1. Schematic overview of oxytocin effects. The role of endogenous (primarily hypothalamus-derived) oxytocin has been investigated in numerous studies relying mostly (in the human setting) on intranasal delivery. Oxytocin has been shown to curb food intake and decrease body weight both in animals and humans (purple arrow). Effects on metabolism furthermore comprise increases in energy expenditure, lipolysis, glucose tolerance and insulin sensitivity (green arrow). The psychosocial effect of oxytocin concerns social, emotional and cognitive functions as well as anxiety- and stress-related processes (blue arrow).

The role of oxytocin in the periphery and in particular in the female reproductive system is well established, first of all with regard to fertilization and parturition. During pregnancy, the uterus increases its oxytocin sensitivity before giving birth, and receptor density increases during labor [25]. The human ovary also expresses oxytocin receptors (OXTR), and oxytocin possibly affects the fertilization process and the very early development of the embryo [26]. The most prominent role of oxytocin in humans concerns lactation. The infant triggers secretion of the peptide by sucking on the mother's nipple, which stimulates additional milk ejection. The male reproductive system has also been observed to be oxytocin-sensitive [27].

The G-protein coupled OXTR [28] can be found in a wide range of brain regions (see ref. [27,29] for review), e.g., in hypothalamus, amygdala, anterior cingulate cortex (ACC), olfactory nucleus, and in limbic areas [30]. Moreover, oxytocin interacts with other neurotransmitters to influence brain function. It has been suggested that serotonin increases oxytocin concentrations [31] and that dopamine interacts with oxytocin [32] to modulate activity of the brain's reward circuitry [32,33] (see also Chapter 4.2 of this review). The latter interaction has been assumed to be of relevance for behavioral disorders such as sexual dysfunction, autism, depression, but also eating disorders (see ref. [34] for further reading). In addition to its expression in the brain, oxytocin is expressed in myenteric and submucous ganglia and nerve fibers of the human gastrointestinal tract [35], with potential consequences for eating behavior and metabolism.

A suitable way to study the contribution of (neuro)peptidergic messengers to human brain function is the intranasal route of administration, which largely bypasses the blood-brain barrier (BBB) and delivers neuropeptides directly to the CNS. In humans, intranasally administered peptides have been found to reach the CNS within 45 min after delivery [36]. Since intra-neuronal transport of neuropeptides from the nasal mucosa to the olfactory bulb normally takes several hours [37], it is assumed that intranasally administered neuropeptides travel to the CNS via extra-neuronal pathways, bypassing the BBB paracellularly by diffusing into the subarachnoidal space across the olfactory epithelia and through intercellular clefts between sustentacular cells and olfactory neurons [38]. Passage of intranasally delivered peptides to the brain may also be established along cranial and trigeminal nerve branches [39]. Most recently, bulk flow within the perivascular space of cerebral blood vessels has been identified as another transport mechanism after intranasal administration [40]. Research relying on nasal spray application (mainly of 24–30 IU) of oxytocin indicates that the concentration of the peptide increases in both saliva and peripheral blood, with peak plasma concentrations at 10–40 min, or even 90 min following intranasal application [41–43]. Recent experiments by