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Research report

Oxytocin and vasopressin in rodent behaviors related to social dysfunctions in autism spectrum disorders

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HIGHLIGHTS

- Neurobiology of brain oxytocin and vasopressin (neuroanatomy, central release, receptor distribution).
- Oxytocin and vasopressin in rodent social behaviors (affiliative behavior, social cognition, social approach).
- Translational aspects of brain oxytocin and vasopressin in social behaviors.

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ABSTRACT

Autism spectrum disorders (ASD) and social anxiety disorder involve various forms of social deficits like impaired affiliative behavior, social cognition and social approach. Although the neurobiological underpinnings of these disorders are largely unknown, rodent and human studies suggest an involvement of the evolutionary highly conserved oxytocin (OXT) and vasopressin (AVP), as these neuropeptides modulate various aspects of mammalian social behaviors.

In this review we summarize the current knowledge regarding the involvement of brain OXT and AVP in rodent social behaviors related to social dysfunctions in ASD.

Starting with an introduction into the neurobiology of the central OXT and AVP systems (neuroanatomy, central release, receptor distribution) we describe the distinct roles OXT and AVP play in basic social behaviors in rodents, i.e. affiliative behavior (pair-bonding and maternal behavior), social cognition (social memory), and social approach (social preference or social avoidance). The regulatory capacity of OXT and AVP to modulate social behaviors in various rodent species implies a high translational potential, in particular that dys-regulations in the brain neuropeptide systems may underlie social dysfunctions in ASD. It also suggests that the brain OXT and AVP systems are promising pharmacotherapeutic targets to improve social behaviors and to reverse social deficits.

1. Introduction

Numerous psychiatric disorders including major depression, anxiety disorders, or schizophrenia are mainly characterized by emotional dysfunctions such as exaggerated anxiety and depression-related symptoms, but also by profound impairment of social interactions. Autism spectrum disorders (ASD), including Asperger's syndrome, are primarily defined by deficits in sociability, which are, however, also often accompanied by emotional disturbances. Social dysfunctions of ASD patients include deficits in affiliative behavior, social cognition, and cognitive and affective empathy, as well as social withdrawal and social phobia. These symptoms become apparent during standard nonverbal behavioral tests, as patients show reduced eye contact and affective expression, and impaired recognition of facial expressions of emotion [1–3].

The neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) become increasingly attractive as potential therapeutic targets in the context of ASD research. This is mainly due to the fact that they are key regulators of social behaviors as has been revealed and confirmed both in laboratory animals, such as rats and mice, and humans using complementary behavioral paradigms. Neuropeptides of the arginine vasotocin family, including OXT and AVP as well as the related vasotocin (found in birds and fish), isotocin (fish), and mesotocin (marsupials, birds), are ubiquitous within vertebrates and evolutionary highly conserved, both in structure and function [4]. Another key feature explaining their value in translational research. Furthermore, brain OXT, in particular, mediates the beneficial effects of positive social interactions for the individual mental and physical fitness [31].

In this review we will highlight the involvement of OXT and AVP in the regulation of social behaviors in well defined

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behavioral models in rodents, which are suitable for the investigation of the neurobiological underpinnings of ASD-related deficits in human sociability. In particular, based on a summary of the basic neurobiology of the OXT and AVP systems, we will focus on neuropeptidergic regulation of affiliative behavior, social cognition, and social approach, which are of particular relevance for ASD.

2. Neurobiology and peripheral functions of OXT and AVP

OXT and AVP are circular nonapeptides differing in only two amino acid positions [5,6]. OXT and AVP are mainly synthesized in a well-defined arrangement of magnocellular neurons located within the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus at the base of the diencephalon, with little or no co-localization of the neuropeptides. Via axonal projections guided through the median eminence, OXT- and AVP-containing vesicles reach the posterior pituitary. In the pituitary they are stored and released into the blood stream in response to appropriate physiological stimuli via neurohemal contact zones between neuronal terminals and capillaries [7,8]. With respect to their physiological functions in the periphery, OXT, and its related neuropeptide mesotocin, have been originally reported as hormonal key regulators of female reproduction in all mammals including placentalia, monotremes (both OXT), and marsupials (mesotocin). Oxytocin means "quick birth", and, in placental mammals, it is secreted in response to parturition-related stimuli and promotes uterine contractions during parturition. In lactation, stimulated by suckling offspring, OXT (and mesotocin) is essential for the milk ejection via actions at OXT receptors (OXTR) at the myoepithelial cells of the mammary ducts. However, OXT exerts also other peripheral effects such as regulation of glucose metabolism, regulation of adrenal functions, and sperm transport. The main physiological function of circulating AVP is best characterized by its second name, i.e. antidiuretic hormone, as AVP regulates osmotic and cardiovascular homeostasis by promoting water resorption via AVP 2 receptors of the renal distal tubuli and collecting ducts (antidiuresis). By binding to AVP 1a receptors (AVPR1a), plasma AVP increases the constriction of vascular smooth muscle cells and, thus, blood pressure. Since OXT and AVP are synthesized in and released from neurons, circulate in blood after neurohypophysial secretion, and act as true hormones in the periphery of the body, they can be called neurohormones.

3. The brain OXT and AVP systems

3.1. Neuroanatomy

Starting with the fundamental discoveries of Pedersen and DeWied [9,10], both OXT and AVP emerged as potential neurotransmitters/neuromodulators of the brain regulating various behaviors. Briefly, initial experiments by Pedersen and Prange [10] showed that OXT is crucially involved in the onset of maternal care, as central administration of the neuropeptide triggers spontaneous maternal behavior in virgin rats. Concerning the behavioral properties of AVP, DeWied [9] was able to demonstrate that posterior pituitary peptides, including AVP, act centrally as regulators of learning and memory, as they reduce the extinction rate of active avoidance in male rats.

Early neuroanatomical studies in rats discovered neurophysin-containing fibers, which not only project to the neurohypophysis, but also to different target regions of the brain. As neurophysin is a specific 10-kDa carrier protein co-located with OXT and AVP in secretory vesicles, this confirms the existence of direct oxytocinergic and vasopressinergic pathways within the central nervous system [11,12]. Recently, magnocellular OXT neurons were found to project both to the neurohypophysis and to central targets such as the amygdala [13]. Further, there are distinct populations of parvocellular OXT and AVP neurons in the PVN reaching the median eminence and the hindbrain, but also limbic brain regions including the medial septum, the ventral and dorsal hippocampus, and the amygdala [14]. Additionally, extrahypothalamic AVP cells in the medial amygdala project to the lateral septum and to the ventral hippocampus [15], whereas AVP cells from the BST innervate prefrontal and hindbrain regions, including the lateral septum, the ventral septal area, the vertical diagonal band of Broca, the lateral habenular nucleus, the olfactory tubercle, and the locus coeruleus [16]. AVP neurons of the suprachiasmatic nucleus also project to the medial preoptic area (MPOA) and the thalamus [17].

These neuroanatomical findings indicate a complex brain neuropeptidergic network. Since the target regions of centrally projecting neuropeptidergic neurons are mostly involved in the regulation of emotionality, stress coping, and social behaviors, these systems gain more and more attention in ASD-related research.

3.2. Central release

Based on these neuroanatomical findings and the description of multiple behavioral effects, monitoring of neuronal release of OXT and AVP within distinct brain regions in a physiological or behavioral context became a particular challenge. Such locally restricted release should determine the concentration of biologically active neuropeptides in the extracellular fluid (ECF) of a given brain area and, subsequently, the cascade of intracellular events of target neurons beginning with neuropeptide-receptor binding.

Numerous microdialysis and push–pull-perfusion studies, performed mainly in rats and sheep, but also mice [18], demonstrated local OXT and/or AVP release within hypothalamic and other limbic brain regions in response to classical physiological (birth, suckling, hyperosmotic stimulation), but also pharmacological, stressful and social stimuli [for detailed reviews see 8, 19, 20]. Prerequisites for such studies are microdialysate probes with a recovery of about 2–3% in vitro in combination with highly specific radioimmunoassays for OXT and AVP, with high sensitivity allowing the quantification of pg-amounts in the microdialysate samples [21,22]. In this context, regions which were extensively studied include the hypothalamic SON, PVN and suprachiasmatic nucleus, but also the septum, MPOA, olfactory bulb, amygdala, and BST. Interestingly, within the hypothalamic SON, Pow and Morris [23] could provide first evidence for neuropeptide release from magnocellular dendrites and somata using electronmicroscopic techniques, which could be confirmed by microdialysis studies [20]. Until now, it is not known whether this non-synaptic release is restricted to the hypothalamic OXT/AVP neurons of the SON and PVN, or is a general mechanism of neuropeptidergic neurotransmission.

Of particular interest in the context of neuropeptides in autism research is the finding that central release of OXT and AVP occurs in response to various social stimuli, both reproduction-related as well as non-reproduction-related (see Table 1). The former include mother–offspring interactions, maternal aggression, and socio-sexual interactions, like mating in males and females [24–30]. Such central release of OXT seems beneficial for an individual's emotional stability under these conditions [for review 31]. However, we will mainly focus on neuropeptide release in response to non-reproductive social stimuli, for example, the exposure to an unknown adult or juvenile con-specific.

Neuropeptide release has been studied primarily in two distinct rodent models of intermale interaction, i.e. the social defeat paradigm, during which a smaller and subordinate male intruder is defeated by the larger dominant resident male, and the