Send Orders for Reprints to reprints@benthamscience.net

Endocrine, Metabolic & Immune Disorders - Drug Targets, **2020**, *20*, **000-000**

REVIEW ARTICLE

Oxytocin Signaling Pathway: From Cell Biology to Clinical Implications

Michele Iovino[1], Tullio Messana[2], Anna Tortora[1], Consuelo Giusti[1], Giuseppe Lisco[3], Vito Angelo Giagulli[1], Edoardo Guastamacchia[1], Giovanni De Pergola[4] and Vincenzo Triggiani[1,*]

[1]*Interdisciplinary Department of Medicine-Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases. University of Bari "Aldo Moro", School of Medicine, Policlinico, Piazza Giulio Cesare 11, 70124, Bari, Italy;* [2]*Infantile Neuropsychiatry, IRCCS – Institute of Neurological Sciences, Bologna, Italy;* [3]*Hospital Unit of Endocrinology, Perrino Hospital, Brindisi, Italy;* [4]*Clinical Nutrition Unit, Medical Oncology, Department of Internal Medicine and Clinical Oncology, University of Bari, School of Medicine, Policlinico, Piazza Giulio Cesare 11, 70124, Bari, Italy*

ARTICLE HISTORY

Received: October 23, 2019
Revised: April 04, 2020
Accepted: April 16, 2020

DOI:
10.2174/1871530320666200520093730

Abstract: ***Background:*** In addition to the well-known role played in lactation and parturition, Oxytocin (OT) and OT receptor (OTR) are involved in many other aspects such as the control of maternal and social behavior, the regulation of the growth of the neocortex, the maintenance of blood supply to the cortex, the stimulation of limbic olfactory area to mother-infant recognition bond, and the modulation of the autonomic nervous system via the vagal pathway. Moreover, OT and OTR show anti-inflammatory, anti-oxidant, anti-pain, anti-diabetic, anti-dyslipidemic and anti-atherogenic effects.

Objective: The aim of this narrative review is to summarize the main data coming from the literature dealing with the role of OT and OTR in physiology and pathologic conditions focusing on the most relevant aspects.

Methods: Appropriate keywords and MeSH terms were identified and searched in Pubmed. Finally, references of original articles and reviews were examined.

Results: We report the most significant and updated data on the role played by OT and OTR in physiology and different clinical contexts.

Conclusion: Emerging evidence indicates the involvement of OT system in several pathophysiological mechanisms influencing brain anatomy, cognition, language, sense of safety and trust and maternal behavior, with the possible use of exogenous administered OT in the treatment of specific neuropsychiatric conditions. Furthermore, it modulates pancreatic β-cell responsiveness and lipid metabolism leading to possible therapeutic use in diabetic and dyslipidemic patients and for limiting and even reversing atherosclerotic lesions.

Keywords: Oxytocin, oxytocin receptor, maternal behavior, social behavior, metabolic homeostasis, atherosclerosis, pain, neuroinflammation, autism, schizophrenia, depression, bipolar disorder.

1. INTRODUCTION

In addition to the well-known role played in lactation and parturition, OT and OT receptor (OTR) are involved in the control of many functions as well as in pathologic conditions with emerging possible therapeutic implications. The aim of this paper was to review the literature dealing with the role of OT and OTR in physiology and in pathologic conditions, summarizing the main concepts emerging from the analysis of the data. Therefore, appropriate keywords and MeSH terms related to Oxytocin and Oxytocin Receptor and their possible functions were identified and searched in Pubmed and references of original articles and reviews were examined.

More exactly, we searched on PubMed the terms that include the following: "Oxytocin" AND "Oxytocin Receptor" AND "Maternal behavior" AND "social behavior" AND "atherosclerosis" AND "pain" AND "neuroinflammation" AND "autism" AND "schizophrenia" AND "depression" AND "bipolar disorder". We particularly selected original articles and reviews written in English until September 2019.

This narrative review reports, therefore, the most significant and updated data on the role played by OT both in physiology and in different clinical conditions.

2. GENERAL ASPECTS OF OT SECRETION AND REGULATION

Oxytocin (OT) is a neuropeptide synthesized by magnocellular neurosecretory (MCN) neurons of the supraoptic (SON) and paraventricular (PVN) nuclei, localized in the anterior hypothalamus, playing an important role in the re-

*Address correspondence to this author at the Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, Interdisciplinary Department of Medicine, University of Bari, School of Medicine, Policlinico. P.O. Box: 70124, Bari, Italy; Tel/Fax: ++39-080-547-8814;
E-mail: vincenzo.triggiani@uniba.it.

1871-5303/20 $65.00+.00

productive organs, such as breast and uterus, and some aspects of social behaviors in many species. The SON contains only MCN neurons which synthesize either OT and VP, whereas the PVN contains also parvocellular neurosecretory (PCN) neurons and sends OTergic and VPergic projections to other brain and spinal cord sites [1, 2].

OT gene encodes a precursor protein that is processed to synthesize OT and its protein carrier neurophysin I [3]. This process is activated via stimulation of nipples and cervix receptors during lactation and parturition. The signals originating from these receptors stimulate SON and PVN MCNs to secrete OT via brain pathways as the spinal cord (SP), the medial forebrain bundle (MFB), the dorsal lateral fasciculus (DLF), the mammillary peduncle (MP) and the nucleus incertus (NI) [4 - 6]. OT and its corresponding carrier protein, neurophysin I, are packaged into neurosecretory granules and transported via axoplasmic flow to axon terminals in the posterior pituitary (PP) and hence are released into the systemic circulation in response to action potentials that depolarize the axon terminals by the opening of voltage-dependent calcium channels inducing exocytosis of the secretory granules [7, 8].

Circulating OT is not able to cross the blood-brain-barrier (BBB) but is transported into the brain by the receptor for advanced glycation end-products (RAGE) on the endothelial cells of the capillary of the BBB. It has been observed that expression of RAGE, a member of the immunoglobulin superfamily that binds various ligands on the capillary of endothelial cells is necessary for the transport of OT into the brain. In fact, mice RAGE KO are unable to increase brain OT following exogenous administration and show reduced maternal behavior [9].

Peripheral signals as relaxin, secreted from the ovary during pregnancy, and gonadal steroids as 17βestradiol, secreted during lactation, stimulate OT synthesis via circumventricular organs as subfornical organ (SFO) and organum vasculosum laminae terminalis (OVLT) [10 - 15], located into the anteroventral region of the third ventricle (AV3V), and synapsing on SON and PVN MCNs by afferent projections [8, 16 - 20]. In addition, estrogen receptors are expressed in various brain nuclei including OTergic and VPergic neurons of SON and PVN [12, 13].

The synaptic inputs that these efferent projections transmit to SON and PVN MCNs mobilize several neurotransmitters and neuropeptides, that once released into the intersynaptic space regulate synaptic actions in an autocrine or paracrine mechanism and stimulate OT release via activation of ligand-gated ion channels, induce rapid changes in membrane potential, and G protein-coupled receptors (GPCRs) that activate a large variety of different signaling cascades that regulate action potential firing [21, 22].

3. MOLECULAR MECHANISMS INVOLVED IN OT SECRETION AND ACTION

3.1. Role of OT Receptor (OTR)

The OTR is a Gq/11 protein-linked receptor, a member of transmembrane GPCRs family, activated by OT release via regulation of ligand-gated ionotropic receptors, ligand-induced trafficking of the GPCRs to the nucleus and different ion channels (K+ and Ca++) [21, 22]. Studies using light microscopic autoradiography showed OT-binding sites in the central nervous system (CNS). OTergic neurons of SON and PVN project to brain areas containing high concentrations of OTR that are the olfactory bulb, nucleus accumbens septi, bed nucleus of the stria terminalis, hypothalamic suprachiasmatic, arcuate and ventromedial nuclei, limbic structures as amygdaloid nuclei, hippocampus, septal nuclei, the nucleus of the solitary tract, the cingulate cortex and spinal cord [23]. OTR has also been identified in peripheral tissue as kidney, heart, thymus, pancreas and adipocytes [24].

GPCRs play a role in the transmission of information from the extracellular environment to the cellular compartment. This mechanism is rapidly attenuated via ligand removal from the extracellular environment, receptor desensitization, endocytosis and down-regulation [25]. The stimulation of OTR causes desensitization and internalization, therefore OTR is sequestered into the intracellular space. Studies carried out using binding and fluorescence assay indicated that almost 85% of the OTR had returned to the cell surface, after 4 h, completely restored, thus showing that OTR recycling is involved in the mechanism of the resensitization. Conti and coworkers [26] showed that the interaction between OTR and β-arrestin indicates the rate recycling of OTRs. In addition, studies of receptor recycling pathways demonstrate the location of OTR in vesicles containing the Rab 4 and Rab 5 small GTPase, which are markers of the "short cycle", thus showing that OTRs promote resensitization via the short cycle of receptor recycling [26]. Finally, intracellular serine after phosphorylation plays a crucial role in OTR trafficking and mediates the interaction OTR-βarrestin. A similar mechanism is observed for VP V2 receptor-mediated trafficking of aquaporin 2 (AQP2) vesicles to cell apical plasma membrane for collecting duct by phosphorylation of the C-terminal tail of AQP2 at serine 256 [7, 27].

Sex differences have been reported for OTR expression showing left lateralization in the female auditory cortex and in right auditory cortex in males. This observation indicates that the higher expression of OTR plays a role in predisposing female cortex to maternal behavior and modulating synaptic transmission via cortical inhibitory interneurons. The GABA-A agonist muscimol injected in the left or right auditory cortex showed an inhibitory role in pup retrieval behavior only when administered in the left but not right auditory cortex, while OT reduces synaptic inhibition induced by GABA in multiple brain areas [28]. This action on inhibitory interneurons modulates GABAergic transmission and increases synaptic excitability and the autocrine mechanism of OT-induced OT release in PVN [28]. Sex-specific differences of OTR expression and function might be related to different factors. OT in females has more access to the central nervous system because the BBB permeability is more permissive in females [29]. Moreover, the saturation of OTR to OT secretion during social interaction occurs more rapidly in males than in females [30]. A higher expression of OTR in female left auditory cortex has been described, strictly conditioning the maturation of maternal behavior by the left lateralization of the auditory cortex [31].

3.2. OT Gene Expression

Signals arising from suckling and cervical stretch reach SON and PVN MCNs, via afferent pathways in the brainstem and spinal cord [4 - 6], and trigger trafficking of the neurokinin 3 receptor (NK3R) in OTergic and VPergic neurons. The NK3R is associated with a nuclear chaperone protein called importin β1 which facilitates its movements through the nuclear pores inducing OT and VP synthesis in the Golgi complex and rough endoplasmic reticulum [32 - 34]. This trafficking of the NK3R to the nucleus plays an important role in the regulation of genes involved in the increased secretion of OT during lactation and parturition, and VP to osmotic stimuli (Fig. **1**).

It has been reported that MCN and PCN neurons of SON and PVN express a large variety of genes controlling the synthesis of OT, VP, and their carrier proteins neurophysin I and II. Suckling and cervical stretch produce multiple changes in gene expression levels. In lactating female rats, a significant increase has been observed in OT mRNA transcription at the level of MCN and PCN neurons of SON and PVN while osmotic stimuli increased more VP hnRNA but lowering OT hnRNA [35, 36]. GABAergic and NAergic regulation of MCN and PCN neurons within PVN has been investigated with bicuculline, a GABA-A receptor antagonist, and NA injected directly into the PVN. This pharmacological approach induced a significant increase in OT and VP hnRNA and c-Fos immunoreactivity, thus showing a stimulatory NAergic and inhibitory GABAergic control of OT and VP gene expression [37-39]. A relationship between OT and VP gene expression has been observed in OT KO mice. VP mRNA in SON and PVN was significantly lower in KO mice compared to wild-type even if an up-regulation of VP gene expression in OT KO mice was observed after osmotic stimuli indicating a compensatory up-regulation of VP gene expression [40]. Differential kinetics of OT and VP hnRNA expression has been observed in the SON under osmotic stimuli. VP hnRNA levels increased few minutes after osmotic stimuli, while OT hnRNA gene expression increased only three days following salt loading thus showing that OT gene transcription is not chronologically related with VP gene transcription in SON, thus highlighting two different excitation-secretion-transcription mechanisms involved in the regulation of OT and VP synthesis [41].

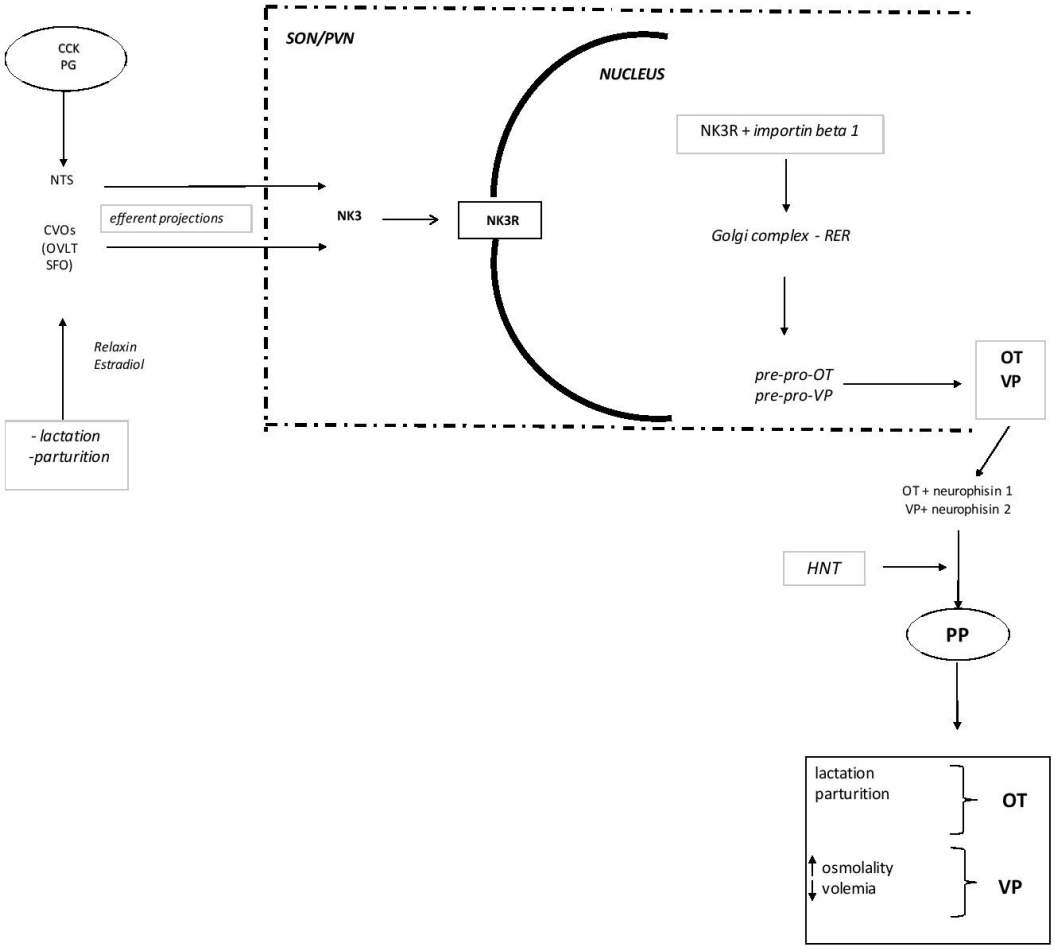

Fig. (1). Anatomical, molecular and physiological mechanisms involved in OT and VP secretion. CCK: cholecystokinin; PG: prostaglandins; NTS: Nucleus of the solitary tract; CVOs: circumventricular organs; OVLT: organum vasculosum lamina terminalis; SFO: subfornical organ; SON: supraoptic nucleus; PVN: paraventricular nucleus; NK3: neurokinin 3; NK3R: neurokinin 3 receptor; RER: rough endoplasmic reticulum; HNT: hypothalamo-neurohypophyseal tract; PP: posterior pituitary; ↑ increase; ↓ decrease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.3. Dendritic Plasticity and Synaptogenesis of SON and PVN

SON and PVN MCNs release neurohypophyseal hormones OT and vasopressin (VP) at the dendritic level in order to play an autocrine control. After the second postnatal week of life in rats, the dendritic arbor increases and the glutamatergic postsynaptic receptor becomes functionally active.

This dendritic plasticity and synaptogenesis are mediated by an interplay between the postsynaptic dendritic release of OT and VP and presynaptic glutamate release. In fact, *in vivo* administration of OT, VP and the glutamatergic receptor agonist N-methyl-D-aspartate (NMDA) stimulate dendritic plasticity and synaptogenesis; on the other hand, antagonists of OT, VP and NMDA inhibit the maturation of glutamatergic synaptic transmission and dendritic arbor increase of SON MCNs [42]. In addition, synaptic plasticity is mainly evident during lactation with an increase in glutamatergic synapses in OTergic and VPergic neurons of SON [43].

3.4. Glial Regulation

The glial cells, mainly the astrocytes, regulate synaptic inputs inducing morphological plasticity of SON and PVN MCNs during lactation and dehydration. Histological changes are observed in MCNs as increased direct soma-somatic contacts by retraction of fine glial processes, increased cells with the dilated rough endoplasmic reticulum, increased direct juxtaposition of MC neuronal surface, and decrease of lysosomes during lactation and osmotic stimuli [44, 45]. In addition to morphological plasticity, astrocytes trigger the release of glutamate, ATP, purines, D-serine, TNF-α as gliotransmitters and express GPCRs [46 - 53]. In rat PVN, the excitatory effect of noradrenaline (NA) is mediated by ATP released from glial cells, thus showing the role of ATP as gliotransmitter in the regulation of postsynaptic efficacy. ATP binds to purinergic receptor (P2X7), localized at the postsynaptic level of MCNs, inducing the opening of the P2X7 cation-channel with calcium influx in MCNs and hence increasing the postsynaptic efficacy to glutamate of these neurons [54 - 57]. Consequently, this mechanism determines both increased postsynaptic sensitivity to glutamate and strengthened glutamate synapses in order to increase MCNs excitability to synthesize and release OT and VP to osmotic and non-osmotic stimuli [58]. The ultrastructural changes in SON and PVN MCNs observed during lactation indicate that this anatomical remodeling of glial cells plays an important role in the stimulatory mechanism of action of glutamate synapses increasing glutamatergic tone and inhibiting GABA release by stimulation of glutamatergic receptors that block GABA release [59]. On the other hand, in resting conditions, the GABAergic tone prevails [59], thus showing many brain processes as under the excitatory control of glutamate, via action potential discharge, and GABAergic inhibition, via membrane hyperpolarization [60, 61]; therefore a balanced interaction glutamate-GABA is required to maintain the physiological homeostasis [62, 63].

Kainate-receptors (KARs) are members of the glutamate receptor family and mediate synaptic transmission, post-synaptically by ionotropic inputs, and pre-synaptically regulate GABA and glutamate release. The regulatory action on neurotransmitter release can be switched from stimulation to inhibition and is directly dependent on astrocytic plasticity. Activation of presynaptic KARs induces GABA release in OTergic and VPergic neurons of SON. On the other hand, glutamate increases during lactation, which is shown by reduction in astrocytic coverage of OTergic neurons, and induces inhibition of GABAergic transmission [64]. These data indicate that increased levels of glutamate, released into the confined space of a synaptic cleft, cause the switch induced by KARs. Therefore, the stimulation of GABAergic transmission blocked by the Ca(2+)-permeable KAR antagonist suggests an ionotropic mechanism of action. Instead, a metabotropic mode of action is involved in KAR-mediated inhibition that is blocked by a phospholipase C inhibitor [64]. Glial uptake of glutamate reduces the action potential discharge in SON and PVN MCNs under resting conditions; on the other hand, during osmotic and non-osmotic stimuli, the glial glutamate uptake decreases inducing neuronal activity, showed by c-Fos immunoreactivity, in SON and PVN MCNs. Therefore, astrocytes control, in MCNs, a direct crosstalk between NMDA and GABA-A postsynaptic receptors in order to maintain this balance [60 - 63].

OT and VP released from the dendrites of SON and PVN MCNs modulate synaptic transmission in two ways; at post-synaptic level, inducing the axoplasmic transport of OT and VP to PP and at presynaptic terminals, inducing an autocrine control of afferent inputs to MCNs. OT acts as a presynaptic agonist in the SON and PVN by the inhibition of glutamatergic receptors. Therefore SON and PVN MCNs play a role both as site receiving afferent signals and regulators of the magnitude of afferent inputs [65].

During osmotic and non-osmotic stimuli, the release of OT and VP depends also on changes of the cytoskeletal organization by the increase of actin filament density. Ultrastructural changes of actin filaments along the hypothalamo-neurohypophyseal tract (HNT), as well as migration, morphogenesis, axonal sprouting and endocytosis, are observed during lactation and dehydration. The increased density of actin filaments is induced by contractile proteins, as plasma membrane phosphoinositides, thus inducing the axoplasmic transport of OT and VP to PP [66 - 69].

4. NEURAL PATHWAYS AND HORMONES REGULATING OT SECRETION

Neural afferent pathways arising from stretching of the cervix during parturition (Ferguson reflex) and suckling of the nipple by the newborn (milk let-down reflex of Ely and Petersen) reach and synapse on OTergic neurons of SON and PVN via mesencephalic and diencephalic pathways as the SC, MFB, DLF, and MP [4-6]. The synapses that these neural pathways form on MCNs of SON and PVN express several neurotransmitters and neurohormones.

4.1. Dopaminergic Regulation

SON and PVN MCNs receive dopamine(DA)-ergic inputs from pathways originating in the arcuate and periventricular nuclei [70, 71]. In lactating suckled rats, DA and apomorphine facilitate the milk-ejection reflex increasing the

activity of OTergic neurons [72]. DA depolarizes SON MCNs in hypothalamic explants. Similar responses have been observed for quinpirole, a D2 agonist, but not a D1 agonist, whereas the action of DA is selectively antagonized by two D2 receptor antagonists, sulpiride and spiperone. These results show that DA depolarizes SON MCNs by stimulation of D2 receptors located at the soma-dendritic level and involves an intracellular Ca(2+)-dependent mechanism [73].

4.2. Noradrenergic Regulation

OTergic neurons of the SON and PVN receive noradrenaline(NA)-ergic afferent projections from the A1 and A2 cell groups of the medulla oblongata [70, 74]. Electrophysiological studies showed that stimulation of A1 and A2 NAergic neurons enhanced the activity of SON and PVN MCNs. Chemical lesions of PVN NAergic terminal plexus by local application of the neurotoxin 6-OHDA blocked the stimulatory effect of A1 and A2 NAergic neurons, thus showing NAergic inputs arising from A1 and A2 medullary neurons to facilitate the activity of SON and PVN MCNs [75, 76].

In addition, it has been observed that histamine(H)-ergic and NAergic interactions control the OT and VP synthesis and release. Central administration of H or NA increases significantly OT and VP secretion. These responses were antagonized by H1 receptor antagonist mepyramine or H2 receptor antagonist cimetidine. Moreover, systemic pretreatment with imetit, which inhibits neuronal synthesis and release of H, significantly decreased the OT and VP secretion to NA [77], thus showing that NAergic inputs stimulate OT and VP secretion via involvement of Hergic neurons at the level of SON and PVN MCNs.

In vitro experiments, using perfused explant of the hypothalamo-neurohypophyseal tract, synergistic responses between purine(P)-ergic and adrener(A)-ergic agonists have been observed. ATP increased OT and VP release, and this increase was synergized after the infusion of the α1-Aergic agonist phenylephrine that resulted in a threefold to fourfold increase of OT and VP. This effect was antagonized by a P-receptor antagonist, a protein kinase C inhibitor, and actinomycin, an inhibitor of gene transcription [78], thus showing that the significant increase of OT and VP required Pergic receptor activation and gene transcription.

4.3. Serotoninergic Regulation

The mesencephalic dorsal raphe nuclei (DRN), classified as B7-B8-B9 [74, 79, 80], the most important site of serotonin (5-HT) neuronal cell bodies in the brain, are involved in the synthesis and release of OT and VP. Afferent projections originating in the DRN synapse in the SON and PVN [81, 82] and the enhancement of 5-HT in cultures of isolated rat neurohypophyseal tissue produce a significant increase in OT and VP, thus showing a 5-HTergic control of OT and VP secretion at the level of posterior pituitary [83]. The 5-HTergic receptors involved in OT secretion are primarily the 5-HT1A, 5-HT2C and 5-HT4. Indeed the stimulation of these receptors increased the level of OT mRNA both in the SON and PVN [72, 84].

4.4. GABAergic Regulation

GABAergic pathways originate in the limbic system and CVOs synapse on SON and PVN MCNs [85, 86]. GABA and its synthesizing enzyme, glutamic acid decarboxylase (GAD), have been revealed in OT-and VP-secreting neurons of SON and PVN as well as in the HNT [87, 88]. In addition, GABA microiontophoretically injected reduces significantly the activity of SON and PVN MCNs [89 - 91].

OT and VP release induced by hyperosmotic stress is inhibited by GABAergic neurons. It has been reported that chronic hyperosmotic stress reduced GABA synaptic inhibition of SON and PVN MCNs. *In vitro* studies performed on hypothalamic neurons of rats submitted to chronic hyperosmotic stress showed that the GABAergic inhibition converted into an excitatory response and the administration of the GABA-A antagonist bicuculline lowered OT and VP release under the chronic hyperosmotic stress. This switch from inhibition to excitation caused the increased release of OT and VP, and antagonized by blocking OT receptors. Therefore, upregulation of transmembrane Cl-gradients in postsynaptic neurons is the mechanism mediating the inhibitory-to-excitatory switch of GABAergic transmission [92].

4.5. Opioid Peptides Regulation

Endogenous opioid peptide system modulates OTergic and VPergic neurons of SON and PVN both on the basal secretion and the release of osmotic and non-osmotic stimuli. Inhibitory mechanisms of basal secretion act at the level of terminal axons, whereas pre-synaptic inhibition of afferent inputs to MCNs plays a role during lactation or parturition [93]. The endogenous opioid peptide system consists of three families of opioid peptides: endorphins, enkephalins (ENK) and dynorphins; and three families of receptors: μ (MOR), δ (DOR) and κ (KOR). ENKergic pathways involved in SON and PVN MCNs activity originate in the nucleus of the solitary tract (NTS) of the medulla oblongata [94], the bed nucleus of the stria terminalis (BST), the centromedial amygdala [95] and the hypothalamo-septal pathway [96]. In addition, opioid synapses in the PP have been observed and the neurohypophyseal ENK content was significantly reduced following electrolytic lesions of SON [97], thus showing ENK originating in SON and PVN MCNs to reach the PP via axoplasmic transport. Opioid peptides inhibit OT release in lactation [98, 99]. It has been observed that the opioid peptide dynorphin, centrally administered, attenuated the increase of OT secretion during dehydration. This effect was prevented by KOR antagonists, thus indicating that KORs were required for the biological response [99 - 101]. Moreover, the synthesis and release of both OT and VP, from SON and PVN MCNs, following an acute increase of angiotensin II (ANG II) in cerebrospinal fluid (CSF) are inhibited by leucin-ENK, centrally administered [102].

4.6. Hormonal Regulation

The peptide hormone relaxin, released by the ovary during the pregnancy, stimulates the secretion of OT increasing the firing rate of SON and PVN MCNs via SFO and OVLT [10, 11]. The mechanism of action played by relaxin during labor is the relaxation of pelvic ligaments and uterine muscu-

lature, softening of the cervix and pubic symphysis, broadening of the pubic bone. Circulating relaxin is a peptide too large and hence is not able to cross the blood-brain-barrier (BBB), therefore its action is mediated by activation of relaxin receptors located within the SFO and OVLT [103] that lack the BBB. Direct efferent axons originating in the SFO and OVLT synapse on SON and PVN MCNs [16, 17, 19, 104], thus showing that signals induced by relaxin during the pregnancy and parturition reach OTergic neurons via SFO and OVLT [104]. 17βestradiol (E2) stimulates the dendrosomatic release of OT [14] and modulates the response of OTergic neurons in lactating rats [15]. The stimulatory effects of E2 on OT synthesis and release are mediated via SFO and OVLT that contain estrogen receptors (ERs) [12, 13, 105]. ERs subtypes include the ERα, ERβ and the GPCR 30 that are located both in OTergic and VPergic neurons of SON and PVN [12, 13]. ERβ plays an inhibitory role in the regulation of OT and VP mRNA expression. It has been reported that ERβ KO mice are unable to decrease OT and VP gene expression after E2 treatment [106]. Hyperosmotic stimuli decrease ERβ expression in SON and PVN MCNs, therefore a down-regulation of ERβ, in response to osmotic or non-osmotic stimuli, removing an inhibitory control, stimulates OT and VP release [107].

Also the gonadal steroid progesterone (P) influences OTergic neurons during the pregnancy. Indeed, the initial phase of parturition is characterized by a P decrease. This fall of plasma P levels, removing the inhibitory control on uterine tone and neurons secreting OT, provokes high expression of uterine OT receptors and a positive feedback between these receptors and OTergic neurons in the SON and PVN. Therefore, during parturition, prostaglandins (PG) induce uterine contractions stimulating OT release, and consequently, OT induces PG secretion that further enhances uterine contractions. The anatomical pathway involved in this mechanism, and triggered by uterine contractions, is the vagus nerve which projects neurons of the NTS in the medulla oblongata, and hence from NTS to hypothalamic OTergic cells of SON and PVN [108, 109].

Cholecystokinin octapeptide (CCK-8) stimulates OT release. It has been reported that systemic administration of CCK-8 induced a dose-dependent increase in plasma OT levels and gastric vagotomy reduced this stimulatory effect of CCK-8 on OT secretion [110]. In addition, the intravenous or intraperitoneal injection of CCK-8 increases the firing frequency of OTergic neurons but not VPergic neurons [111] and activates C-fos mRNA expression in OTergic neurons of SON and PVN [112]. Moreover, the administration of selective CCK-A receptor antagonists, but not CCK-B receptor antagonists, before the injection of CCK-8 prevented both plasma OT release and nuclear C-fos expression in SON and PVN MCNs [113,114], thus showing ascending gastric vagus to modulate hypothalamic OTergic and VPergic neurons via NTS NAergic neurons of the dorsal medulla oblongata [115 - 117], the A2 cell group [61, 65] (Fig. **2**).

5. PHYSIOLOGICAL EFFECTS OF OT

In addition to the effects produced during parturition and lactation, OT mediates the development of maternal behavior, genetic regulation of the growth of the neocortex, and maintenance of the blood supply to the cortex thus inducing human intellectual development, social sensitivity and human sociality. Hormones of pregnancy, as estrogen and progesterone, prime the brain for the synthesis of OT and OTR for parturition. OTR are located in limbic areas that process olfactory information. Parturition triggers the signal originating in the uterus that reaches SON and PVN OTergic neurons to stimulate the release of OT both into the circulation in order to cause the expulsion of the fetus and into the brain in order to enable the limbic olfactory area for mother-infant recognition bond. Furthermore, OT influences the autonomic nervous system by stimulation of vagal pathways, and exerts anti-inflammatory, anti-oxidant, anti-pain effects, and modulates metabolic homeostasis. All these properties make OT a hormone playing an important role in the control of emotional and physical health.

5.1. Maternal Behavior

Maternal behavior represents the emotive and physiological interactions between mother and sons during gestation, birth and postnatal period [118]. Increased immunoreactive levels of OT and OTR have been reported within several brain areas in pregnant, parturient and lactating female rats mainly in the ventral septal area [119], SON [120, 121] and PVN [120]. OTR mRNA was highly expressed at parturition in the SON, PVN, brainstem areas, medial preoptic area (mPOA), amygdala, hippocampus and olfactory bulb [122], thus showing that uterine contractions during labor are controlled by OTergic pathways. In the postpartum period, c-Fos and OTR mRNA expression returned to levels observed in virgin rats [122], thus suggesting that the increased OTR expression in the brain plays a crucial role in the induction of birth. OT i.c.v. injected induces in virgin rats all aspects of maternal behavior as nest building, linking and grouping pups, arched-back nursing, crouching over pups, lactation, maternal aggression and pup retrieval. However, these maternal behaviors induced by OT require high plasma estradiol levels. In fact, only female virgin ovariectomized rats receiving estradiol benzoate showed full maternal behavior following OT administration [123].

The pharmacological approach to maternal behavior showed the involvement of brain DAergic and 5-HTergic neurons in the neural circuit subserving maternal behavior. DAergic neurons localized at the level of ventral tegmental area (VTA) and substantia nigra (SN), two brain areas involved in affiliative behaviors as sexual behavior [124] are directly activated by OT, but are also indirectly inhibited by local GABA neurons [125]. Xiao *et al*. (2017) identified two distinct projections arising from PVN parvocellular OTergic neurons, synapsing to VTA and SN neurons. OTR mRNA is expressed in DAergic neurons of the VTA and in GABAergic neurons of the SN. Therefore, OT released at VTA level increases DAergic activity, while inducing inhibition of SN DA neurons via local GABAergic interneurons. DAergic efferent projections arising from VTA and SN synapsing in the prefrontal cortex, caudate putamen, nucleus accumbens septi, and ventral hippocampus play opposite actions. VTA DAergic axons stimulate social interaction [126], while SN DAergic axons inhibit exploratory behavior via the control of the motor activity [127]. Therefore, activation of VTA

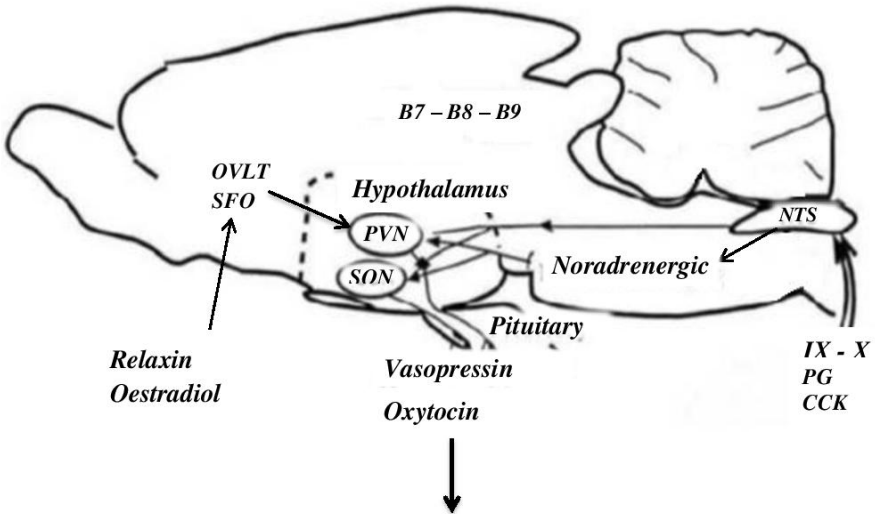

Fig. (2). Midsaggital section of rat brain showing neural nuclei, peptides and neurotransmitters involved in OT and VP secretion. NTS: nucleus of the solitary tract; PVN: paraventricular nucleus; SON: supraoptic nucleus; OVLT: organum vasculosum lamina terminalis; SFO: subfornical organ; B7-B8-B9: 5-HTergic mesencephalic neurons. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

DAergic neurons by OT stimulates social behavior, and on the other hand, inhibition of SN DAergic neurons reduces exploratory motor behavior thus showing OT-DA crosstalk to play a significant role in social interaction.

It has been observed that the DA reuptake inhibitor amfonelic acid and the 5-HTergic reuptake inhibitor fluoxetine increased several aspects of maternal behavior as nest building, linking and grouping pups. Concerning maternal aggressive postpartum behavior toward an intruder, DAergic stimulation decreased, while 5HTergic activation increased aggression [128]. DA and 5-HT induce these behavioral responses modifying OT levels mainly within the hippocampus and amygdala [129].

Individual variations in maternal behavior have been observed in many species. Virgin female rats showed high induction to maternal behavior following constant exposure to pups, compared to low licking and grooming mothers. Significantly higher levels of OTR have been reported in mothers with high maternal behavior in brain region as mPOA, lateral septum, PVN and BNST, whereas maternal aggression depends on the levels of these receptors in the central nucleus of the amygdala. OTR antagonist, centrally administered, reverses these behaviors turning mothers from high to low licking and grooming. In addition, estradiol administration increases OTR binding in mPOA and lateral septum of female offspring with high but not low licking and grooming [130], thus suggesting that estradiol increases maternal behavior via OTergic neurotransmission [130].

OT KO mice showed normal maternal behavior but the inability to nurse. Postpartum OT administration to OT KO mice restored milk ejection but did not restore fertility and parturition in these animals [131]. However, Pedersen *et al*. [132] showed that fewer OT KO female mice retrieved pups to a corner of the cage and mothered pups in the center of the cage. Also licking and grooming were lower compared to wild-type mice. These data indicate that OT plays a role in several expressions of maternal behavior and in the motivation to retrieve pups to a more secure location. Postpartum maternal behavior is attributed to the control of hypothalamic corticotropin-releasing factor (CRF). mRNA expression for CRF receptor subtype 1 (CRFR 1), subtype 2 (CRFR 2) and CRF-binding protein (CRFBP), was similar between virgin and lactating rats in the mPOA. Under stress conditions, activation mainly of CRFR 1 in the mPOA produces anxiogenic actions and reduces locomotion, while CRFR 1 inhibition increased maternal aggression. The activation of CRFR 1 within the mPOA increased local OT levels. This OT release plays a regulatory role in order to inhibit the negative mechanism of action induced by CRFR on maternal behavior [133]. Neuroanatomical data showed the reciprocal interaction between OT and CRF at the level of dorsolateral BNST, a limbic forebrain structure that expresses OTR and CRFRs and play a critical role in social behavior. Dabrowska *et al*. [134] demonstrated that OTergic BNST axons express CRFR 2 which is localized at the presynaptic level on terminal axons. When Astressin 2B, a selective antagonist of CRFR 2, was directly injected into the BNST, OT content in BSNT increased consistently thus showing the inhibitory role played by CRFR 2 on OT release. In addition, CRF by itself provoked a delayed increase of OT in the BNST [135]. These data indicate that CRFRs modulate the release of OT in the BNST, thus confirming that this forebrain structure is involved in behavioral interactions [136].

Lactation releasing of OT increases the mother-infant relationship both as nourishment and as social and cognitive behavior. Moreover, lactation inhibits ovarian function inducing amenorrhea by the contraceptive effect of OT [137]. Therefore, this lactational amenorrhea also plays a protective role for the mother in order to block frequent gestations. Another form of social and cognitive behavior between mother and baby is the presence of OT in milk. In addition, during lactation, the high plasma OT levels reduce the responsiveness of mother to stress [138].

OT significantly released during parturition converts GABAergic inhibition into an excitatory response. This switch from inhibition to excitation stimulates OT release

and is antagonized by blocking OT receptors that aggravate the severity of hypoxia during delivery [139]. In fact, maternal OT inhibits fetal neurons and consequently increases their resistance to hypoxia during childbirth in order to protect cortical tissue. The strong release of OT during parturition modulates also the synchronization of the fetal hippocampal neurons to transition from fetal to postnatal life. During fetal life, in fact, synchronized activity is absent in hippocampal neurons. At birth, these neurons generate spontaneously synchronous non-synaptic calcium plateaus that are under the control of OT, thus showing the important role played by OT in the preparation of the fetal brain to parturition [140, 141].

5.2. Sex-Differences in OT Secretion and Related Effects

Even if OT plays a pivotal role in social cognition, motivation and behavior in both sexes, there is evidence for some sex differences in these behavioral aspects: in women, OT facilitates positive social judgment [142], approach behavior in social context [143], communal and familial social behavior [144], and altruism behavior [145]. In men, it promotes negative social judgment [142], fidelity during a monogamous relationship [146], tendency to competition [144], selfish behavior [145]. Finally, in couple conflict, intranasal OT administration determines the reduction of sympathetic activity and emotional arousal in women, and on the other hand in men, the autonomic nervous system reactivity is increased as well as emotional arousal [147].

In the search of extrahypothalamic brain sites involved in emotional and social behaviors mediated by OT, the amygdala, a limbic area involved in fear and social behavior, has received particular attention because it expresses a high concentration of OTR [148]. Kirsch *et al*. [149] showed, after intranasal administration of OT, reduced activation of the amygdala and reduced synaptic inputs from amygdala to hippocampus and septum, regions involved in behavioral manifestations of fear. A quantitative meta-analysis of neuroimaging studies conducted by Stevens and Hamann [150] found sex differences in the activation of amygdala in response to positive and negative emotions. Women, during negative emotion, showed greater activation than men in the left amygdala, thalamus, hypothalamus mammillary bodies and medial prefrontal cortex. On the other hand, men, during positive emotions, showed greater activation than women in the left amygdala and inferior frontal gyrus. Therefore, as reported by Gao and coworkers [151], OT administration induces activation of amygdala in a sex-dependent manner in women facilitating positive social context, whereas the effect is negative in men. The cytoarchitecture of the amygdala shows three subregions: the laterobasal (LB), the centromedial (CM) and the superficial (SF) [152]. Gao *et al*. [151], using probabilistic maps that differentiate the LB area from the CM and SF subregions, suggested that OT acts mainly on LB subregion of the left amygdala, thus confirming the important role played in emotional and social behavior, and in reward learning [153].

5.3. Effects of OT on Neuroinflammation

Recent studies have shown that OT plays an important role in the control of brain microglial reactivity. Activation of microglia, the innate immune brain cells, induces the release of various pro-inflammatory cytokines, chemokines and free radicals. These inflammatory substances cause detrimental effects on neurogenesis affecting neural progenitor cell proliferation, migration, neural maturation and synaptic structural plasticity of newly born neurons [154].

Glucocorticoids (GCs), released from the zona fasciculata of the adrenal gland, with anti-inflammatory and immunosuppressive properties, have shown also pro-inflammatory mechanisms. In fact, GCs potentiate spinal neuroinflammation [155] and systemic inflammatory response [156] determining alterations in the morphology of microglia and the inflammatory response of the hippocampus [157]. In addition, exposure to prenatal stress increases the activation of microglia in the hippocampus and cortex and induces the release of cytokines [158].

It has been reported that psychological stress stimulates OT release [159]. Moreover, OT administration reduced significantly ACTH, corticosterone [160] and cortisol [161] plasma levels both in basal conditions and in response to stress, and reduced molecular responses of the hypothalamo-pituitary-adrenal axis [162]. Therefore, we can hypothesize that OT protects the brain from pro-inflammatory cytokines induced by GCs.

OT is able to induce social neuroprotection after cerebral injury. It has been observed that OTR antagonist eliminated the neuroprotective effect of social housing. On the other hand, OT administered in socially isolated mice restored neuroprotection induced by social housing and inhibited *in vitro* microglia activation, the mechanisms causing neuroinflammation after cerebral ischemia [163]. In addition, OT centrally administered in socially isolated mice reduced the effect of spared nerve injury on depressive-like behavior and blunted IL-1β protein levels within the frontal cortex, while OTR antagonist induced depressive-like behavior and augmented frontal cortex IL-1β protein levels [164]. Moreover, neuroinflammation and mitochondrial dysfunction observed in depressive disorders are improved by OT. Indeed, intracerebroventricular administration of OT in mice attenuates the depressive-like behavior induced by maternal separation stress via reduction of the hippocampal expression of immune-inflammatory genes and modulates mitochondrial function [165]. Thus it has been evident that OT reduces neuroinflammatory responses and depressive-like behavior.

5.4. OT-Mediated Analgesia

OT induces analgesia during parturition both in mother and the baby via reduction of the depolarizing action of GABA on nociceptive neurons as has been observed in neonatal trigeminal neurons [166], and protects mothers from postpartum depression [167]. There is also evidence demonstrating the role of endogenous opioids in the control of pain threshold [168]. OT-induced antinocicention in the nucleus accumbens septi was blunted by k- and μ-receptor antagonist thus showing the involvement of k- and μ-receptors in OT-induced antinociception [169]. Moreover, endocannabinoids (eCB) are able to suppress pain pathways and may play an important role in OT analgesia, since eCB antagonists sup-

press OT-induced analgesic effect. Therefore, OT reduces pain via opioid and cannabinoid pathways [170].

Parvocellular neurosecretory OTergic (PCN/OT) neurons project to the spinal cord (SC) and to the dorsal vagal complex [171]. Synaptic inputs arising from PCOT neurons play a role in analgesic functions. This nociception OT-modulated comprises a peripheral and central component. Intravenous administration of OT induces two different responses, dose-related, on spinal nociception and pain responses. A significant reduction of the action potentials of C-type nociceptive fibers was observed following low doses of OT, whereas an increase, hence a pro-nociceptive effect, was observed after high doses. In addition, these effects were inhibited by the pretreatment with an OT antagonist thus showing that OT modulates nociception via C-type nociceptive fibers [172]. Centrally, increased OT levels have been observed in the SC of rats showing pain symptoms induced by inflammation. These effects are mediated via stimulation of neurosteroidogenesis induced by OTR which potentiates GABA-A receptor-mediated synaptic inhibition in lamina II SC neurons exerting long-lasting analgesia [173].

Eliava *et al*. [174] identified a population of PCOT neurons controlling MCN neurons, suppressing inflammatory pain and inducing analgesia via two pathways: releasing OT from axons synapsing on SC neurons and suppressing their activity, furthermore stimulating OT release from SON and hence from posterior pituitary into the periphery [174]. Therefore, it has been hypothesized that the anti-nociceptive effect of OT is mediated by synaptic crosstalk between MCN and PCN neurons within the SON and PVN. OT modulates pain signals via PCN-OT neurons that project and synapse on sensory wide dynamic range (WDR) neurons located in the SC deep lamina and on OTR, and OTergic neurons in the SON that release OT peripherally. These separate projections indicate the existence of two pathways modulating pain: in a fast manner via innervation of SC WDR neurons and in a slow manner via peripheral OT release [174].

5.5. Growth of the Neocortex

There is evidence showing the role of OT in brain development. Leuner and coworkers [175] reported the stimulation of OT in neurogenesis and the inhibition of apoptosis. During the development of the neocortex, the neurons arising from progenitor neuronal cells in the ventricular and periventricular areas of the embryonic brain are submitted to differentiation, migration and growth, which results in the formation of neocortex cytoarchitecture. OT may induce neocortical growth by stimulation of undifferentiated stem cells to grow into cortical cells [176] and/or by inhibition of programmed apoptosis. OT is also capable of stimulating adult neurogenesis and inhibiting apoptosis in rats submitted to stress induced by glucocorticoid administration or cold water swim [175], thus showing OT stimulates neuronal proliferation and protects from suppressive actions of stress caused by glucocorticoids. Furthermore, neural differentiation of mouse adipose tissue-derived stem cells (ADSCs) has been investigated *in vitro* in the presence of different concentrations of OT. This treatment, even in low OT doses, showed a stimulatory effect of OT on proliferation and differentiation of ADSCs. In addition, OT upregulated mRNA expression of OTR. These results indicate that OT improves neural differentiation thus showing a significant role in neurogenesis and in the regeneration of adult neurons [177]. Moreover, in mouse knockout model deleting OTR, it has been observed that endogenous OT synaptic inputs, arising from PVN OTergic neurons and projecting directly to the CA3 region of the hippocampus, stimulate neurogenesis of dentate granule cells in adult mouse hippocampus via an indirect non-cell autonomous mechanism by OTR expressed in CA3 pyramidal neurons [178].

5.6. Vascular Effects

OT is synthesized in the PVN, one of the brain centers involved in the control of arterial pressure. Furthermore, brainstem nuclei act as the NTS where the vagus nerve synapses contain a high concentration of OT receptors. OT controls blood supply to the brain via heart rate, blood vessel and kidney directly and by affecting other mediators such as atrial natriuretic peptide (ANP), nitric oxide (NO), and α2-adrenergic receptors [179]. Furthermore, brainstem nuclei act as the NTS, where the vagus nerve synapses contain a high concentration of OTR [180, 181]. OT reduces sympathetic activation of vessel contraction [182] and dilates blood vessels innervated by parasympathetic nerves [183]. OT neuron activation inhibits hypertension induced by hypoxia/hypercapnia in rats [184] thus showing stimulation of OTergic neurons improving autonomic control of blood pressure.

In addition, emerging evidence indicates the role of the immune system in the pathogenesis of hypertension. Oxidative stress stimulates inflammatory responses via inhibition of endothelial progenitor cells that play an important role in the repair and maintenance of vascular endothelium, and stimulation of inflammatory cytokines, that induce T-lymphocyte activation and vascular infiltration of leukocytes, thus facilitating the development of hypertension. OT through its regulating immunologic activity reduces hypertension [185 - 187].

5.7. Metabolic Homeostasis

Emerging evidence indicates that OT increases glucose uptake and stimulates lipid utilization in adipose tissue and skeletal muscle. These data suggest the role of OT in the pathogenesis of insulin resistance, obesity and dyslipidemia. It has been observed that mice KO for OT gene and/or reduced OTR gene mRNA expression induce obesity under normal conditions of motor activity, “ad libitum” food intake and increased levels of leptin. In humans, plasma OT levels are significantly decreased in diabetic obese patients and intranasal OT administration leads to a significant weight loss and improvement in insulin sensitivity, pancreatic β-cell responsivity and lipid metabolism thus suggesting a physiologic role of OT in metabolic homeostasis and possible therapeutic use [188, 189].

6. CLINICAL IMPLICATIONS

OT and VP may be involved in some cardiovascular and neuropsychiatric diseases as respectively atherosclerotic coronary dysfunction, and autism, schizophrenia and depres-

sion [190, 191]. These vascular and social disorders show genetic and functional anomalies in gene expression, synthesis of polypeptide sequence and release of OT and VP.

6.1. Atherosclerotic Cardiovascular Disease

OT maintains cardiovascular integrity by inhibition of atherosclerotic lesions and its administration can reverse coronary artery occlusion. This effect is the result of the protection of the heart and vascular system from metabolic and inflammatory diseases as diabetes and hyperlipidemia. OT reduces the progression of atherosclerosis via OTR signaling pathways that involve phosphatidylinositol 3-kinase-Akt-endothelial nitric oxide synthase cascades and extracellular signal-regulated protein kinase 1/2 [192]. Moreover, AMP-activated protein kinase, Ca(2+)/calmodulin-dependent protein kinase signaling are also involved in the process that decelerates the progression of atherosclerosis by suppression of inflammatory cytokines [193]. Endoplasmic reticulum (ER) stress, the target of events producing atherosclerotic lesions, is the common cause of cardiovascular diseases [192]. ER stress reduces significantly OT mRNA [194] and OTR expression is decreased in the heart by 40% ischemia/reperfusion injury in C57B6 mice [195]. Moreover, OT administration plays cardiovascular protective effects inhibiting the development of atherosclerosis [196] and repairing heart lesions caused by myocardial infarction and improves, partially, diabetes and fat metabolism [197].

6.2. OT in Autism Disorders (AD)

AD leads to developmental impairments showing deficits in social interaction, reduced range of interests and activities, verbal skills impairments and repetitive behavior.

Investigations in children with AD by Modhal *et al*. showed significantly lower plasma OT levels than normal children [198]. These same authors subsequently demonstrated that OT, as bioactive α-amidated peptide, was decreased but OT, as C-terminal extended peptide, was increased thus showing alterations in OT pro-hormone processing [199]. However, studies on adults with AD reported increased plasma OT levels [200]. The discrepancy in these data might be the result of both molecular processing mechanisms and social behavior changes during the life of adults with AD.

The heritability of AD has been estimated at 55-80% thus showing a genetic role in this disorder. A meta-analysis of OT receptor (OTR) and OTR single-nucleotide polymorphisms (SNPs) indicated a significant association of AD with SNPs [201]. In addition, OTR was also found to be associated with AD in a gene-based test [201].

CD 38 is a transmembrane glycoprotein expressed in most tissues that cleave NAD (+) and NADP (+) generating cyclic ADP, nicotinic acid adenine dinucleotide phosphate (NAADP) and adenosine diphosphate ribose (ADPR), that are essential for the formation of intracellular Ca (2+) signaling molecules [202]. CD 38 knockout (KO) female and male mice show a strong impairment of maternal and social behavior with increased locomotor activity, amnesia and ultrasonic vocalization [153 - 155]. Moreover, plasma OT levels are significantly decreased in CD 38 KO mice [203 - 205]. Subcutaneous injection of OT restores maternal behavior in CD 38 KO mice and OT secretion stimulated by depolarization and Ca (2+) elevation in OTergic neurons was absent in CD 38 KO mice [206, 207]. These data indicate the key role played by CD 38 in OT synthesis and release, and in the regulation of maternal and social behavior [207]. In subjects with AD, two genetic variants of CD 38 have been observed and a mutation that caused tryptophan to replace arginine at amino acid residue 140 [208]. Multiple genetic loci within OTergic neurons may contribute to social, maternal and repetitive behaviors, and to OT secretion thus playing a role in the development of AD [209 - 212].

The OTR is a GPCR, that is coupled via Gq proteins to phospholipase C-β [7, 8, 180], and plays a role in a variety of social behaviors [213], via binding of OT to its receptor. The presence of two SNPs and a haplotype constructed from them in OTR, as well as over transmission of the G allele across the OTR gene region, are associated with AD, thus showing variants of OTR gene a risk factor for AD [214, 215]. A meta-analysis on 3491 subjects with AD showed a significant relationship between OTR SNPs and AD, including Asperger Syndrome [216, 217].

In search of neural structures involved in OTR gene, variant investigations with multimodal neuroimaging identified structural alterations in the hypothalamic-limbic circuits [218, 219]; as the reduction of volume and function of the hypothalamus, and increased volume of the amygdala and hippocampus [220], two limbic structures were found modulating emotional behavior and memory process.

OT has been employed in AD therapy; conflicting data has been observed as genetic alteration of OTR SNPs may cause a failure to respond to OT therapy [220 - 227]. However, Kosaka *et al*. [227] observed that OT efficacy is dose-dependent. Intranasal OT induced beneficial effects at doses > 21 IU/die, and not when OT was administered at doses < 18 UI/die as shown by Clinical Global Impression-Improvement (CGI-I) scores.

6.3. OT in Schizophrenia

OT exerts anxiolytic and antidepressive actions, protective aggression and maternal behavior [149, 227 - 237]. The antipsychotic effects of OT are exerted at the mesolimbic level by inhibition of DAergic mechanisms thus showing an action similar to antipsychotic drugs [238]. Moreover, OT pathways are impaired in the mouse model of psychosis [238]. Neurophysin I, the protein carrier for OT, is significantly increased in cerebrospinal fluid (CSF) of patients with schizophrenia [239 - 240]. In addition, the administration of the DA agonist apomorphine in schizophrenic subjects increased the OTergic tone [241]. Increased plasma OT levels are associated with reduced psychotic symptom severity as evaluated by Positive and Negative Syndrome Scale (PNSS) scores [242, 243].

Variants of OT gene and haplotype block within OT locus are significantly associated with schizophrenia [244 - 245]. The antipsychotic drug clozapine is able to stimulate OT release and when administered in schizophrenic patients, it reduced the severity of symptoms [246]. Therefore, the OT therapy, as adjunctive treatment, induces beneficial re-

sponses and prevention of hospitalization when injected at the dose of 10 and 20 IU/die [247 - 248]. Similar data have been reported particularly for negative symptoms and depressed mood [249]. Goldman and coworkers [250] observed, following intranasal OT administration, facial emotions decreased in both patients receiving 10 or 20 IU/die, although the group treated with 20 UI/die showed a better improvement in facial fear [251].

Intranasal administration of OT, at the dose of 40 IU twice a day for 3 weeks, in association with antipsychotic drugs induced significantly reduced scores on the PANSS and CGI-I [252], and improvement in verbal memory and cognition [253]. Moreover, beneficial effects were observed on suspiciousness/persecutory, anxiety and paranoia subscales [253]. Finally, in a randomized, double-blind, placebo-controlled study, patients in therapy with risperidone receiving intranasal OT showed a better response on the PANSS total score, positive subscale, negative subscale and psychopathology score [254].

6.4. OT in Major Depressive Disorder (MDD) and Bipolar Disorder (BD)

Anxiolytic effects of OT have been reported via inhibition of stress induced by corticosteroid hormones [160]. In addition, Rotzinger and coworkers [255] showed behavioral effects of OT in the rodent model of depression and anxiety. It is of interest that nocturnal OT secretion is significantly reduced in MD [256], as well as low plasma OT levels are present in MDD patients [257].

A gender difference in plasma OT levels has been reported in female patients that showed significantly lower OT concentration [258]. The temperament dimension of reward dependence in MDD is strictly correlated with plasma OT levels, in fact, MDD female patients showed greater variability in pulsatile OT release during 1-hour task session, and increased plasma OT levels during 1-hour affiliation-focused imagery session, thus showing a dysregulated OT secretion in MDD women [259].

Low plasma OT levels during pregnancy may indicate the development of postpartum depression (PPD). Skrundz *et al*. [260] measured OT plasma levels during the third trimester of pregnancy and assessed PPD symptoms using the Edinburgh Postnatal Depression Scale. A significant relationship between plasma OT levels and PPD symptoms at two weeks postpartum was observed. The group that developed PPD showed low plasmatic levels of OT, thus showing that OT is a predictive factor of PPD. These data suggest that increasing OT release in women with low plasma OT levels during pregnancy may represent a preventive therapeutic approach to PPD.

Genetic studies indicate two variants of OTR in MDD patients [261]. OTR SNPs interacted with familial risk for depression and anxiety in adolescent girls [262] as well as in PPD [213].

Beneficial effects of intranasal OT therapy, at the dose of 8 IU twice a day, in association with escitalopram, at the dose of 20 mg once a day, have been reported [263].

CONCLUSION

Emerging evidence indicates the involvement of OT and OTR in several pathophysiological mechanisms as described above.

OT therapy may induce beneficial effects centrally because OT administered via intranasal route crosses the BBB and easily reaches brain nuclei involved in the control of blood pressure and social behavior. Peripherally, it stimulates parturition and modulates pancreatic β-cell responsiveness and lipid metabolism, and in addition, it may suppress and even reverse atherosclerotic lesions. OT influences brain anatomy via the growth of the neocortex that produces cognition and language, a sense of safety and trust.

Therefore, although patients with genetic disorders of OTR respond to exogenous OT with less efficacy because the binding of OT to its receptor is instable, encouraging data indicate a favorable effect of OT in several diseases and possible therapeutic applications.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

FUNDING

None.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Sofroniew, M.V. Morphology of vasopressin and oxytocin neurones and their central and vascular projections. *Prog. Brain Res.,* **1983**, *60*, 101-114. http://dx.doi.org/10.1016/S0079-6123(08)64378-2 PMID: 6198686

[2] Zimmerman, E.A.; Nilaver, G.; Hou-Yu, A.; Silverman, A.J. Vasopressinergic and oxytocinergic pathways in the central nervous system. *Fed. Proc.,* **1984**, *43*(1), 91-96. PMID: 6690342

[3] Brownstein, M.J.; Russell, J.T.; Gainer, H. Synthesis, transport, and release of posterior pituitary hormones. *Science,* **1980**, *207*(4429), 373-378. http://dx.doi.org/10.1126/science.6153132 PMID: 6153132

[4] Leng, G.; Brown, C.H.; Russell, J.A. Physiological pathways regulating the activity of magnocellular neurosecretory cells. *Prog. Neurobiol.,* **1999**, *57*(6), 625-655. http://dx.doi.org/10.1016/S0301-0082(98)00072-0 PMID: 10221785

[5] Russell, J.A.; Leng, G.; Douglas, A.J. The magnocellular oxytocin system, the fount of maternity: adaptations in pregnancy. *Front. Neuroendocrinol.,* **2003**, *24*(1), 27-61. http://dx.doi.org/10.1016/S0091-3022(02)00104-8 PMID: 12609499

[6] Urban, I.; Moss, R.L.; Cross, B.A. Problems in electrical stimulation of afferent pathways for oxytocin release. *J. Endocrinol.,* **1971**, *51*(2), 347-358. http://dx.doi.org/10.1677/joe.0.0510347 PMID: 5166156

[7] Iovino, M.; Guastamacchia, E.; Giagulli, V.A.; Licchelli, B.; Iovino, E.; Triggiani, V. Molecular mechanisms involved in the control of neurohypophyseal hormones secretion. *Curr. Pharm. Des.,* **2014**, *20*(42), 6702-6713. http://dx.doi.org/10.2174/1381612820666140905150730 PMID: 25190061

[8] Iovino, M.; Giagulli, V.A.; Licchelli, B.; Iovino, E.; Guastamacchia, E.; Triggiani, V. Synaptic inputs of neural efferent pathways to vasopressin- and oxytocin-secreting neurons of supraoptic and paraventricular hypothalamic nuclei. *Endocr. Metab. Immune Disord. Drug Targets,* **2016**, *16*(42), 6702-6713.

[9] Yamamoto, Y.; Liang, M.; Higashida, H. Vascular RAGE transports oxytocin into the brain to elicit its maternal bonding behavior in mice. *Comm. Biol,* **2019**, *2*, 76.

[10] Way, S.A.; Leng, G. Relaxin increases the firing rate of supraoptic neurones and increases oxytocin secretion in the rat. *J. Endocrinol.,* **1992**, *132*(1), 149-158. http://dx.doi.org/10.1677/joe.0.1320149 PMID: 1737954

[11] Wilson, B.C.; Summerlee, A.J. Effects of exogenous relaxin on oxytocin and vasopressin release and the intramammary pressure response to central hyperosmotic challenge. *J. Endocrinol.,* **1994**, *141*(1), 75-80. http://dx.doi.org/10.1677/joe.0.1410075 PMID: 8014606

[12] Brailoiu, E.; Dun, S.L.; Brailoiu, G.C.; Mizuo, K.; Sklar, L.A.; Oprea, T.I.; Prossnitz, E.R.; Dun, N.J. Distribution and characterization of estrogen receptor G protein-coupled receptor 30 in the rat central nervous system. *J. Endocrinol.,* **2007**, *193*(2), 311-321. http://dx.doi.org/10.1677/JOE-07-0017 PMID: 17470522

[13] Hazell, G.G.; Yao, S.T.; Roper, J.A.; Prossnitz, E.R.; O'Carroll, A.M.; Lolait, S.J. Localisation of GPR30, a novel G protein-coupled oestrogen receptor, suggests multiple functions in rodent brain and peripheral tissues. *J. Endocrinol.,* **2009**, *202*(2), 223-236. http://dx.doi.org/10.1677/JOE-09-0066 PMID: 19420011

[14] Wang, H.; Ward, A.R.; Morris, J.F. Oestradiol acutely stimulates exocytosis of oxytocin and vasopressin from dendrites and somata of hypothalamic magnocellular neurons. *Neuroscience,* **1995**, *68*(4), 1179-1188. http://dx.doi.org/10.1016/0306-4522(95)00186-M PMID: 8544991

[15] Israel, J.M.; Poulain, D.A. 17-Oestradiol modulates *in vitro* electrical properties and responses to kainate of oxytocin neurones in lactating rats. *J. Physiol.,* **2000**, *524*(Pt 2), 457-470. http://dx.doi.org/10.1111/j.1469-7793.2000.t01-2-00457.x PMID: 10766926

[16] Miselis, R.R. The efferent projections of the subfornical organ of the rat: a circumventricular organ within a neural network subserving water balance. *Brain Res.,* **1981**, *230*(1-2), 1-23. http://dx.doi.org/10.1016/0006-8993(81)90388-7 PMID: 7317773

[17] Lind, R.W.; Van Hoesen, G.W.; Johnson, A.K. An HRP study of the connections of the subfornical organ of the rat. *J. Comp. Neurol.,* **1982**, *210*(3), 265-277. http://dx.doi.org/10.1002/cne.902100306 PMID: 7142442

[18] Renaud, L.P.; Rogers, J.; Sgro, S. Terminal degeneration in supraoptic nucleus following subfornical organ lesions: ultrastructural observations in the rat. *Brain Res.,* **1983**, *275*(2), 365-368. http://dx.doi.org/10.1016/0006-8993(83)90999-X PMID: 6626987

[19] Camacho, A.; Phillips, M.I. Horseradish peroxidase study in rat of the neural connections of the organum vasculosum of the lamina terminalis. *Neurosci. Lett.,* **1981**, *25*(3), 201-204. http://dx.doi.org/10.1016/0304-3940(81)90391-8 PMID: 7290524

[20] Sawchenko, P.E.; Swanson, L.W. The organization of forebrain afferents to the paraventricular and supraoptic nuclei of the rat. *J. Comp. Neurol.,* **1983**, *218*(2), 121-144. http://dx.doi.org/10.1002/cne.902180202 PMID: 6886068

[21] Hazell, G.G.; Hindmarch, C.C.; Pope, G.R.; Roper, J.A.; Lightman, S.L.; Murphy, D.; O'Carroll, A.M.; Lolait, S.J. G protein-coupled receptors in the hypothalamic paraventricular and supraoptic nuclei--serpentine gateways to neuroendocrine homeostasis. *Front. Neuroendocrinol.,* **2012**, *33*(1), 45-66. http://dx.doi.org/10.1016/j.yfrne.2011.07.002 PMID: 21802439

[22] Sladek, C.D.; Song, Z. Diverse roles of G-protein coupled receptors in the regulation of neurohypophyseal hormone secretion. *J. Neuroendocrinol.,* **2012**, *24*(4), 554-565. http://dx.doi.org/10.1111/j.1365-2826.2011.02268.x PMID: 22151700

[23] Barberis, C.; Tribollet, E. Vasopressin and oxytocin receptors in the central nervous system. *Crit. Rev. Neurobiol.,* **1996**, *10*(1), 119-154. http://dx.doi.org/10.1615/CritRevNeurobiol.v10.i1.60 PMID: 8853957

[24] Kiss, A.; Mikkelsen, J.D. Oxytocin--anatomy and functional assignments: a minireview. *Endocr. Regul.,* **2005**, *39*(3), 97-105. PMID: 16468232

[25] Grady, E.F.; Böhm, S.K.; Bunnett, N.W. Turning off the signal: mechanisms that attenuate signaling by G protein-coupled receptors. *Am. J. Physiol.,* **1997**, *273*(3 Pt 1), G586-G601. PMID: 9316462

[26] Conti, F.; Sertic, S.; Reversi, A.; Chini, B. Intracellular trafficking of the human oxytocin receptor: evidence of receptor recycling via a Rab4/Rab5 "short cycle". *Am. J. Physiol. Endocrinol. Metab.,* **2009**, *296*(3), E532-E542. http://dx.doi.org/10.1152/ajpendo.90590.2008 PMID: 19126785

[27] Fushimi, K.; Sasaki, S.; Marumo, F. Phosphorylation of serine 256 is required for cAMP-dependent regulatory exocytosis of the aquaporin-2 water channel. *J. Biol. Chem.,* **1997**, *272*(23), 14800-14804. http://dx.doi.org/10.1074/jbc.272.23.14800 PMID: 9169447

[28] Marlin, B.J.; Mitre, M.; D'amour, J.A.; Chao, M.V.; Froemke, R.C. Oxytocin enables maternal behaviour by balancing cortical inhibition. *Nature,* **2015**, *520*(7548), 499-504. http://dx.doi.org/10.1038/nature14402 PMID: 25874674

[29] Oztaş, B.; Koçak, H.; Oner, P.; Küçük, M. Sex-dependent changes in blood-brain barrier permeability and brain NA(+),K(+) ATPase activity in rats following acute water intoxication. *J. Neurosci. Res.,* **2000**, *62*(5), 750-753. http://dx.doi.org/10.1002/1097-4547(20001201)62:5<750::AID-JNR15>3.0.CO;2-8 PMID: 11104514

[30] Sano, Y.; Watanabe, N.; Suzuki, E.; Shimodaira, K.; Kato, N.; Arakawa, H. A cohort study of the level of plasma oxytocin associated with autism spectrum disorder in Japanese males, females and pregnant females. *Clin. Med. Biochem,* **2016**, *2*, 113. http://dx.doi.org/10.4172/2471-2663.1000113

[31] Mitre, M.; Kranz, T.M.; Marlin, B.J.; Schiavo, J.K; Erdjument-Bromage, H.; Zhang, X.; Neubert, T.A.; Hackett, T.A.; Chao, M.V.; Froemke, R.C. Sex-specific differences in oxytocin receptor expression and function for parental behavior. *Journals.sagepub, ,* http://dx.doi.org/10.1089/gg.2017.0017

[32] Haley, G.E.; Flynn, F.W. Agonist and hypertonic saline-induced trafficking of the NK3-receptors on vasopressin neurons within the paraventricular nucleus of the hypothalamus. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **2006**, *290*(5), R1242-R1250. http://dx.doi.org/10.1152/ajpregu.00773.2005 PMID: 16357093

[33] Howe, H.E.; Somponpun, S.J.; Sladek, C.D. Role of neurokinin 3 receptors in supraoptic vasopressin and oxytocin neurons. *J. Neurosci.,* **2004**, *24*(45), 10103-10110. http://dx.doi.org/10.1523/JNEUROSCI.3164-04.2004 PMID: 15537880

[34] Jensen, D.D.; Sundstrom, K.; Flynn, F.W. Expression of the nuclear transport protein importin ß-1 and its association with the neurokinin 3 receptor in the rat hypothalamus following acute hyperosmotic challenge. *Neuroscience,* **2010**, *170*(4), 1020-1027. http://dx.doi.org/10.1016/j.neuroscience.2010.08.015 PMID: 20709160

[35] Yue, C.; Mutsuga, N.; Scordalakes, E.M.; Gainer, H. Studies of oxytocin and vasopressin gene expression in the rat hypothalamus using exon- and intro-specific probes. *Am. J. Physiol. Integr. Comp. Physiol.,* **2006**, *290*, 1233-1241. http://dx.doi.org/10.1152/ajpregu.00709.2005

[36] Yue, C.; Ponzio, T.A.; Fields, R.L.; Gainer, H. Oxytocin and vasopressin gene expression and RNA splicing patterns in the rat supraoptic nucleus. *Physiol. Genomics,* **2008**, *35*(3), 231-242. http://dx.doi.org/10.1152/physiolgenomics.90218.2008 PMID: 18765859

[37] Bali, B.; Kovács, K.J. GABAergic control of neuropeptide gene expression in parvocellular neurons of the hypothalamic paraventricular nucleus. *Eur. J. Neurosci.,* **2003**, *18*(6), 1518-1526. http://dx.doi.org/10.1046/j.1460-9568.2003.02877.x PMID: 14511331

[38] Cole, R.L.; Sawchenko, P.E. Neurotransmitter regulation of cellular activation and neuropeptide gene expression in the paraventricular nucleus of the hypothalamus. *J. Neurosci.,* **2002**, *22*(3), 959-969. http://dx.doi.org/10.1523/JNEUROSCI.22-03-00959.2002 PMID: 11826124

[39] Scordalakes, E.M.; Yue, C.; Gainer, H. Experimental approaches for the study of oxytocin and vasopressin gene expression in the central nervous system. *Prog. Brain Res.,* **2008**, *170*, 43-51. http://dx.doi.org/10.1016/S0079-6123(08)00404-4 PMID: 18655870

[40] Ozaki, Y.; Nomura, M.; Saito, J.; Luedke, C.E.; Muglia, L.J.; Matsumoto, T.; Ogawa, S.; Ueta, Y.; Pfaff, D.W. Expression of the arginine vasopressin gene in response to salt loading in oxytocin gene knockout mice. *J. Neuroendocrinol.,* **2004**, *16*(1), 39-44. http://dx.doi.org/10.1111/j.1365-2826.2004.01119.x PMID: 14962074

[41] Yue, C.; Mutsuga, N.; Sugimura, Y.; Verbalis, J.; Gainer, H. Differential kinetics of oxytocin and vasopressin heteronuclear RNA expression in the rat supraoptic nucleus in response to chronic salt loading *in vivo*. *J. Neuroendocrinol.,* **2008**, *20*(2), 227-232. http://dx.doi.org/10.1111/j.1365-2826.2007.01640.x PMID: 18088359

[42] Chevaleyre, V.; Moos, F.C.; Desarménien, M.G. Interplay between presynaptic and postsynaptic activities is required for dendritic plasticity and synaptogenesis in the supraoptic nucleus. *J. Neurosci.,* **2002**, *22*(1), 265-273. http://dx.doi.org/10.1523/JNEUROSCI.22-01-00265.2002 PMID: 11756510

[43] El Majdoubi, M.; Poulain, D.A.; Theodosis, D.T. The glutamatergic innervation of oxytocin- and vasopressin-secreting neurons in the rat supraoptic nucleus and its contribution to lactation-induced synaptic plasticity. *Eur. J. Neurosci.,* **1996**, *8*(7), 1377-1389. http://dx.doi.org/10.1111/j.1460-9568.1996.tb01600.x PMID: 8758945

[44] Tweedle, C.D.; Hatton, G.I. Ultrastructural changes in rat hypothalamic neurosecretory cells and their associated glia during minimal dehydration and rehydration. *Cell Tissue Res.,* **1977**, *181*(1), 59-72. http://dx.doi.org/10.1007/BF00222774 PMID: 880623

[45] Theodosis, D.T.; Poulain, D.A.; Vincent, J.D. Possible morphological bases for synchronisation of neuronal firing in the rat supraoptic nucleus during lactation. *Neuroscience,* **1981**, *6*(5), 919-929. http://dx.doi.org/10.1016/0306-4522(81)90173-1 PMID: 7242921

[46] Araque, A.; Parpura, V.; Sanzgiri, R.P.; Haydon, P.G. Glutamate-dependent astrocyte modulation of synaptic transmission between cultured hippocampal neurons. *Eur. J. Neurosci.,* **1998**, *10*(6), 2129-2142. http://dx.doi.org/10.1046/j.1460-9568.1998.00221.x PMID: 9753099

[47] Jourdain, P.; Bergersen, L.H.; Bhaukaurally, K.; Bezzi, P.; Santello, M.; Domercq, M.; Matute, C.; Tonello, F.; Gundersen, V.; Volterra, A. Glutamate exocytosis from astrocytes controls synaptic strength. *Nat. Neurosci.,* **2007**, *10*(3), 331-339. http://dx.doi.org/10.1038/nn1849 PMID: 17310248

[48] Parpura, V.; Basarsky, T.A.; Liu, F.; Jeftinija, K.; Jeftinija, S.; Haydon, R.G. Glutamate-mediated astrocyte-neurons. *Proc. Natl. Acad. Sci. USA,* **2000**, *97*(15), 8629-8634. http://dx.doi.org/10.1073/pnas.97.15.8629 PMID: 10900020

[49] Parpura, V.; Haydon, P.G. Physiological astrocytic calcium levels stimulate glutamate release to modulate adjacent neurons. *Proc. Natl. Acad. Sci. USA,* **2000**, *97*(15), 8629-8634. http://dx.doi.org/10.1073/pnas.97.15.8629 PMID: 10900020

[50] Halassa, M.M.; Florian, C.; Fellin, T.; Munoz, J.R.; Lee, S.Y.; Abel, T.; Haydon, P.G.; Frank, M.G. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. *Neuron,* **2009**, *61*(2), 213-219. http://dx.doi.org/10.1016/j.neuron.2008.11.024 PMID: 19186164

[51] Gordon, G.R.; Baimoukhametova, D.V.; Hewitt, S.A.; Rajapaksha, W.R.; Fisher, T.E.; Bains, J.S. Norepinephrine triggers release of glial ATP to increase postsynaptic efficacy. *Nat. Neurosci.,* **2005**, *8*(8), 1078-1086. http://dx.doi.org/10.1038/nn1498 PMID: 15995701

[52] Panatier, A.; Theodosis, D.T.; Mothet, J.P.; Touquet, B.; Pollegioni, L.; Poulain, D.A.; Oliet, S.H. Glia-derived D-serine controls NMDA receptor activity and synaptic memory. *Cell,* **2006**, *125*(4), 775-784. http://dx.doi.org/10.1016/j.cell.2006.02.051 PMID: 16713567

[53] Stellwagen, D.; Malenka, R.C. Synaptic scaling mediated by glial TNF-alpha. *Nature,* **2006**, *440*(7087), 1054-1059. http://dx.doi.org/10.1038/nature04671 PMID: 16547515

[54] Humphrey, P.P.; Buell, G.; Kennedy, I.; Khakh, B.S.; Michel, A.D.; Surprenant, A.; Trezise, D.J. New insights on P2X purinoceptors. *Naunyn Schmiedebergs Arch. Pharmacol.,* **1995**, *352*(6), 585-596. http://dx.doi.org/10.1007/BF00171316 PMID: 9053729

[55] Girdler, G.; Khakh, B.S. ATP-gated P2X channels. *Curr. Biol.,* **2004**, *14*(1), R6. http://dx.doi.org/10.1016/j.cub.2003.12.009 PMID: 14711422

[56] Jarvis, M.F.; Khakh, B.S. ATP-gated P2X cation-channels. *Neuropharmacology,* **2009**, *56*(1), 208-215. http://dx.doi.org/10.1016/j.neuropharm.2008.06.067 PMID: 18657557

[57] Khakh, B.S.; North, R.A. P2X receptors as cell-surface ATP sensors in health and disease. *Nature,* **2006**, *442*(7102), 527-532. http://dx.doi.org/10.1038/nature04886 PMID: 16885977

[58] Tasker, J.G.; Oliet, S.H.; Bains, J.S.; Brown, C.H.; Stern, J.E. Glial regulation of neuronal function: from synapse to systems physiology. *J. Neuroendocrinol.,* **2012**, *24*(4), 566-576. http://dx.doi.org/10.1111/j.1365-2826.2011.02259.x PMID: 22128866

[59] Piet, R.; Vargová, L.; Syková, E.; Poulain, D.A.; Oliet, S.H. Physiological contribution of the astrocytic environment of neurons to intersynaptic crosstalk. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*(7), 2151-2155. http://dx.doi.org/10.1073/pnas.0308408100 PMID: 14766975

[60] Park, J.B.; Skalska, S.; Stern, J.E. Characterization of a novel tonic gamma-aminobutyric acidA receptor-mediated inhibition in magnocellular neurosecretory neurons and its modulation by glia. *Endocrinology,* **2006**, *147*(8), 3746-3760. http://dx.doi.org/10.1210/en.2006-0218 PMID: 16675519

[61] Park, J.B.; Jo, J.Y.; Zheng, H.; Patel, K.P.; Stern, J.E. Regulation of tonic GABA inhibitory function, presympathetic neuronal activity and sympathetic outflow from the paraventricular nucleus by astroglial GABA transporters. *J. Physiol.,* **2009**, *587*(Pt 19), 4645-4660. http://dx.doi.org/10.1113/jphysiol.2009.173435 PMID: 19703969

[62] Potapenko, E.S.; Biancardi, V.C.; Zhou, Y.; Stern, J.E. Astrocytes modulate a postsynaptic NMDA-GABAA-receptor crosstalk in hypothalamic neurosecretory neurons. *J. Neurosci.,* **2013**, *33*(2), 631-640. http://dx.doi.org/10.1523/JNEUROSCI.3936-12.2013 PMID: 23303942

[63] Son, S.J.; Filosa, J.A.; Potapenko, E.S.; Biancardi, V.C.; Zheng, H.; Patel, K.P.; Tobin, V.A.; Ludwig, M.; Stern, J.E. Dendritic peptide release mediates interpopulation crosstalk between neurosecretory and preautonomic networks. *Neuron,* **2013**, *78*(6), 1036-1049. http://dx.doi.org/10.1016/j.neuron.2013.04.025 PMID: 23791197

[64] Bonfardin, V.D.; Fossat, P.; Theodosis, D.T.; Oliet, S.H. Glia-dependent switch of kainate receptor presynaptic action. *J. Neurosci.,* **2010**, *30*(3), 985-995. http://dx.doi.org/10.1523/JNEUROSCI.3389-09.2010 PMID: 20089907

[65] Kombian, S.B.; Hirasawa, M.; Mouginot, D.; Pittman, Q.J. Modulation of synaptic transmission by oxytocin and vasopressin in the supraoptic nucleus. *Prog. Brain Res.,* **2002**, *139*, 235-246. http://dx.doi.org/10.1016/S0079-6123(02)39020-4 PMID: 12436939

[66] Prager-Khoutorsky, M.; Bourque, C.W. Osmosensation in vasopressin neurons: changing actin density to optimize function. *Trends Neurosci.,* **2010**, *33*(2), 76-83. http://dx.doi.org/10.1016/j.tins.2009.11.004 PMID: 19963290

[67] Alonso, G.; Gabrion, J.; Travers, E.; Assenmacher, I. Ultrastructural organization of actin filaments in neurosecretory axons of the rat. *Cell Tissue Res.,* **1981**, *214*(2), 323-341. http://dx.doi.org/10.1007/BF00249215 PMID: 6894105

[68] Letourneau, P.C. Actin in axons: stable scaffolds and dynamic filaments. *Results Probl. Cell Differ.,* **2009**, *48*, 65-90. http://dx.doi.org/10.1007/400_2009_15 PMID: 19582412

[69] Saarikangas, J.; Zhao, H.; Lappalainen, P. Regulation of the actin cytoskeleton-plasma membrane interplay by phosphoinositides. *Physiol. Rev.,* **2010**, *90*(1), 259-289. http://dx.doi.org/10.1152/physrev.00036.2009 PMID: 20086078

[70] Sawchenko, P.E.; Swanson, L.W. The organization of noradrenergic pathways from the brainstem to the paraventricular and supraoptic nuclei in the rat. *Brain Res.,* **1982**, *257*(3), 275-325. http://dx.doi.org/10.1016/0165-0173(82)90010-8 PMID: 6756545

[71] Palkovits, M. Catecholamines in the hypothalamus: an anatomical review. *Neuroendocrinology,* **1981**, *33*(2), 123-128. http://dx.doi.org/10.1159/000123215 PMID: 6167889

[72] Moos, F.; Richard, P. Excitatory effect of dopamine on oxytocin and vasopressin reflex releases in the rat. *Brain Res.,* **1982**, *241*(2), 249-260. http://dx.doi.org/10.1016/0006-8993(82)91061-7 PMID: 7104713

[73] Yang, C.R.; Bourque, C.W.; Renaud, L.P. Dopamine D2 receptor activation depolarizes rat supraoptic neurones in hypothalamic explants. *J. Physiol.,* **1991**, *443*, 405-419. http://dx.doi.org/10.1113/jphysiol.1991.sp018840 PMID: 1688025

[74] Dahlstroem, A.; Fuxe, K. Evidence for the existence of monoamine- containing neurons in the central nervous system. I. demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiol. Scand. Suppl.,* **1964**, *62*(Suppl. 232), 232-, 1-55. PMID: 14229500

[75] Day, T.A.; Ferguson, A.V.; Renaud, L.P. Facilitatory influence of noradrenergic afferents on the excitability of rat paraventricular nucleus neurosecretory cells. *J. Physiol.,* **1984**, *355*, 237-249. http://dx.doi.org/10.1113/jphysiol.1984.sp015416 PMID: 6436476

[76] Tanaka, J.; Kaba, H.; Saito, H.; Seto, K. Inputs from the A1 noradrenergic region to hypothalamic paraventricular neurons in the rat. *Brain Res.,* **1985**, *335*(2), 368-371. http://dx.doi.org/10.1016/0006-8993(85)90496-2 PMID: 2988698

[77] Knigge, U.; Willems, E.; Kjaer, A.; Jørgensen, H.; Warberg, J. Histaminergic and catecholaminergic interactions in the central regulation of vasopressin and oxytocin secretion. *Endocrinology,* **1999**, *140*(8), 3713-3719. http://dx.doi.org/10.1210/endo.140.8.6891 PMID: 10433231

[78] Kapoor, J.R.; Sladek, C.D. Purinergic and adrenergic agonists synergize in stimulating vasopressin and oxytocin release. *J. Neurosci.,* **2000**, *20*(23), 8868-8875. http://dx.doi.org/10.1523/JNEUROSCI.20-23-08868.2000 PMID: 11102496

[79] Stanzani, S.; Russo, A. [Afferent and efferent connections between the hypothalamus and raphe. Study using the technic of retrograde transport of peroxidases]. *Boll. Soc. Ital. Biol. Sper.,* **1981**, *57*(9), 993-998. PMID: 7284125

[80] Barnes, N.M.; Sharp, T. A review of central 5-HT receptors and their function. *Neuropharmacology,* **1999**, *38*(8), 1083-1152. http://dx.doi.org/10.1016/S0028-3908(99)00010-6 PMID: 10462127

[81] Lee, J.S.; Lee, H.S. Reciprocal connections between CART-immunoreactive, hypothalamic paraventricular neurons and serotonergic dorsal raphe cells in the rat: Light microscopic study. *Brain Res.,* **2014**, *1560*, 46-59. http://dx.doi.org/10.1016/j.brainres.2014.03.006 PMID: 24642272

[82] Jørgensen, H.S. Studies on the neuroendocrine role of serotonin. *Dan. Med. Bull.,* **2007**, *54*(4), 266-288. PMID: 18208678

[83] Gálfi, M.; Radács, M.; Juhász, A.; László, F.; Molnár, A.; László, F.A. Serotonin-induced enhancement of vasopressin and oxytocin secretion in rat neurohypophyseal tissue culture. *Regul. Pept.,* **2005**, *127*(1-3), 225-231. http://dx.doi.org/10.1016/j.regpep.2004.12.009 PMID: 15680491

[84] Jørgensen, H.; Riis, M.; Knigge, U.; Kjaer, A.; Warberg, J. Serotonin receptors involved in vasopressin and oxytocin secretion. *J. Neuroendocrinol.,* **2003**, *15*(3), 242-249. http://dx.doi.org/10.1046/j.1365-2826.2003.00978.x PMID: 12588512

[85] Kombian, S.B.; Zidichouski, J.A.; Pittman, Q.J. GABAB receptors presynaptically modulate excitatory synaptic transmission in the rat supraoptic nucleus *in vitro*. *J. Neurophysiol.,* **1996**, *76*(2), 1166-1179. http://dx.doi.org/10.1152/jn.1996.76.2.1166 PMID: 8871228

[86] Yamaguchi, K.; Yamada, T. Roles of forebrain GABA receptors in controlling vasopressin secretion and related phenomena under basal and hyperosmotic circumstances in conscious rats. *Brain Res. Bull.,* **2008**, *77*(1), 61-69. http://dx.doi.org/10.1016/j.brainresbull.2008.04.009 PMID: 18639747

[87] Theodosis, D.T.; Paut, L.; Tappaz, M.L. Immunocytochemical analysis of the GABAergic innervation of oxytocin- and vasopressin-secreting neurons in the rat supraoptic nucleus. *Neuroscience,* **1986**, *19*(1), 207-222. http://dx.doi.org/10.1016/0306-4522(86)90016-3 PMID: 3537841

[88] Decavel, C.; Van den Pol, A.N. GABA: a dominant neurotransmitter in the hypothalamus. *J. Comp. Neurol.,* **1990**, *302*(4), 1019-1037. http://dx.doi.org/10.1002/cne.903020423 PMID: 2081813

[89] Zingg, H.H.; Baertschi, A.J.; Dreifuss, J.J. Action of gamma-aminobutyric acid on hypothalamo-neurohypophysial axons. *Brain Res.,* **1979**, *171*(3), 453-459. http://dx.doi.org/10.1016/0006-8993(79)91049-7 PMID: 476481

[90] Moss, R.L.; Urban, I.; Cross, B.A. Microelectrophoresis of cholinergic and aminergic drugs on paraventricular neurons. *Am. J. Physiol.,* **1972**, *223*(2), 310-318. http://dx.doi.org/10.1152/ajplegacy.1972.223.2.310 PMID: 4558378

[91] Nicoll, R.A.; Barker, J.L. The pharmacology of recurrent inhibition in the supraoptic neurosecretory system. *Brain Res.,* **1971**, *35*(2), 501-511. http://dx.doi.org/10.1016/0006-8993(71)90491-4 PMID: 4400088

[92] Kim, Y.B.; Kim, Y.S.; Kim, W.B.; Shen, F.Y.; Lee, S.W.; Chung, H.J.; Kim, J.S.; Han, H.C.; Colwell, C.S.; Kim, Y.I. GABAergic excitation of vasopressin neurons: possible mechanism underlying sodium-dependent hypertension. *Circ. Res.,* **2013**, *113*(12), 1296-1307. http://dx.doi.org/10.1161/CIRCRESAHA.113.301814 PMID: 24103391

[93] Brown, C.H.; Russell, J.A.; Leng, G. Opioid modulation of magnocellular neurosecretory cell activity. *Neurosci. Res.,* **2000**, *36*(2), 97-120. http://dx.doi.org/10.1016/S0168-0102(99)00121-2 PMID: 10711808

[94] van der Kooy, D.; Koda, L.Y.; McGinty, J.F.; Gerfen, C.R.; Bloom, F.E. The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat. *J. Comp. Neurol.,* **1984**, *224*(1), 1-24. http://dx.doi.org/10.1002/cne.902240102 PMID: 6715573

[95] Poulin, J.F.; Chevalier, B.; Laforest, S.; Drolet, G. Enkephalinergic afferents of the centromedial amygdala in the rat. *J. Comp. Neurol.,* **2006**, *496*(6), 859-876. http://dx.doi.org/10.1002/cne.20956 PMID: 16628615

[96] Poulain, P.; Martin-Bouyer, L.; Beauvillain, J.C.; Tramu, G. Study of the efferent connections of the enkephalinergic magnocellular dorsal nucleus in the guinea-pig hypothalamus using lesions, retrograde tracing and immunohistochemistry: evidence for a projection to the lateral septum. *Neuroscience,* **1984**, *11*(2), 331-343. http://dx.doi.org/10.1016/0306-4522(84)90027-7 PMID: 6201778

[97] Rossier, J.; Pittman, Q.; Bloom, F.; Guillemin, R. Distribution of opioid peptides in the pituitary: a new hypothalamic-pars nervosa enkephalinergic pathway. *Fed. Proc.,* **1980**, *39*(8), 2555-2560. PMID: 6103825

[98] Summy-Long, J.Y.; Miller, D.S.; Rosella-Dampman, L.M.; Hartman, R.D.; Emmert, S.E. A functional role for opioid peptides in the differential secretion of vasopressin and oxytocin. *Brain Res.,* **1984**, *309*(2), 362-366. http://dx.doi.org/10.1016/0006-8993(84)90605-X PMID: 6541075

[99] Van de Heijning, B.J.; Koekkoek-Van den Herik, I.; Maigret, C.; Van Wimersma Greidanus, T.B. Pharmacological assessment of the site of action of opioids on the release of vasopressin and oxytocin in the rat. *Eur. J. Pharmacol.,* **1991**, *197*(2-3), 175-180. http://dx.doi.org/10.1016/0014-2999(91)90518-U PMID: 1680708

[100] Summy-Long, J.Y.; Rosella-Dampman, L.M.; McLemore, G.L.; Koehler, E. Kappa opiate receptors inhibit release of oxytocin from the magnocellular system during dehydration. *Neuroendocrinology,* **1990**, *51*(4), 376-384. http://dx.doi.org/10.1159/000125364 PMID: 1971712

[101] Leng, G.; Bicknell, R.J.; Brown, D.; Bowden, C.; Chapman, C.; Russell, J.A.; Russell, J.A. Stimulus-induced depletion of pro-enkephalins, oxytocin and vasopressin and pro-enkephalin interaction with posterior pituitary hormone release *in vitro*. *Neuroendocrinology,* **1994**, *60*(6), 559-566. http://dx.doi.org/10.1159/000126797 PMID: 7700499

[102] Keil, L.C.; Rosella-Dampman, L.M.; Emmert, S.; Chee, O.; Summy-Long, J.Y. Enkephalin inhibition of angiotensin-stimulated release of oxytocin and vasopressin. *Brain Res.,* **1984**, *297*(2), 329-336. http://dx.doi.org/10.1016/0006-8993(84)90574-2 PMID: 6722545

[103] Sunn, N.; McKinley, M.J.; Oldfield, B.J. Identification of efferent neural pathways from the lamina terminalis activated by blood-borne relaxin. *J. Neuroendocrinol.,* **2001**, *13*(5), 432-437. http://dx.doi.org/10.1046/j.1365-2826.2001.00650.x PMID: 11328453

[104] Leng, G.; Pineda, R.; Sabatier, N.; Ludwig, M. 60 YEARS OF NEUROENDOCRINOLOGY: The posterior pituitary, from Geoffrey Harris to our present understanding. *J. Endocrinol.,* **2015**, *226*(2), T173-T185. http://dx.doi.org/10.1530/JOE-15-0087 PMID: 25901040

[105] Somponpun, S.J.; Johnson, A.K.; Beltz, T.; Sladek, C.D. Osmotic regulation of estrogen receptor-β expression in magnocellular vasopressin neurons requires lamina terminalis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **2004**, *286*(3), R465-R473. http://dx.doi.org/10.1152/ajpregu.00478.2003 PMID: 14604844

[106] Nomura, M.; McKenna, E.; Korach, K.S.; Pfaff, D.W.; Ogawa, S. Estrogen receptor-β regulates transcript levels for oxytocin and arginine vasopressin in the hypothalamic paraventricular nucleus of male mice. *Brain Res. Mol. Brain Res.,* **2002**, *109*(1-2), 84-94. http://dx.doi.org/10.1016/S0169-328X(02)00525-9 PMID: 12531518

[107] Somponpun, S.J.; Sladek, C.D. Osmotic regulation of estrogen receptor-beta in rat vasopressin and oxytocin neurons. *J. Neurosci.,* **2003**, *23*(10), 4261-4269. http://dx.doi.org/10.1523/JNEUROSCI.23-10-04261.2003 PMID: 12764114

[108] Antonijevic, I.A.; Leng, G.; Luckman, S.M.; Douglas, A.J.; Bicknell, R.J.; Russell, J.A. Induction of uterine activity with oxytocin in late pregnant rats replicates the expression of c-fos in neuroendocrine and brain stem neurons as seen during parturition. *Endocrinology,* **1995**, *136*(1), 154-163. http://dx.doi.org/10.1210/endo.136.1.7828526 PMID: 7828526

[109] Hubscher, C.H.; Berkley, K.J. Responses of neurons in caudal solitary nucleus of female rats to stimulation of vagina, cervix, uterine horn and colon. *Brain Res.,* **1994**, *664*(1-2), 1-8. http://dx.doi.org/10.1016/0006-8993(94)91946-1 PMID: 7895018

[110] Kalia, M.; Mesulam, M.M. Brain stem projections of sensory and motor components of the vagus complex in the cat: I. The cervical vagus and nodose ganglion. *J. Comp. Neurol.,* **1980**, *193*(2), 435-465. http://dx.doi.org/10.1002/cne.901930210 PMID: 7440777

[111] Norgren, R. Projections from the nucleus of the solitary tract in the rat. *Neuroscience,* **1978**, *3*(2), 207-218. http://dx.doi.org/10.1016/0306-4522(78)90102-1 PMID: 733004

[112] Verbalis, J.G.; McCann, M.J.; McHale, C.M.; Stricker, E.M. Oxytocin secretion in response to cholecystokinin and food: differentiation of nausea from satiety. *Science,* **1986**, *232*(4 756), 141 7-1419. http://dx.doi.org/10.1126/science.3715453

[113] Renaud, L.P.; Tang, M.; McCann, M.J.; Stricker, E.M.; Verbalis, J.G. Cholecystokinin and gastric distension activate oxytocinergic cells in rat hypothalamus. *Am. J. Physiol.,* **1987**, *253*(4 Pt 2), R661-R665. PMID: 3661761

[114] Verbalis, J.G.; Stricker, E.M.; Robinson, A.G.; Hoffman, G.E. Cholecystokinin activates C-fos expression in hypothalamic oxytocin and corticotropin-releasing hormone neurons. *J. Neuroendocrinol.,* **1991**, *3*(2), 205-213. http://dx.doi.org/10.1111/j.1365-2826.1991.tb00264.x PMID: 19215523

[115] Luckman, S.M.; Hamamura, M.; Antonijevic, I.; Dye, S.; Leng, G. Involvement of cholecystokinin receptor types in pathways controlling oxytocin secretion. *Br. J. Pharmacol.,* **1993**, *110*(1), 378-384. http://dx.doi.org/10.1111/j.1476-5381.1993.tb13820.x PMID: 8220899

[116] Miller, T.R.; Bianchi, B.R.; Witte, D.G.; Lin, C.W. Peripheral cholecystokinin type A receptors mediate oxytocin secretion *in vivo*. *Regul. Pept.,* **1993**, *43*(1-2), 107-112. http://dx.doi.org/10.1016/0167-0115(93)90413-3 PMID: 8426907

[117] Iovino, M.; Vanacore, A.; Steardo, L. Alpha 2-adrenergic stimulation within the nucleus tractus solitarius attenuates vasopressin release induced by depletion of cardiovascular volume. *Pharmacol. Biochem. Behav.,* **1990**, *37*(4), 821-824. http://dx.doi.org/10.1016/0091-3057(90)90568-3 PMID: 1982697

[118] Hardy, S.B. *Mothers and Others: The Evolutionary Origins of Mutual Understanding*; Belknap Press, Harvard Univ. Press: Cambridge, MA, **2009**.

[119] Landgraf, R.; Neumann, I.; Pittman, Q.J. Septal and hippocampal release of vasopressin and oxytocin during late pregnancy and parturition in the rat. *Neuroendocrinology,* **1991**, *54*(4), 378-383. http://dx.doi.org/10.1159/000125917 PMID: 1758580

[120] Caldwell, J.D.; Greer, E.R.; Johnson, M.F.; Prange, A.J., Jr; Pedersen, C.A. Oxytocin and vasopressin immunoreactivity in hypothalamic and extrahypothalamic sites in late pregnant and postpartum rats. *Neuroendocrinology,* **1987**, *46*(1), 39-47. http://dx.doi.org/10.1159/000124794 PMID: 3614554

[121] Landgraf, R.; Neumann, I.; Russell, J.A.; Pittman, Q.J. Push-pull perfusion and microdialysis studies of central oxytocin and vasopressin release in freely moving rats during pregnancy, parturition, and lactation. *Ann. N. Y. Acad. Sci.,* **1992**, *652*, 326-339. http://dx.doi.org/10.1111/j.1749-6632.1992.tb34364.x PMID: 1626836

[122] Meddle, S.L.; Bishop, V.R.; Gkoumassi, E.; van Leeuwen, F.W.; Douglas, A.J. Dynamic changes in oxytocin receptor expression and activation at parturition in the rat brain. *Endocrinology,* **2007**, *148*(10), 5095-5104. http://dx.doi.org/10.1210/en.2007-0615 PMID: 17628000

[123] Pedersen, C.A.; Ascher, J.A.; Monroe, Y.L.; Prange, A.J., Jr Oxytocin induces maternal behavior in virgin female rats. *Science,* **1982**, *216*(4546), 648-650. http://dx.doi.org/10.1126/science.7071605 PMID: 7071605

[124] Iovino, M.; Messana, T.; Iovino, E.; De Pergola, G.; Guastamacchia, E.; Giagulli, V.A.; Triggiani, V. Neuroendocrine Mechanisms Involved in Male Sexual and Emotional Behavior. *Endocr. Metab. Immune Disord. Drug Targets,* **2019**, *19*(4), 472-480. http://dx.doi.org/10.2174/1871530319666190131155310 PMID: 30706797

[125] Xiao, L.; Priest, M.F.; Nasenbeny, J.; Lu, T.; Kozorovitskiy, Y. Biased oxytocinergic modulation of midbrain dopamine systems. *Neuron,* **2017**, *95*(2), 368-384.e5. http://dx.doi.org/10.1016/j.neuron.2017.06.003 PMID: 28669546

[126] Gunaydin, L.A.; Grosenick, L.; Finkelstein, J.C.; Kauvar, I.V.; Fenno, L.E.; Adhikari, A.; Lammel, S.; Mirzabekov, J.J.; Airan, R.D.; Zalocusky, K.A.; Tye, K.M.; Anikeeva, P.; Malenka, R.C.; Deisseroth, K. Natural neural projection dynamics underlying social behavior. *Cell,* **2014**, *157*(7), 1535-1551. http://dx.doi.org/10.1016/j.cell.2014.05.017 PMID: 24949967

[127] Patel, J.C.; Rossignol, E.; Rice, M.E.; Machold, R.P. Opposing regulation of dopaminergic activity and exploratory motor behavior by forebrain and brainstem cholinergic circuits. *Nat. Commun.,* **2012**, *3*, 1172. http://dx.doi.org/10.1038/ncomms2144 PMID: 23132022

[128] Johns, J.M.; Joyner, P.W.; McMurray, M.S.; Elliott, D.L.; Hofler, V.E.; Middleton, C.L.; Knupp, K.; Greenhill, K.W.; Lomas, L.M.; Walker, C.H. The effects of dopaminergic/serotonergic reuptake inhibition on maternal behavior, maternal aggression, and oxytocin in the rat. *Pharmacol. Biochem. Behav.,* **2005**, *81*(4), 769-785. http://dx.doi.org/10.1016/j.pbb.2005.06.001 PMID: 15996723

[129] Champagne, F.; Diorio, J.; Sharma, S.; Meaney, M.J. Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. *Proc. Natl. Acad. Sci. USA,* **2001**, *98*(22), 12736-12741. http://dx.doi.org/10.1073/pnas.221224598 PMID: 11606726

[130] Pedersen, C.A. Oxytocin control of maternal behavior. Regulation by sex steroids and offspring stimuli. *Ann. N. Y. Acad. Sci.,* **1997**, *807*, 126-145.

http://dx.doi.org/10.1111/j.1749-6632.1997.tb51916.x PMID: 9071347

[131] Young, W.S., III; Shepard, E.; Amico, J.; Hennighausen, L.; Wagner, K.U.; LaMarca, M.E.; McKinney, C.; Ginns, E.I. Deficiency in mouse oxytocin prevents milk ejection, but not fertility or parturition. *J. Neuroendocrinol.,* **1996**, *8*(11), 847-853. http://dx.doi.org/10.1046/j.1365-2826.1996.05266.x PMID: 8933362

[132] Pedersen, C.A.; Vadlamudi, S.V.; Boccia, M.L.; Amico, J.A. Maternal behavior deficits in nulliparous oxytocin knockout mice. *Genes Brain Behav.,* **2006**, *5*(3), 274-281. http://dx.doi.org/10.1111/j.1601-183X.2005.00162.x PMID: 16594980

[133] Klampfl, S.M.; Schramm, M.M.; Gaßner, B.M.; Hübner, K.; Seasholtz, A.F.; Brunton, P.J.; Bayerl, D.S.; Bosch, O.J. Maternal stress and the MPOA: Activation of CRF receptor 1 impairs maternal behavior and triggers local oxytocin release in lactating rats. *Neuropharmacology,* **2018**, *133*, 440-450. http://dx.doi.org/10.1016/j.neuropharm.2018.02.019 PMID: 29477300

[134] Dabrowska, J.; Hazra, R.; Ahern, T.H.; Guo, J.D.; McDonald, A.J.; Mascagni, F.; Muller, J.F.; Young, L.J.; Rainnie, D.G. Neuroanatomical evidence for reciprocal regulation of the corticotrophin-releasing factor and oxytocin systems in the hypothalamus and the bed nucleus of the stria terminalis of the rat: Implications for balancing stress and affect. *Psychoneuroendocrinology,* **2011**, *36*(9), 1312-1326. http://dx.doi.org/10.1016/j.psyneuen.2011.03.003 PMID: 21481539

[135] Martinon, D.; Dabrowska, J. Corticotropin-releasing factor receptors modulate oxytocin release in the dorsolateral bed nucleus of the stria terminalis (BNST) in male rats. *Front. Neurosci.,* **2018**, *12*, 183. http://dx.doi.org/10.3389/fnins.2018.00183 PMID: 29618970

[136] Janeček, M.; Dabrowska, J. Oxytocin facilitates adaptive fear and attenuates anxiety responses in animal models and human studies-potential interaction with the corticotropin-releasing factor (CRF) system in the bed nucleus of the stria terminalis (BNST). *Cell Tissue Res.,* **2019**, *375*(1), 143-172. http://dx.doi.org/10.1007/s00441-018-2889-8 PMID: 30054732

[137] Niswender, G.D.; Davis, T.L.; Griffith, R.J.; Bogan, R.L.; Monser, K.; Bott, R.C.; Bruemmer, J.E.; Nett, T.M. Judge, jury and executioner: the auto-regulation of luteal function. *Soc. Reprod. Fertil. Suppl.,* **2007**, *64*, 191-206. http://dx.doi.org/10.5661/RDR-VI-191 PMID: 17491148

[138] Carter, C.S.; Altemus, M. Integrative functions of lactational hormones in social behavior and stress management. *Ann. N. Y. Acad. Sci.,* **1997**, *807*, 164-174. http://dx.doi.org/10.1111/j.1749-6632.1997.tb51918.x PMID: 9071349

[139] Tyzio, R.; Cossart, R.; Khalilov, I.; Minlebaev, M.; Hübner, C.A.; Represa, A.; Ben-Ari, Y.; Khazipov, R. Maternal oxytocin triggers a transient inhibitory switch in GABA signaling in the fetal brain during delivery. *Science,* **2006**, *314*(5806), 1788-1792. http://dx.doi.org/10.1126/science.1133212 PMID: 17170309

[140] Crépel, V.; Aronov, D.; Jorquera, I.; Represa, A.; Ben-Ari, Y.; Cossart, R. A parturition-associated nonsynaptic coherent activity pattern in the developing hippocampus. *Neuron,* **2007**, *54*(1), 105-120. http://dx.doi.org/10.1016/j.neuron.2007.03.007 PMID: 17408581

[141] Khazipov, R.; Tyzio, R.; Ben-Ari, Y. Effects of oxytocin on GABA signalling in the foetal brain during delivery. *Prog. Brain Res.,* **2008**, *170*, 243-257. http://dx.doi.org/10.1016/S0079-6123(08)00421-4 PMID: 18655887

[142] Hoge, E.A.; Anderson, E.; Lawson, E.A.; Bui, E.; Fischer, L.E.; Khadge, S.D.; Barrett, L.F.; Simon, N.M. Gender moderates the effect of oxytocin on social judgments. *Hum. Psychopharmacol.,* **2014**, *29*(3), 299-304. http://dx.doi.org/10.1002/hup.2402 PMID: 24911580

[143] Preckel, K.; Scheele, D.; Kendrick, K.M.; Maier, W.; Hurlemann, R. Oxytocin facilitates social approach behavior in women. *Front. Behav. Neurosci.,* **2014**, *8*, 191. http://dx.doi.org/10.3389/fnbeh.2014.00191 PMID: 24904342

[144] Fischer-Shofty, M.; Levkovitz, Y.; Shamay-Tsoory, S.G. Oxytocin facilitates accurate perception of competition in men and kinship in women. *Soc. Cogn. Affect. Neurosci.,* **2013**, *8*(3), 313-317. http://dx.doi.org/10.1093/scan/nsr100 PMID: 22446301

[145] Scheele, D.; Striepens, N.; Kendrick, K.M.; Schwering, C.; Noelle, J.; Wille, A.; Schläpfer, T.E.; Maier, W.; Hurlemann, R. Opposing effects of oxytocin on moral judgment in males and females. *Hum. Brain Mapp.,* **2014**, *35*(12), 6067-6076. http://dx.doi.org/10.1002/hbm.22605 PMID: 25094043

[146] Scheele, D.; Striepens, N.; Güntürkün, O.; Deutschländer, S.; Maier, W.; Kendrick, K.M.; Hurlemann, R. Oxytocin modulates social distance between males and females. *J. Neurosci.,* **2012**, *32*(46), 16074-16079. http://dx.doi.org/10.1523/JNEUROSCI.2755-12.2012 PMID: 23152592

[147] Ditzen, B.; Nater, U.M.; Schaer, M.; La Marca, R.; Bodenmann, G.; Ehlert, U.; Heinrichs, M. Sex-specific effects of intranasal oxytocin on autonomic nervous system and emotional responses to couple conflict. *Soc. Cogn. Affect. Neurosci.,* **2013**, *8*(8), 897-902. http://dx.doi.org/10.1093/scan/nss083 PMID: 22842905

[148] Bale, T.L.; Davis, A.M.; Auger, A.P.; Dorsa, D.M.; McCarthy, M.M. CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. *J. Neurosci.,* **2001**, *21*(7), 2546-2552. http://dx.doi.org/10.1523/JNEUROSCI.21-07-02546.2001 PMID: 11264328

[149] Kirsch, P.; Esslinger, C.; Chen, Q.; Mier, D.; Lis, S.; Siddhanti, S.; Gruppe, H.; Mattay, V.S.; Gallhofer, B.; Meyer-Lindenberg, A. Oxytocin modulates neural circuitry for social cognition and fear in humans. *J. Neurosci.,* **2005**, *25*(49), 11489-11493. http://dx.doi.org/10.1523/JNEUROSCI.3984-05.2005 PMID: 16339042

[150] Stevens, J.S.; Hamann, S. Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. *Neuropsychologia,* **2012**, *50*(7), 1578-1593. http://dx.doi.org/10.1016/j.neuropsychologia.2012.03.011 PMID: 22450197

[151] Gao, S.; Becker, B.; Luo, L.; Geng, Y.; Zhao, W.; Yin, Y.; Hu, J.; Gao, Z.; Gong, Q.; Hurlemann, R.; Yao, D.; Kendrick, K.M. Oxytocin, the peptide that bonds the sexes also divides them. *Proc. Natl. Acad. Sci. USA,* **2016**, *113*(27), 7650-7654. http://dx.doi.org/10.1073/pnas.1602620113 PMID: 27325780

[152] Amunts, K.; Kedo, O.; Kindler, M.; Peperhoff, P.; Mohiberg, H.; Shah, N.J.; Habel, U.; Sneider, F.; Ziles, K. Cytoarchitectonic mapping of the human amygdala and entorhinal cortex: intersubject variability and probability maps. *Anat. Embryol. (Berl.),* **2005**, *210*(5-6), 343-352. http://dx.doi.org/10.1007/s00429-005-0025-5 PMID: 16208455

[153] Adolphs, R. What does the amygdala contribute to social cognition? *Ann. N. Y. Acad. Sci.,* **2010**, *1191*, 42-61. http://dx.doi.org/10.1111/j.1749-6632.2010.05445.x PMID: 20392275

[154] Ming, G.L.; Song, H. Adult neurogenesis in the mammalian central nervous system. *Annu. Rev. Neurosci.,* **2005**, *28*, 223-250. http://dx.doi.org/10.1146/annurev.neuro.28.051804.101459 PMID: 16022595

[155] Loram, L.C.; Taylor, F.R.; Strand, K.A.; Frank, M.G.; Sholar, P.; Harrison, J.A.; Maier, S.F.; Watkins, L.R. Prior exposure to glucocorticoids potentiates lipopolysaccharide induced mechanical allodynia and spinal neuroinflammation. *Brain Behav. Immun.,* **2011**, *25*(7), 1408-1415. http://dx.doi.org/10.1016/j.bbi.2011.04.013 PMID: 21536123

[156] Yeager, M.P.; Rassias, A.J.; Pioli, P.A.; Beach, M.L.; Wardwell, K.; Collins, J.E.; Lee, H.K.; Guyre, P.M. Pretreatment with stress cortisol enhances the human systemic inflammatory response to bacterial endotoxin. *Crit. Care Med.,* **2009**, *37*(10), 2727-2732. http://dx.doi.org/10.1097/CCM.0b013e3181a592b3 PMID: 19885996

[157] Diz-Chaves, Y.; Pernía, O.; Carrero, P.; Garcia-Segura, L.M. Prenatal stress causes alterations in the morphology of microglia and the inflammatory response of the hippocampus of adult female mice. *J. Neuroinflammation,* **2012**, *9*, 71-96. http://dx.doi.org/10.1186/1742-2094-9-71 PMID: 22520439

[158] Ślusarczyk, J.; Trojan, E.; Głombik, K.; Budziszewska, B.; Kubera, M.; Lasoń, W.; Popiołek-Barczyk, K.; Mika, J.; Wędzony, K.; Basta-Kaim, A. Prenatal stress is a vulnerability factor for altered morphology and biological activity of microglia cells. *Front. Cell. Neurosci.,* **2015**, *9*, 82. http://dx.doi.org/10.3389/fncel.2015.00082 PMID: 25814933

[159] Sanders, G.; Freilicher, J.; Lightman, S.L. Psychological stress of exposure to uncontrollable noise increases plasma oxytocin in high emotionality women. *Psychoneuroendocrinology,* **1990**, *15*(1), 47-58. http://dx.doi.org/10.1016/0306-4530(90)90046-C PMID: 2367615

[160] Neumann, I.D.; Wigger, A.; Torner, L.; Holsboer, F.; Landgraf, R. Brain oxytocin inhibits basal and stress-induced activity of the hypothalamo-pituitary-adrenal axis in male and female rats: partial action within the paraventricular nucleus. *J. Neuroendocrinol.,* **2000**, *12*(3), 235-243. http://dx.doi.org/10.1046/j.1365-2826.2000.00442.x PMID: 10718919

[161] Ditzen, B.; Schaer, M.; Gabriel, B.; Bodenmann, G.; Ehlert, U.; Heinrichs, M. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biol. Psychiatry,* **2009**, *65*(9), 728-731. http://dx.doi.org/10.1016/j.biopsych.2008.10.011 PMID: 19027101

[162] Windle, R.J.; Shanks, N.; Lightman, S.L.; Ingram, C.D. Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats. *Endocrinology,* **1997**, *138*(7), 2829-2834. http://dx.doi.org/10.1210/endo.138.7.5255 PMID: 9202224

[163] Karelina, K.; Stuller, K.A.; Jarrett, B.; Zhang, N.; Wells, J.; Norman, G.J.; DeVries, A.C. Oxytocin mediates social neuroprotection after cerebral ischemia. *Stroke,* **2011**, *42*(12), 3606-3611. http://dx.doi.org/10.1161/STROKEAHA.111.628008 PMID: 21960564

[164] Norman, G.J.; Karelina, K.; Morris, J.S.; Zhang, N.; Cochran, M.; Courtney DeVries, A. Social interaction prevents the development of depressive-like behavior post nerve injury in mice: a potential role for oxytocin. *Psychosom. Med.,* **2010**, *72*(6), 519-526. http://dx.doi.org/10.1097/PSY.0b013e3181de8678 PMID: 20466999

[165] Amini-Khoei, H.; Mohammadi-Asl, A.; Amiri, S.; Hosseini, M-J.; Momeny, M.; Hassanipour, M.; Rastegar, M.; Haj-Mirzaian, A.; Mirzaian, A.H.; Sanjarimoghaddam, H.; Mehr, S.E.; Dehpour, A.R. Oxytocin mitigated the depressive-like behaviors of maternal separation stress through modulating mitochondrial function and neuroinflammation. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2017**, *76*, 169-178. http://dx.doi.org/10.1016/j.pnpbp.2017.02.022 PMID: 28259722

[166] Mazzuca, M.; Minlebaev, M.; Shakirzyanova, A.; Tyzio, R.; Taccola, G. Newborn analgesia mediated by oxytocin during delivery. *Front. Cell Neurosci,* **2011**, *5*, 3. http://dx.doi.org/10.3389/fncel.2011.00003

[167] Stuebe, A.M.; Grewen, K.; Meltzer-Brody, S. Association between maternal mood and oxytocin response to breastfeeding. *J. Womens Health (Larchmt.),* **2013**, *22*(4), 352-361. http://dx.doi.org/10.1089/jwh.2012.3768 PMID: 23586800

[168] Burkett, J.P.; Spiegel, L.L.; Inoue, K.; Murphy, A.Z.; Young, L.J. Activation of μ-opioid receptors in the dorsal striatum is necessary for adult social attachment in monogamous prairie voles. *Neuropsychopharmacology,* **2011**, *36*(11), 2200-2210. http://dx.doi.org/10.1038/npp.2011.117 PMID: 21734650

[169] Gu, X.L.; Yu, L.C. Involvement of opioid receptors in oxytocin-induced antinociception in the nucleus accumbens of rats. *J. Pain,* **2007**, *8*(1), 85-90. http://dx.doi.org/10.1016/j.jpain.2006.07.001 PMID: 17097925

[170] Russo, R.; D'Agostino, G.; Mattace Raso, G.; Avagliano, C.; Cristiano, C.; Meli, R.; Calignano, A. Central administration of oxytocin reduces hyperalgesia in mice: implication for cannabinoid and opioid systems. *Peptides,* **2012**, *38*(1), 81-88. http://dx.doi.org/10.1016/j.peptides.2012.08.005 PMID: 22917880

[171] Sawchenko, P.E.; Swanson, L.W. Immunohistochemical identification of neurons in the paraventricular nucleus of the hypothalamus that project to the medulla or to the spinal cord in the rat. *J. Comp. Neurol.,* **1982**, *205*(3), 260-272. http://dx.doi.org/10.1002/cne.902050306 PMID: 6122696

[172] Juif, P.E.; Poisbeau, P. Neurohormonal effects of oxytocin and vasopressin receptor agonists on spinal pain processing in male rats. *Pain,* **2013**, *154*(8), 1449-1456. http://dx.doi.org/10.1016/j.pain.2013.05.003 PMID: 23707282

[173] Juif, P.E.; Breton, J.D.; Rajalu, M.; Charlet, A.; Goumon, Y.; Poisbeau, P. Long-lasting spinal oxytocin analgesia is ensured by the stimulation of allopregnanolone synthesis which potentiates GABA(A) receptor-mediated synaptic inhibition. *J. Neurosci.,* **2013**, *33*(42), 16617-16626. http://dx.doi.org/10.1523/JNEUROSCI.3084-12.2013 PMID: 24133265

[174] Eliava, M.; Melchior, M.; Knobloch-Bollmann, H.S.; Wahis, J.; da Silva Gouveia, M.; Tang, Y.; Ciobanu, A.C.; Triana Del Rio, R.; Roth, L.C.; Althammer, F.; Chavant, V.; Goumon, Y.; Gruber, T.; Petit-Demoulière, N.; Busnelli, M.; Chini, B.; Tan, L.L.; Mitre, M.; Froemke, R.C.; Chao, M.V.; Giese, G.; Sprengel, R.; Kuner, R.; Poisbeau, P.; Seeburg, P.H.; Stoop, R.; Charlet, A.; Grinevich, V. A new population of parvocellular OT neurons controlling magnocellular neuron activity and inflammatory pain processing. *Neuron,* **2016**, *89*(6), 1291-1304. http://dx.doi.org/10.1016/j.neuron.2016.01.041 PMID: 26948889

[175] Leuner, B.; Caponiti, J.M.; Gould, E. Oxytocin stimulates adult neurogenesis even under conditions of stress and elevated glucocorticoids. *Hippocampus,* **2012**, *22*(4), 861-868. http://dx.doi.org/10.1002/hipo.20947 PMID: 21692136

[176] Gutkowska, J.; Jankowski, M. Oxytocin revisited: its role in cardiovascular regulation. *J. Neuroendocrinol.,* **2012**, *24*(4), 599-608. http://dx.doi.org/10.1111/j.1365-2826.2011.02235.x PMID: 21981277

[177] Jafarzadeh, N.; Javeri, A.; Khaleghi, M.; Taha, M.F. Oxytocin improves proliferation and neural differentiation of adipose tissue-derived stem cells. *Neurosci. Lett.,* **2014**, *564*, 105-110. http://dx.doi.org/10.1016/j.neulet.2014.02.012 PMID: 24548623

[178] Lin, Y.T.; Chen, C.C.; Huang, C.C.; Nishimori, K.; Hsu, K.S. Oxytocin stimulates hippocampal neurogenesis via oxytocin receptor expressed in CA3 pyramidal neurons. *Nat. Commun.,* **2017**, *8*(1), 537. http://dx.doi.org/10.1038/s41467-017-00675-5 PMID: 28912554

[179] Petersson, M. Cardiovascular effects of oxytocin. *Prog. Brain Res.,* **2002**, *139*, 281-288. http://dx.doi.org/10.1016/S0079-6123(02)39024-1 PMID: 12436943

[180] Gimpl, G.; Fahrenholz, F. The oxytocin receptor system: structure, function, and regulation. *Physiol. Rev.,* **2001**, *81*(2), 629-683. http://dx.doi.org/10.1152/physrev.2001.81.2.629 PMID: 11274341

[181] Welch, M.G.; Tamir, H.; Gross, K.J.; Chen, J.; Anwar, M.; Gershon, M.D. Expression and developmental regulation of oxytocin (OT) and oxytocin receptors (OTR) in the enteric nervous system (ENS) and intestinal epithelium. *J. Comp. Neurol.,* **2009**, *512*(2), 256-270. http://dx.doi.org/10.1002/cne.21872 PMID: 19003903

[182] Olszewski, P.K.; Klockars, A.; Schiöth, H.B.; Levine, A.S. Oxytocin as feeding inhibitor: maintaining homeostasis in consummatory behavior. *Pharmacol. Biochem. Behav.,* **2010**, *97*(1), 47-54. http://dx.doi.org/10.1016/j.pbb.2010.05.026 PMID: 20595062

[183] Nielsen, S.H.; Magid, E.; Spannow, J.; Christensen, S.; Lam, H.R.; Petersen, J.S. Renal function after myocardial infarction and cardiac arrest in rats: role of ANP-induced albuminuria? *Acta Physiol. Scand.,* **1997**, *160*(4), 301-310. http://dx.doi.org/10.1046/j.1365-201X.1997.00162.x PMID: 9338510

[184] Jameson, H.; Bateman, R.; Byrne, P.; Dyavanapalli, J.; Wang, X.; Jain, V.; Mendelowitz, D. Oxytocin neuron activation prevents hypertension that occurs with chronic intermittent hypoxia/hypercapnia in rats. *Am. J. Physiol. Heart Circ. Physiol.,* **2016**, *310*(11), H1549-H1557. http://dx.doi.org/10.1152/ajpheart.00808.2015 PMID: 27016581

[185] Wang, P.; Yang, H.P.; Tian, S.; Wang, L.; Wang, S.C.; Zhang, F.; Wang, Y.F. Oxytocin-secreting system: A major part of the neuroendocrine center regulating immunologic activity. *J. Neuroimmunol.,* **2015**, *289*, 152-161. http://dx.doi.org/10.1016/j.jneuroim.2015.11.001 PMID: 26616885

[186] Wang, Y.-F. Center role of the oxytocin-secreting system in neuroendocrine-immune network revisited. *J. Clin. Exp. Neuroimmunol., ,* **2016**, *1*, 102.

[187] Iovino, M.; Messana, T.; De Pergola, G.; Iovino, E.; Guastamacchia, E.; Licchelli, B.; Vanacore, A.; Giagulli, V.A.; Triggiani, V. Brain angiotensinergic regulation of the immune system: implications for cardiovascular and neuroendocrine responses. *Endocr. Metab. Immune Disord. Drug Targets,* **2020**, *20*(1), 15-24. http://dx.doi.org/10.2174/1871530319666190617160934 PMID: 31237219

[188] Deblon, N.; Veyrat-Durebex, C.; Bourgoin, L.; Caillon, A.; Bussier, A.L.; Petrosino, S.; Piscitelli, F.; Legros, J.J.; Geenen, V.; Foti, M.; Wahli, W.; Di Marzo, V.; Rohner-Jeanrenaud, F. Mechanisms of the anti-obesity effects of oxytocin in diet-induced obese rats. *PLoS One,* **2011**, *6*(9), e25565.

[189] Blevins, J. E.; Baskin, D. G. Translational and therapeutic potential of oxytocin as an anti-obesity strategy: insights from rodents, non-human primates and humans. *Physiol. Behav,* **2015**, *152*(Pt B), 438-449. http://dx.doi.org/10.1016/j.physbeh.2015.05.023

[190] Iovino, M.; Iacoviello, M.; De Pergola, G.; Licchelli, B.; Iovino, E.; Guastamacchia, E.; Giagulli, V.A.; Triggiani, V. Vasopressin in heart failure. *Endocr. Metab. Immune Disord. Drug Targets,* **2018**, *18*(5), 458-465. http://dx.doi.org/10.2174/1871530318666180212095235 PMID: 29437026

[191] Iovino, M.; Messana, T.; De Pergola, G.; Iovino, E.; Dicuonzo, F.; Guastamacchia, E.; Giagulli, V.A.; Triggiani, V. The role of neurohypophyseal hormones vasopressin and oxytocin in neuropsychiatric disorders. *Endocr. Metab. Immune Disord. Drug Targets,* **2018**, *18*(4), 341-347. http://dx.doi.org/10.2174/1871530318666180220104900 PMID: 29468985

[192] Wang, S.C.; Meng, D.; Yang, H.; Wang, X.; Jia, S.; Wang, P.; Wang, Y-F. Pathological basis of cardiac arrhythmias: vicious cycle of immune-metabolic dysregulation. *Cardiovasc. Disord. Med.,* **2018**, *3*, 1-7.

[193] Jankowski, M.; Broderick, T.L.; Gutkowska, J. Oxytocin and cardioprotection in diabetes and obesity. *BMC Endocr. Disord,* **2016**, *16*, 34. http://dx.doi.org/10.1186/s12902-016-0110-1

[194] Morishita, Y.; Arima, H.; Hiroi, M.; Hayashi, M.; Hagiwara, D.; Asai, N.; Ozaki, N.; Sugimura, Y.; Nagasaki, H.; Shiota, A.; Takahashi, M.; Oiso, Y. Poly(A) tail length of neurohypophysial hormones is shortened under endoplasmic reticulum stress. *Endocrinology,* **2011**, *152*(12), 4846-4855. http://dx.doi.org/10.1210/en.2011-1415 PMID: 21971157

[195] Indrambarya, T.; Boyd, J.H.; Wang, Y.; McConechy, M.; Walley, K.R. Low-dose vasopressin infusion results in increased mortality and cardiac dysfunction following ischemia-reperfusion injury in mice. *Crit. Care,* **2009**, *13*(3), R98. http://dx.doi.org/10.1186/cc7930 PMID: 19549333

[196] Wang, P.; Wang, S.C.; Yang, H.; Lv, C.; Jia, S.; Liu, X.; Wang, X.; Meng, D.; Qin, D.; Zhu, H.; Wang, Y.F. Therapeutic Potential of Oxytocin in Atherosclerotic Cardiovascular Disease: Mechanisms and Signaling Pathways. *Front Neurosci,* **2019**, *13*, 454.

[197] Plante, E.; Menaouar, A.; Danalache, B.A.; Yip, D.; Broderick, T.L.; Chiasson, J.L.; Jankowski, M.; Gutkowska, J. Oxytocin treatment prevents the cardiomyopathy observed in obese diabetic male db/db mice. *Endocrinology,* **2015**, *156*(4), 1416-1428. http://dx.doi.org/10.1210/en.2014-1718 PMID: 25562615

[198] Modahl, C.; Green, L.; Fein, D.; Morris, M.; Waterhouse, L.; Feinstein, C.; Levin, H. Plasma oxytocin levels in autistic children. *Biol. Psychiatry,* **1998**, *43*(4), 270-277. http://dx.doi.org/10.1016/S0006-3223(97)00439-3 PMID: 9513736

[199] Green, L.; Fein, D.; Modahl, C.; Feinstein, C.; Waterhouse, L.; Morris, M. Oxytocin and autistic disorder: alterations in peptide forms. *Biol. Psychiatry,* **2001**, *50*(8), 609-613. http://dx.doi.org/10.1016/S0006-3223(01)01139-8 PMID: 11690596

[200] Jansen, L.M.; Gispen-de Wied, C.C.; Wiegant, V.M.; Westenberg, H.G.; Lahuis, B.E.; van Engeland, H. Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder. *J. Autism Dev. Disord.,* **2006**, *36*(7), 891-899. http://dx.doi.org/10.1007/s10803-006-0124-z PMID: 16865550

[201] LoParo, D.; Waldman, I.D. The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: a meta-analysis. *Mol. Psychiatry,* **2015**, *20*(5), 640-646. http://dx.doi.org/10.1038/mp.2014.77 PMID: 25092245

[202] Malavasi, F.; Deaglio, S.; Funaro, A.; Ferrero, E.; Horenstein, A.L.; Ortolan, E.; Vaisitti, T.; Aydin, S. Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology. *Physiol. Rev.,* **2008**, *88*(3), 841-886. http://dx.doi.org/10.1152/physrev.00035.2007 PMID: 18626062

[203] Liu, H.X.; Lopatina, O.; Higashida, C.; Tsuji, T.; Kato, I.; Takasawa, S.; Okamoto, H.; Yokoyama, S.; Higashida, H. Locomotor activity, ultrasonic vocalization and oxytocin levels in infant CD38 knockout mice. *Neurosci. Lett.,* **2008**, *448*(1), 67-70. http://dx.doi.org/10.1016/j.neulet.2008.09.084 PMID: 18926879

[204] Higashida, H.; Yokoyama, S.; Kikuchi, M.; Munesue, T. CD38 and its role in oxytocin secretion and social behavior. *Horm. Behav.,* **2012**, *61*(3), 351-358. http://dx.doi.org/10.1016/j.yhbeh.2011.12.011 PMID: 22227279

[205] Higashida, H.; Yokoyama, S.; Munesue, T.; Kikuchi, M.; Minabe, Y.; Lopatina, O. CD38 gene knockout juvenile mice: a model of oxytocin signal defects in autism. *Biol. Pharm. Bull.,* **2011**, *34*(9), 1369-1372. http://dx.doi.org/10.1248/bpb.34.1369 PMID: 21881219

[206] Lopatina, O.; Liu, H.X.; Amina, S.; Hashii, M.; Higashida, H. Oxytocin-induced elevation of ADP-ribosyl cyclase activity, cyclic ADP-ribose or Ca(2+) concentrations is involved in autoregulation of oxytocin secretion in the hypothalamus and posterior pituitary in male mice. *Neuropharmacology,* **2010**, *58*(1), 50-55. http://dx.doi.org/10.1016/j.neuropharm.2009.06.012 PMID: 19540855

[207] Jin, D.; Liu, H.X.; Hirai, H.; Torashima, T.; Nagai, T.; Lopatina, O.; Shnayder, N.A.; Yamada, K.; Noda, M.; Seike, T.; Fujita, K.; Takasawa, S.; Yokoyama, S.; Koizumi, K.; Shiraishi, Y.; Tanaka, S.; Hashii, M.; Yoshihara, T.; Higashida, K.; Islam, M.S.; Yamada, N.; Hayashi, K.; Noguchi, N.; Kato, I.; Okamoto, H.; Matsushima, A.; Salmina, A.; Munesue, T.; Shimizu, N.; Mochida, S.; Asano, M.; Higashida, H. CD38 is critical for social behaviour by regulating oxytocin secretion. *Nature,* **2007**, *446*(7131), 41-45. http://dx.doi.org/10.1038/nature05526 PMID: 17287729

[208] Munesue, T.; Yokoyama, S.; Nakamura, K.; Anitha, A.; Yamada, K.; Hayashi, K.; Asaka, T.; Liu, H.X.; Jin, D.; Koizumi, K.; Islam, M.S.; Huang, J.J.; Ma, W.J.; Kim, U.H.; Kim, S.J.; Park, K.; Kim, D.; Kikuchi, M.; Ono, Y.; Nakatani, H.; Suda, S.; Miyachi, T.; Hirai, H.; Salmina, A.; Pichugina, Y.A.; Soumarokov, A.A.; Takei, N.; Mori, N.; Tsujii, M.; Sugiyama, T.; Yagi, K.; Yamagishi, M.; Sasaki, T.; Yamasue, H.; Kato, N.; Hashimoto, R.; Taniike, M.; Hayashi, Y.; Hamada, J.; Suzuki, S.; Ooi, A.; Noda, M.; Kamiyama, Y.; Kido, M.A.; Lopatina, O.; Hashii, M.; Amina, S.; Malavasi, F.; Huang, E.J.; Zhang, J.; Shimizu, N.; Yoshikawa, T.; Matsushima, A.; Minabe, Y.; Higashida, H. Two genetic variants of CD38 in subjects with autism spectrum disorder and controls. *Neurosci. Res.,* **2010**, *67*(2), 181-191. http://dx.doi.org/10.1016/j.neures.2010.03.004 PMID: 20435366

[209] Allen-Brady, K.; Miller, J.; Matsunami, N.; Stevens, J.; Block, H.; Farley, M.; Krasny, L.; Pingree, C.; Lainhart, J.; Leppert, M.; McMahon, W.M.; Coon, H. A high-density SNP genome-wide linkage scan in a large autism extended pedigree. *Mol. Psychiatry,* **2009**, *14*(6), 590-600. http://dx.doi.org/10.1038/mp.2008.14 PMID: 18283277

[210] Ebstein, R.P.; Israel, S.; Lerer, E.; Uzefovsky, F.; Shalev, I.; Gritsenko, I.; Riebold, M.; Salomon, S.; Yirmiya, N. Arginine vasopressin and oxytocin modulate human social behavior. *Ann. N. Y. Acad. Sci.,* **2009**, *1167*, 87-102. http://dx.doi.org/10.1111/j.1749-6632.2009.04541.x PMID: 19580556

[211] Hovey, D.; Zettergren, A.; Jonsson, L.; Melke, J.; Anckarsäter, H.; Lichtenstein, P.; Westberg, L. Associations between oxytocin-related genes and autistic-like traits. *Soc. Neurosci.,* **2014**, *9*(4), 378-386. http://dx.doi.org/10.1080/17470919.2014.897995 PMID: 24635660

[212] Francis, S.M.; Kistner-Griffin, E.; Yan, Z.; Guter, S.; Cook, E.H.; Jacob, S. Variants in adjacent oxytocin/vasopressin gene region and

associations with ASD diagnosis and other autism elated endophenotypes. *Front. Neurosci.,* **2016**, *10*, 195-213. http://dx.doi.org/10.3389/fnins.2016.00195 PMID: 27242401

[213] Jonas, W.; Mileva-Seitz, V.; Girard, A.W.; Bisceglia, R.; Kennedy, J.L.; Sokolowski, M.; Meaney, M.J.; Fleming, A.S.; Steiner, M. MAVAN Research Team. Genetic variation in oxytocin rs2740210 and early adversity associated with postpartum depression and breastfeeding duration. *Genes Brain Behav.,* **2013**, *12*(7), 681-694. http://dx.doi.org/10.1111/gbb.12069 PMID: 23941164

[214] Jacob, S.; Brune, C.W.; Carter, C.S.; Leventhal, B.L.; Lord, C.; Cook, E.H., Jr Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. *Neurosci. Lett.,* **2007**, *417*(1), 6-9. http://dx.doi.org/10.1016/j.neulet.2007.02.001 PMID: 17383819

[215] Lerer, E.; Levi, S.; Salomon, S.; Darvasi, A.; Yirmiya, N.; Ebstein, R.P. Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. *Mol. Psychiatry,* **2008**, *13*(10), 980-988. http://dx.doi.org/10.1038/sj.mp.4002087 PMID: 17893705

[216] Di Napoli, A.; Warrier, V.; Baron-Cohen, S.; Chakrabarti, B. Genetic variation in the oxytocin receptor (OXTR) gene is associated with Asperger Syndrome. *Mol. Autism,* **2014**, *5*(1), 48-64. http://dx.doi.org/10.1186/2040-2392-5-48 PMID: 25264479

[217] Ma, W.J.; Hashii, M.; Munesue, T.; Hayashi, K.; Yagi, K.; Yamagishi, M.; Higashida, H.; Yokoyama, S. Non-synonymous single-nucleotide variations of the human oxytocin receptor gene and autism spectrum disorders: a case-control study in a Japanese population and functional analysis. *Mol. Autism,* **2013**, *4*(1), 22-46. http://dx.doi.org/10.1186/2040-2392-4-22 PMID: 23815867

[218] Tost, H.; Kolachana, B.; Hakimi, S.; Lemaitre, H.; Verchinski, B.A.; Mattay, V.S.; Weinberger, D.R.; Meyer-Lindenberg, A. A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*(31), 13936-13941. http://dx.doi.org/10.1073/pnas.1003296107 PMID: 20647384

[219] Wang, J.; Qin, W.; Liu, B.; Wang, D.; Zhang, Y.; Jiang, T.; Yu, C. Variant in OXTR gene and functional connectivity of the hypothalamus in normal subjects. *Neuroimage,* **2013**, *81*, 199-204. http://dx.doi.org/10.1016/j.neuroimage.2013.05.029 PMID: 23684879

[220] Schneider-Hassloff, H.; Straube, B.; Jansen, A.; Nuscheler, B.; Wemken, G.; Witt, S.H.; Rietschel, M.; Kircher, T. Oxytocin receptor polymorphism and childhood social experiences shape adult personality, brain structure and neural correlates of mentalizing. *Neuroimage,* **2016**, *134*, 671-684. http://dx.doi.org/10.1016/j.neuroimage.2016.04.009 PMID: 27109357

[221] Andari, E.; Duhamel, J.R.; Zalla, T.; Herbrecht, E.; Leboyer, M.; Sirigu, A. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*(9), 4389-4394. http://dx.doi.org/10.1073/pnas.0910249107 PMID: 20160081

[222] Yatawara, C.J.; Einfeld, S.L.; Hickie, I.B.; Davenport, T.A.; Guastella, A.J. The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: a randomized clinical crossover trial. *Mol. Psychiatry,* **2016**, *21*(9), 1225-1231. http://dx.doi.org/10.1038/mp.2015.162 PMID: 26503762

[223] Kosaka, H.; Munesue, T.; Ishitobi, M.; Asano, M.; Omori, M.; Sato, M.; Tomoda, A.; Wada, Y. Long-term oxytocin administration improves social behaviors in a girl with autistic disorder. *BMC Psychiatry,* **2012**, *12*, 110-119. http://dx.doi.org/10.1186/1471-244X-12-110 PMID: 22888794

[224] Watanabe, T.; Kuroda, M.; Kuwabara, H.; Aoki, Y.; Iwashiro, N.; Tatsunobu, N.; Takao, H.; Nippashi, Y.; Kawakubo, Y.; Kunimatsu, A.; Kasai, K.; Yamasue, H. Clinical and neural effects of six-week administration of oxytocin on core symptoms of autism. *Brain,* **2015**, *138*(Pt 11), 3400-3412. http://dx.doi.org/10.1093/brain/awv249 PMID: 26336909

[225] Dadds, M.R.; MacDonald, E.; Cauchi, A.; Williams, K.; Levy, F.; Brennan, J. Nasal oxytocin for social deficits in childhood autism: a randomized controlled trial. *J. Autism Dev. Disord.,* **2014**, *44*(3), 521-531. http://dx.doi.org/10.1007/s10803-013-1899-3 PMID: 23888359

[226] Guastella, A.J.; Gray, K.M.; Rinehart, N.J.; Alvares, G.A.; Tonge, B.J.; Hickie, I.B.; Keating, C.M.; Cacciotti-Saija, C.; Einfeld, S.L. The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: a randomized controlled trial. *J. Child Psychol. Psychiatry,* **2015**, *56*(4), 444-452. http://dx.doi.org/10.1111/jcpp.12305 PMID: 25087908

[227] Kosaka, H.; Okamoto, Y.; Munesue, T.; Yamasue, H.; Inohara, K.; Fujioka, T.; Anme, T.; Orisaka, M.; Ishitobi, M.; Jung, M.; Fujisawa, T.X.; Tanaka, S.; Arai, S.; Asano, M.; Saito, D.N.; Sadato, N.; Tomoda, A.; Omori, M.; Sato, M.; Okazawa, H.; Higashida, H.; Wada, Y. Oxytocin efficacy is modulated by dosage and oxytocin receptor genotype in young adults with high-functioning autism: a 24-week randomized clinical trial. *Transl. Psychiatry,* **2016**, *6*(8)e872 http://dx.doi.org/10.1038/tp.2016.152 PMID: 27552585

[228] Carter, C.S. Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology,* **1998**, *23*(8), 779-818. http://dx.doi.org/10.1016/S0306-4530(98)00055-9 PMID: 9924738

[229] Carter, C.S. Developmental consequences of oxytocin. *Physiol. Behav.,* **2003**, *79*(3), 383-397. http://dx.doi.org/10.1016/S0031-9384(03)00151-3 PMID: 12954433

[230] Carter, C.S.; Pournajafi-Nazarloo, H.; Kramer, K.M.; Ziegler, T.E.; White-Traut, R.; Bello, D.; Schwertz, D. Oxytocin: behavioral associations and potential as a salivary biomarker. *Ann. N. Y. Acad. Sci.,* **2007**, *1098*, 312-322. http://dx.doi.org/10.1196/annals.1384.006 PMID: 17435137

[231] Neumann, I.D.; Landgraf, R. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends Neurosci.,* **2012**, *35*(11), 649-659. http://dx.doi.org/10.1016/j.tins.2012.08.004 PMID: 22974560

[232] Landgraf, R.; Wigger, A. Born to be anxious: neuroendocrine and genetic correlates of trait anxiety in HBA rats. *Stress,* **2003**, *6*111119 http://dx.doi.org/10.1080/1025389031000104193

[233] Appenrodt, E.; Schnabel, R.; Schwarzberg, H. Vasopressin administration modulates anxiety-related behavior in rats. *Physiol. Behav.,* **1998**, *64*(4), 543-547. http://dx.doi.org/10.1016/S0031-9384(98)00119-X PMID: 9761230

[234] Insel, T.R.; Young, L.J. The neurobiology of attachment. Nat. Rev. Neurosci., 2001, 2, 129-136. [15] Macdonald, K.; Macdonald, T.M. The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harv. Rev. Psychiatry,* **2010**, *18*, 1-21.

[235] Heinrichs, M.; Baumgartner, T.; Kirschbaum, C.; Ehlert, U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol. Psychiatry,* **2003**, *54*(12), 1389-1398. http://dx.doi.org/10.1016/S0006-3223(03)00465-7 PMID: 14675803

[236] Domes, G.; Heinrichs, M.; Gläscher, J.; Büchel, C.; Braus, D.F.; Herpertz, S.C. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biol. Psychiatry,* **2007**, *62*(10), 1187-1190. http://dx.doi.org/10.1016/j.biopsych.2007.03.025 PMID: 17617382

[237] Kosfeld, M.; Heinrichs, M.; Zak, P.J.; Fischbacher, U.; Fehr, E. Oxytocin increases trust in humans. *Nature,* **2005**, *435*(7042), 673-676. http://dx.doi.org/10.1038/nature03701 PMID: 15931222

[238] Macdonald, K.; Feifel, D. Oxytocin in schizophrenia: a review of evidence for its therapeutic effects. *Acta Neuropsychiatr.,* **2012**, *24*(3), 130-146. http://dx.doi.org/10.1111/j.1601-5215.2011.00634.x PMID: 22736892

[239] Linkowski, P.; Geenen, V.; Kerkhofs, M.; Mendlewicz, J.; Legros, J.J. Cerebrospinal fluid neurophysins in affective illness and in schizophrenia. *Eur. Arch. Psychiatry Neurol. Sci.,* **1984**, *234*(3), 162-165. http://dx.doi.org/10.1007/BF00461555 PMID: 6489403

[240] Beckmann, H.; Lang, R.E.; Gattaz, W.F. Vasopressin--oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls. *Psychoneuroendocrinology,* **1985**, *10*(2), 187-191. http://dx.doi.org/10.1016/0306-4530(85)90056-3 PMID: 4034849

[241] Legros, J.J.; Gazzotti, C.; Carvelli, T.; Franchimont, P.; Timsit-Berthier, M.; von Frenckell, R.; Ansseau, M. Apomorphine stimula-

tion of vasopressin- and oxytocin-neurophysins. Evidence for increased oxytocinergic and decreased vasopressinergic function in schizophrenics. *Psychoneuroendocrinology,* **1992**, *17*(6), 611-617. http://dx.doi.org/10.1016/0306-4530(92)90019-4 PMID: 1287681

[242] Kay, S.R.; Fiszbein, A.; Opler, L.A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.,* **1987**, *13*(2), 261-276. http://dx.doi.org/10.1093/schbul/13.2.261 PMID: 3616518

[243] Rubin, L.H.; Carter, C.S.; Drogos, L.; Pournajafi-Nazarloo, H.; Sweeney, J.A.; Maki, P.M. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. *Schizophr. Res.,* **2010**, *124*(1-3), 13-21. http://dx.doi.org/10.1016/j.schres.2010.09.014 PMID: 20947304

[244] Souza, R.P.; Ismail, P.; Meltzer, H.Y.; Kennedy, J.L. Variants in the oxytocin gene and risk for schizophrenia. *Schizophr. Res.,* **2010**, *121*(1-3), 279-280. http://dx.doi.org/10.1016/j.schres.2010.04.019 PMID: 20547038

[245] Teltsh, O.; Kanyas-Sarner, K.; Rigbi, A.; Greenbaum, L.; Lerer, B.; Kohn, Y. Oxytocin and vasopressin genes are significantly associated with schizophrenia in a large Arab-Israeli pedigree. *Int. J. Neuropsychopharmacol.,* **2012**, *15*(3), 309-319. http://dx.doi.org/10.1017/S1461145711001374 PMID: 21899794

[246] Souza, R.P.; de Luca, V.; Meltzer, H.Y.; Lieberman, J.A.; Kennedy, J.L. Schizophrenia severity and clozapine treatment outcome association with oxytocinergic genes. *Int. J. Neuropsychopharmacol.,* **2010**, *13*(6), 793-798. http://dx.doi.org/10.1017/S1461145710000167 PMID: 20196918

[247] Bujanow, W. Hormones in the treatment of psychoses. *BMJ,* **1972**, *4*(5835), 298. http://dx.doi.org/10.1136/bmj.4.5835.298-c PMID: 5083904

[248] Bujanow, W. Letter: Is oxytocin an anti-schizophrenic hormone? *Can. Psychiatr. Assoc. J.,* **1974**, *19*(3), 323. http://dx.doi.org/10.1177/070674377401900323 PMID: 4841051

[249] Bakharev, V.D.; Tikhomirov, S.M.; Lozhkina, T.K. Psychotropic properties of oxytocin. *Neurosci. Behav. Physiol.,* **1986**, *16*(2), 160-164. http://dx.doi.org/10.1007/BF01186517 PMID: 3748373

[250] Goldman, M.B.; Gomes, A.M.; Carter, C.S.; Lee, R. Divergent effects of two different doses of intranasal oxytocin on facial affect discrimination in schizophrenic patients with and without polydipsia. *Psychopharmacology (Berl.),* **2011**, *216*(1), 101-110. http://dx.doi.org/10.1007/s00213-011-2193-8 PMID: 21301811

[251] Feifel, D.; Macdonald, K.; Nguyen, A.; Cobb, P.; Warlan, H.; Galangue, B.; Minassian, A.; Becker, O.; Cooper, J.; Perry, W.; Lefebvre, M.; Gonzales, J.; Hadley, A. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. *Biol. Psychiatry,* **2010**, *68*(7), 678-680. http://dx.doi.org/10.1016/j.biopsych.2010.04.039 PMID: 20615494

[252] Feifel, D.; Macdonald, K.; Cobb, P.; Minassian, A. Adjunctive intranasal oxytocin improves verbal memory in people with schizophrenia. *Schizophr. Res.,* **2012**, *139*(1-3), 207-210. http://dx.doi.org/10.1016/j.schres.2012.05.018 PMID: 22682705

[253] Pedersen, C.A.; Gibson, C.M.; Rau, S.W.; Salimi, K.; Smedley, K.L.; Casey, R.L.; Leserman, J.; Jarskog, L.F.; Penn, D.L. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. *Schizophr. Res.,* **2011**, *132*(1), 50-53. http://dx.doi.org/10.1016/j.schres.2011.07.027 PMID: 21840177

[254] Modabbernia, A.; Rezaei, F.; Salehi, B.; Jafarinia, M.; Ashrafi, M.; Tabrizi, M.; Hosseini, S.M.; Tajdini, M.; Ghaleiha, A.; Akhondzadeh, S. Intranasal oxytocin as an adjunct to risperidone in patients with schizophrenia : an 8-week, randomized, double-blind, placebo-controlled study. *CNS Drugs,* **2013**, *27*(1), 57-65. http://dx.doi.org/10.1007/s40263-012-0022-1 PMID: 23233269

[255] Rotzinger, S.; Lovejoy, D.A.; Tan, L.A. Behavioral effects of neuropeptides in rodent models of depression and anxiety. *Peptides,* **2010**, *31*(4), 736-756. http://dx.doi.org/10.1016/j.peptides.2009.12.015 PMID: 20026211

[256] Zetzsche, T.; Frasch, A.; Jirikowski, G.; Murck, H.; Steiger, A. Nocturnal oxytocin secretion is reduced in major depression. *Biol. Psychiatry,* **1996**, *39*, 584. http://dx.doi.org/10.1016/0006-3223(96)84235-1

[257] Anderberg, U.M.; Uvnäs-Moberg, K. Plasma oxytocin levels in female fibromyalgia syndrome patients. *Z. Rheumatol.,* **2000**, *59*(6), 373-379. http://dx.doi.org/10.1007/s003930070045 PMID: 11201002

[258] Ozsoy, S.; Esel, E.; Kula, M. Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. *Psychiatry Res.,* **2009**, *169*(3), 249-252. http://dx.doi.org/10.1016/j.psychres.2008.06.034 PMID: 19732960

[259] Cyranowski, J.M.; Hofkens, T.L.; Frank, E.; Seltman, H.; Cai, H.M.; Amico, J.A. Evidence of dysregulated peripheral oxytocin release among depressed women. *Psychosom. Med.,* **2008**, *70*(9), 967-975. http://dx.doi.org/10.1097/PSY.0b013e318188ade4 PMID: 19005082

[260] Skrundz, M.; Bolten, M.; Nast, I.; Hellhammer, D.H.; Meinlschmidt, G.; Meinlschmidt, G. Plasma oxytocin concentration during pregnancy is associated with development of postpartum depression. *Neuropsychopharmacology,* **2011**, *36*(9), 1886-1893. http://dx.doi.org/10.1038/npp.2011.74 PMID: 21562482

[261] Costa, B.; Pini, S.; Gabelloni, P.; Abelli, M.; Lari, L.; Cardini, A.; Muti, M.; Gesi, C.; Landi, S.; Galderisi, S.; Mucci, A.; Lucacchini, A.; Cassano, G.B.; Martini, C. Oxytocin receptor polymorphisms and adult attachment style in patients with depression. *Psychoneuroendocrinology,* **2009**, *34*(10), 1506-1514. http://dx.doi.org/10.1016/j.psyneuen.2009.05.006 PMID: 19515497

[262] Thompson, R.J.; Parker, K.J.; Hallmayer, J.F.; Waugh, C.E.; Gotlib, I.H. Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls. *Psychoneuroendocrinology,* **2011**, *36*(1), 144-147. http://dx.doi.org/10.1016/j.psyneuen.2010.07.003 PMID: 20708845

[263] Scantamburlo, G.; Ansseau, M.; Geenen, V.; Legros, J.J. Intranasal oxytocin as an adjunct to escitalopram in major depression. *J. Neuropsychiatry Clin. Neurosci.,* **2011**, *23*(2)E5 http://dx.doi.org/10.1176/jnp.23.2.jnpe5 PMID: 21677229