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Review

Pathophysiological function of oxytocin secreted by neuropeptides: A mini review

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Abstract

Oxytocin (OXT) is well known for its ability to stimulate milk ejection and uterine contraction. OXT is also involved in several physiological and pathological functions such as antinociception, anxiety, feeding, social recognition and stress responses. Previous studies showed that neuropeptides such as cholecystokinin (CCK) activate OXT-secreting magnocellular neuron in the supraoptic (SON) and the paraventricular nuclei (PVN) of the hypothalamus and cause OXT release from the axon terminal in the posterior pituitary into the systemic circulation. Our recent studies showed that central administration of adrenomedullin (AM) family (AM, AM2 (identical to intermedin) and AM5) induced the expression of the c-*fos* gene in the SON and the PVN and elicited the marked increase of plasma OXT levels in conscious rats. Here, we review pathophysiological properties of OXT in whole body and effects of novel peptides such as AM family as well as other peptides on OXT release.

Keywords: Adrenomedullin family; Cholecystokinin; Hypothalamus; Neuropeptides; Paraventricular nucleus; Supraoptic nucleus

Contents

Abbreviations: AM, adrenomedullin; α-MSH, α-melanocyte stimulating hormone; AP, area postrema; AVP, arginine vasopressin; AVPV, the anteroventral periventricular nucleus; BNST, the bed nucleus of the stria terminalis; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CeA, the central nucleus of the amygdala; CGRP, calcitonin gene-related peptide; CNS, central nervous system; LHA, the lateral hypothalamic area; NAcc, the nucleus accumbens; NTS, the nucleus of the solitary tract; OLETF, Otsuka Long-Evans Tokushima Fatty rat; OTR, oxytocin receptor; OXT, oxytocin; POMC, proopiomelanocortin; PrRP, prolactin-releasing peptide; PVN, the paraventricular nucleus; RFRP, RFamide-related peptides; SON, the supraoptic nucleus; VLM, the ventrolateral medulla; VMH, the ventromedial nucleus of hypothalamus.

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1. Introduction

Oxytocin (OXT), a nine amino acid neuropeptide, was discovered in 1906 as the extracts with uterus-contracting effects from pituitary [1]. OXT was the first peptide hormone to be sequenced and synthesized in 1953 [2–4]. OXT and Arginine vasopression (AVP) are closely related peptides synthesized primarily in magnocellular neurons of the hypothalamus localized in the supraoptic (SON) and the paraventricular nuclei (PVN), which project their axon terminals into the posterior pituitary where it is released into the systemic circulation [5,6].

OXT is well known for its roles in reproduction, especially during and after childbirth. A large amount of OXT is released after distension of the cervix and uterus during labor to help birth, and after stimulation of the nipples to milk ejection. Previous many studies showed that OXT is involved in several of physiological and pathological functions such as antinociception, anxiety, feeding, social recognition and stress responses [7–12] (Fig. 1).

In this review, we focus on (1) synthesis and distribution of OXT, (2) physiological functions of OXT, and (3) novel peptides, which stimulate OXT release (Table 1).

2. Synthesis and distribution of OXT

2.1. Regulation of synthesis and release of OXT

OXT is produced in the magnocellular neurosecretary cells of the SON and the PVN of the hypothalamus and is released into the systemic circulation from axon terminals in the neurohypophysis, particularly during parturition, lactation and in response to osmotic challenge [13]. The parvocellular OXT cells in the PVN, project their axon terminals to the brainstem and the spinal cord where OXT regulates autonomic functions [14]. Additional parvocellular OXT cells are found in the preoptic area and the lateral hypothalamus, whereas accessory magnocellular OXT cells are found scattered across the hypothalamus.

OXT is well known for its roles in reproduction, especially during and after childbirth. The pulsatile OXT release into the circulation is stimulated by vaginocervical stimulation associated with labor and suckling stimulus on the nipple. The uterine muscle increases its OXT receptor (OTR) and sensitivity to OXT during the latter few months of pregnancy. That level of OXT release from the neurohypophysis is considerably increased at the time of labor. In lactation, OXT causes milk to be expressed from the alveoli into the ducts of the breast that the baby can obtain it by suckling. The suckling stimulus on the nipple of the breast causes signals to be transmitted through sensory nerves to the OXT-secreting magnocellular neurons in the SON and the PVN. OXT in plasma is carried to the breast, where it causes contraction of myoepithelial cells that lie outside of and form a latticework surrounding the alveoli of the mammary glands. In less than a minute after baby's suckling, milk begins to flow.

OXT is also recognized as having endocrine and paracrine roles in male reproduction. OXT is synthesized within the mammalian testis, epididymis and prostate and OTRs in the reproductive tract supports a local action for OXT [15–23]. In ejaculation, a burst of OXT is released from the neurohypophysis into the systemic circulation and stimulates contractions of the reproductive tract for sperm release [24–26]. OXT has a paracrine role in stimulating contractility of the seminiferous tubules, epididymis and the prostate gland.

Interestingly, OXT is also released from soma and dendrites during parturition and lactation [27]. Although OXT released from soma and dendrites of magnocellular neurons in the SON and the PVN may act in a paracrine to activate distant receptors [27], OXT-like immunoreactivity (LI) fibers can be found throughout the brain, including the nucleus accumbens (NAcc), lateral septum, amygdala, and some areas in the hindbrain, brainstem, and spinal cord