

The role of neuropeptides (oxytocin, vasopressin, neuropeptide S) in the development of cognitive impairment in Alzheimer's disease

Avliyakulyeva A.M.¹, Kindyakova E.K.¹, Kuzmina S.V.², Gorina Y.V.^{1,3}, Lopatina O.L.^{1,3}

¹ V.F. Voino-Yasentsky Krasnoyarsk State Medical University
1, Partizana Zheleznyaka Str., Krasnoyarsk, 660022, Russian Federation

² Kazan State Medical University
49, Butlerova Str., Kazan, 420012, Russian Federation

³ School of Fundamental Biology and Biotechnology, Siberian Federal University
79, Svobodny Av., Krasnoyarsk, 660041, Russian Federation

ABSTRACT

Every year, the number of people diagnosed with Alzheimer's disease is rapidly increasing. Despite numerous studies, it was not possible to select a therapy that would reliably slow down the course of the disease and result in its complete cure. In this case, any consideration of the issue related to the search for drugs to eliminate cognitive and psychoemotional disorders in Alzheimer's disease is a pressing problem that deserves special attention.

We collected articles from the PubMed database published over the past 10 years. The aim of this review was to analyze the latest experimental data and results regarding the relationship between Alzheimer's disease and the activity of neuropeptides, such as oxytocin, vasopressin, and neuropeptide S, and describing the effects that occur upon their administration. This will allow for a more complete understanding of the problem and update information on this issue. The ability of neuropeptides to restore impaired cognitive functions in an animal model of Alzheimer's disease is examined in more detail.

Detailed information on the relationship and positive effect of the studied neuropeptides on Alzheimer's disease allows to consider these neuropeptides as potential drugs for the treatment of this disease.

Keywords: Alzheimer's disease, neuropeptides, oxytocin, vasopressin, neuropeptide S

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Роль нейропептидов (окситоцин, вазопрессин, нейропептид S) в развитии когнитивных нарушений при болезни Альцгеймера

Авлиякулыева А.М.¹, Киндякова Е.К.¹, Кузьмина С.В.², Горина Я.В.^{1,3}, Лопатина О.Л.^{1,3}

¹ Красноярский государственный медицинский университет (КрасГМУ) им. проф. В.Ф. Войно-Ясенецкого Россия, 660022, г. Красноярск, ул. Партизана Железняка, 1

² Казанский государственный медицинский университет (Казанский ГМУ) Россия, 420012, г. Казань, ул. Бутлерова, 49

³ Институт фундаментальной биологии и биотехнологии (ИФБиБТ), Сибирский федеральный университет (СФУ) Россия, 660041, г. Красноярск, пр. Свободный, 79

РЕЗЮМЕ

С каждым годом количество людей с диагностированной болезнью Альцгеймера стремительно увеличивается. Несмотря на многочисленные исследования, подобрать терапию, которая бы надежно замедляла течение болезни и приводила бы к полному излечению, не удалось. В таком случае любое рассмотрение вопроса, касающегося поиска лекарственных веществ для коррекции когнитивных и психоэмоциональных нарушений при развитии болезни Альцгеймера, является актуальной проблемой, заслуживающей особого внимания.

Проводился сбор статей из базы данных PubMed, опубликованных за последние 10 лет. Целью настоящего обзора является анализ последних экспериментальных данных и результатов, касающихся взаимосвязи между болезнью Альцгеймера и активностью таких нейропептидов, как окситоцин, вазопрессин и нейропептид S, а также описывающих эффекты, которые возникают при их введении. Это позволит более полно понять проблематику и обеспечит актуализацию сведений по данному вопросу. Наиболее подробно рассматривается способность нейропептидов восстанавливать нарушенные когнитивные функции у лабораторных животных с моделью болезни Альцгеймера.

Детально изложенная информация о наличии взаимосвязи и положительном влиянии изучаемых нейропептидов на болезнь Альцгеймера позволяет рассматривать данные нейропептиды в качестве потенциальных лекарственных препаратов для лечения данного заболевания.

Ключевые слова: болезнь Альцгеймера, нейропептиды, окситоцин, вазопрессин, нейропептид S

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INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Current estimates indicate that 44 million people worldwide are diagnosed with dementia at present. It is predicted that by 2050, this number will increase by more than 3 times as the population ages. The prevalence of AD increases approximately twofold every 5 years after the age of 65 [1].

Although significant efforts have been made to study this disease, it is difficult to treat due to its complex multifactorial pathological physiology. To date, there is no therapy that has been proven to influence the pathology and course of the disease. Currently, approved drugs provide only temporary symptomatic relief, so the search and development of new drugs for the treatment of AD is underway [1, 2].

This disease is caused by hereditary mutations in the genes encoding the transmembrane amyloid precursor protein (APP), or the proteins presenilin 1 and presenilin 2 [3], associated with Aβ metabolism, which is the main biomarker of AD [4].

Early diagnosis and proper treatment of the disease can significantly improve the quality of life and functioning of patients, as well as reduce the severity of cognitive (memory loss, disorientation) and neurobehavioral disorders (depression, apathy, delusions, hallucinations, sleep disorders). Cholinesterase inhibitors (Donepezil, Galantamine, and Rivastigmine) and a glutamate NMDA receptor antagonist (Memantine) are drugs approved by clinical guidelines for the basic treatment of AD [5, 6]. Unfortunately, these drugs cannot provide a full recovery, but can only reduce the severity of cognitive and behavioral disorders. This is the reason for the active search for new medicinal substances that would not only slow down the development and severity of symptoms, but also provide targeted effects on key links in the pathogenesis of the disease.

HYPOTHALAMIC HORMONES: OXYTOCIN AND VASOPRESSIN

Vasopressin (AVP) and oxytocin (OXT) are two related neuropeptides that differ in only two amino acids. They are evolutionarily ancient and highly conserved neuropeptides in phylogeny that regulate a wide range of physiological functions [7].

Neuropeptides are produced mainly in the supraoptic nuclei (SON) and paraventricular nuclei (PVN) of the hypothalamus [8] and are transported to the posterior pituitary gland, where they are stored and ultimately released into the bloodstream, exerting an endocrine effect [9]. They are also synthesized in some other cells of the central nervous system and peripheral organs. Thus, AVP is additionally synthesized by cells of the suprachiasmatic nucleus, bed nucleus of the stria terminalis, and medial nucleus of the amygdala [10]. OXT is also produced by neurons of the peripheral nervous system: in osteoblasts of the bone marrow, liver, in nerve fibers of the gastrointestinal tract, subcutaneous adipose tissue [11], cardiomyocytes, adipose tissue, beta and alpha cells of the islets of Langerhans in the pancreas [12].

An interesting fact is that magnocellular neurons of the SON and PVN can release OXT and AVP from non-synaptic areas such as dendrites [13] via bulk

transmission. This type of transmission results in a much more diffuse signal, which can potentially affect a large number of neurons within the intercellular space, since the distance over which such a signal propagates significantly exceeds the size of the synaptic cleft. The release of OXT and AVP is caused by various osmotic, reproductive, and social stimuli. The excretion of OXT and AVP occurs during childbirth as well as aggressive and social interactions. OXT is also released during mating, lactation, and in response to subtler social stimuli, including vocalization, eye contact, and touch [14].

When released into the systemic circulation, neuropeptides have an endocrine effect. Thus, AVP regulates salt and water balance, and OXT stimulates uterine contraction and lactation [9]. In addition to endocrine effects, these neuropeptides play an important role in the organization of central processes. The OXT/AVP system is involved in the formation of social, working, spatial, and episodic memory, mediated by the CA2 and CA3 regions of the hippocampus, the amygdala, and the prefrontal cortex [15]. These neuropeptides model important processes in the hippocampus, such as neuronal excitability, synaptic plasticity, and social recognition memory. They influence not only memory formation, but also regulate social learning and behavior, including peer recognition, social attachment, and parental behavior (Fig. 1).

Currently, it is known that one receptor for OXT (OXTR) and three receptors for AVP (AVPR1A, AVPR1B, AVPR2) exist. These receptors, with the exception of AVPR2, are widely distributed in all regions of the hippocampus, especially in the CA2 region, which is involved in both encoding and retrieval of social memory and development of social aggression [16]. The OXT/AVP system is plastic, and its functions depend on the context, which includes life experience and the cause of stress or injury [17].

There is compelling evidence of the neurotropic effects of OXT. For example, administration of OXT stimulates neurogenesis in the hippocampus, whereas deletion of OXTR in mice causes irreversible pathological changes in the hippocampus. Selective removal of OXTR within adult-borne granule cells (abGCs) disrupts gene expression programs that influence dendritic growth and spine development. As a result, cells with underdeveloped synapses and impaired function are formed [18].

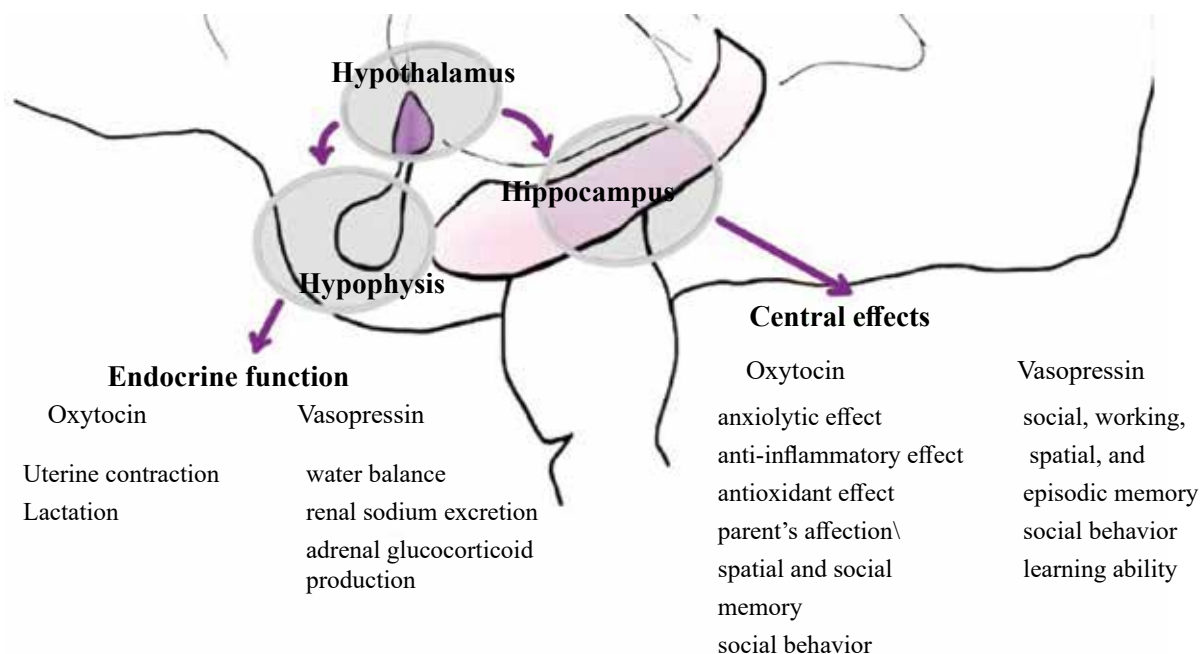


Fig. 1. Central and peripheral effects of oxytocin and vasopressin on the body

ALZHEIMER'S DISEASE AND SOCIAL COMMUNICATION DISORDERS

Characteristic signs of behavior during the development of AD and dementia are agitation and aggressive and impulsive behavior, whose

manifestation only intensifies as the disease progresses. These symptoms are associated with disturbances in emotional processing, especially inability to perceive and recognize the emotions of others [19]. All this leads to impaired social cognition and difficulties in social interaction (Fig. 2).

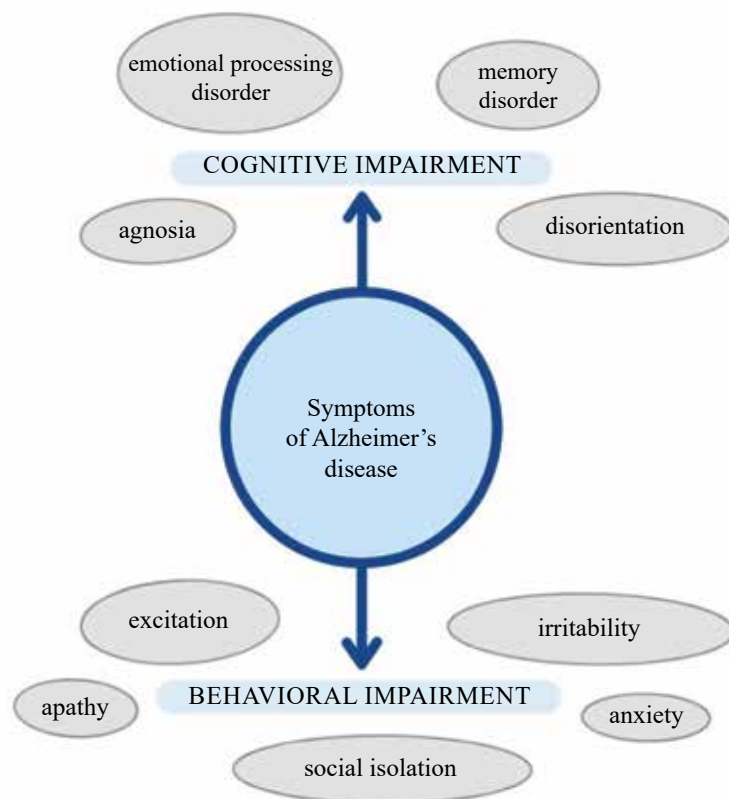


Fig. 2. Symptoms of Alzheimer's disease

Most studies were focused on assessing cognitive function, but the assessment of psychoemotional impairment may be a sensitive method for studying the clinical state in AD, which may lead to the introduction of new and effective treatment methods [20]. There are large-scale studies that support the effectiveness of psychosocial interventions to slow the progression of cognitive impairment in patients with AD. These psychosocial interventions include reminiscence therapy, art therapy, a walking program, and much more [21].

THE RELATIONSHIP BETWEEN ALZHEIMER'S DISEASE AND NEUROPEPTIDES

The functioning of the OXT / AVP system alters in neurodegenerative diseases. Based on this, it was suggested that these neuropeptides may play an important role in the development of social, emotional, and cognitive dysfunction in AD.

Oxytocin and Alzheimer's disease

OXT is considered to be a potential drug for the treatment of AD, since various studies have found that this neuropeptide has a wide range of effects that can lead to positive changes in the complex therapy of the disease. Social recognition memory allows a person to remember relatives and identify them as already familiar. This ability is important for normal social behavior and formation and stability of social interactions. One of the symptoms of AD is inability to recognize people patients know, which creates additional difficulties for patients and caregivers.

Newman's social behavior neural network (SBNN) hypothesis proposes interconnections between brain regions, such as the amygdala, bed nucleus of the stria terminalis, lateral septum, medial preoptic area, ventromedial hypothalamus, and anterior hypothalamus. The SBNN is believed to control various types of motivated social behavior, including defensive aggression, social recognition memory, parental behavior, and social communication. It is important to note that OXT / AVP and their receptors are found in all regions of the SBNN, which indicates their involvement in the regulation of social behavior [22].

OXT plays an important role in the regulation of social recognition memory during social interactions, whereas conditional deletion of OXTR in the CA2 / CA3a regions of the hippocampus impairs the formation of social recognition memory. In the experiment, Y. T. Lin et al. compared the performance of wild-type mice and OXTR knockout mice in a three-chamber

sociability test. A group of knockout mice had a defect in retaining long-term social recognition memory, since 7 days after training their memory deteriorated significantly. The data obtained suggest that OXTR signaling is particularly important for maintaining long-term social recognition memory [23].

The results of another study show the importance of OXTR for the identification of various social stimuli, not only in the CA2 / CA3 region, but also in the dentate gyrus. When a Cre-expressing virus was injected into the anterior dentate gyrus of 8-week-old male mice with a conditional knockout of OXTR, an impairment in the ability to discriminate social stimuli was observed. The animals did not show preference for a new individual and had discrimination coefficients significantly lower than those in the control group [24].

Long-term potentiation (LTP) underlies learning and memory formation. In neurodegeneration and aging, LTP decreases, which is manifested by a decline in human cognitive abilities. Due to the accumulation of A β in the brain, suppression of LTP in the hippocampus is observed in AD. J. Takahashi et al. studied synaptic plasticity in hippocampal slices of male mice 5–7 weeks old. OXT was found to reverse the LTP impairment caused by perfusion of A β 25–35 into the hippocampus. This effect was mediated by OXTR, since LTP restoration was impaired when an OXTR antagonist was administered. The authors also associated this effect with phosphorylation of ERK kinase and the influx of Ca²⁺ ions through Ca²⁺-permeable AMPA receptors, since the addition of their antagonists to the hippocampal slices impaired the ability of oxytocin to restore LTP [25].

A number of studies confirm the positive effect of OXT on spatial memory. Intracerebroventricular administration of native OXT into the ventricle and intranasal administration of an OXT derivative to mice (ddY line) contributed to the restoration of spatial memory in the Y-maze and the Morris water maze, impairments in which were caused by the administration of A β 25–35. This improvement was induced by OXT, since administration of the OXTR antagonist led to inhibition of improvements in spontaneous alternation and deterioration of spatial memory. The role of the neuropeptide may be associated with the restoration of spatial memory impairments specifically in neurodegenerative conditions [26].

Intracerebroventricular administration is impractical and somewhat traumatic, and neuropeptides administered in this way have a low ability to penetrate

the blood – brain barrier [26]. Due to these disadvantages, alternative intranasal administration appears to be more promising due to its non-invasive nature and ease of use.

A number of studies have proven that intranasal administration of OXT will facilitate the penetration of the peptide into the brain in the required amount. A study of the pharmacokinetics of the neuropeptide after intranasal administration showed that more than 95% of OXT was transported to the brain directly from the nasal cavity [27]. The peptide penetrates the brain by direct transport of the substance through the olfactory and trigeminal nerve fibers innervating the nasal cavity [28].

S.O. El-Ganainy et al. studied the effect of intranasal administration of OXT on rats (Sprague – Dawley line) with a model of AD. In the Morris water maze test, a decrease in the latent period was observed, which indicated that rats had a high ability of spatial learning after treatment with OXT. There was a decrease in A β 1–42 in the hippocampus in a group of rats that were treated with OXT in combination with galantamine. OXT treatment also suppressed the activation of caspase-3, which inhibited the process of apoptosis and prevented neuronal death and formation of neurofibrillary tangles. This was consistent with the results of a histopathological study, which noted orderly arrangement of hippocampal pyramidal cells and an improvement in their morphology [29].

Microglia are immune cells in the brain that play a key role in the occurrence of neuroinflammation [30]. Deposition of A β , tau protein, and neuronal damage leads to microglial activation, which contributes to the persistence of inflammation and the formation of reactive oxygen species [31]. Activated microglia stimulate neurons to overproduce A β , causing synaptic loss and the formation of extracellular plaques and neurofibrillary tangles. This leads to increased activation of microglia [32], and a positive feedback loop is formed that contributes to the development of AD.

Since activated microglia are considered one of the important components in the pathogenesis of AD, it is necessary to search for and study the ability of substances to inhibit their activation, which is what the authors of the following study did. IHC analysis of brain sections from old APP / PS1 mice (with mutations in the amyloid precursor protein and presenilin-1 genes) revealed increased Iba-1 (lupus anticoagulant) immunoreactivity in the CA1 region of the hippocampus, which indicated activated microglia. Intranasal administration of OXT to control groups caused a

decrease in Iba-1 immunoreactivity around amyloid plaques compared to the controls receiving normal saline. When a purified culture of microglia was exposed to A β , its activation was observed, accompanied by an increase in Iba-1 and CD68 immunoreactivity (cluster of differentiation 68). Treatment of the culture with OXT contributed to the attenuation of microglial activation induced by A β [33].

In AD, developing neuroinflammation is characterized by drastically increased production of proinflammatory cytokines (interleukin (IL)-1, IL-6, tumor necrosis factor alpha (TNF α)) and activation of enzymes that synthesize low-molecular inflammatory mediators [34]. It should be noted that there are data supported by experiments on the anti-inflammatory activity of OXT. Pretreatment of microglial cells suppressed the synthesis of proinflammatory cytokines provoked by the administration of lipopolysaccharide. The anti-inflammatory effects of OXT are associated with inhibition of eukaryotic initiation factor-2 α (eIF-2 α)-targeting kinases. It results in inhibition of the p/eIF2 α /ATF4 pathway, decreased expression of TNF α and IL-6, and inhibited activation of inflammasomes, which suppresses the synthesis of IL-1 β [35].

When the medial part of the hypothalamus is damaged, the level of OXT mRNA decreased, which led to increased activation of the nuclear factor- κ B (NF- κ B) pathway and increased expression of TNF α and IL-1 β mRNA, which may be the reason for a decrease in anti-inflammatory protection [36]. Pretreatment of primary microglia and BV-2 microglia cells (cells isolated from C57/BL6 mice) with OXT resulted in significant inhibition of lipopolysaccharide-induced microglial activity, as reflected by suppression of the expression and release of cyclooxygenase-2 (COX-2) and inducible synthase nitric oxide (iNOS). During neuroinflammation, proinflammatory cytokines accumulate in glia, which can lead to neuronal damage and progression of neurodegenerative diseases [37]. Due to this, an important element of AD therapy is inhibition of neuroinflammation, which can be achieved through the use of OXT as a drug.

The results of a recent study that revealed the effect of OXT on the generation and deposition of amyloid plaques are worth noting. Mice (APP/PS1 strain) treated with OXT showed a decrease in plaque area and decreased A β immunoreactivity in the hippocampus. The neuropeptide also affected the morphology of amyloid plaques. The main groups of mice that received OXT had plaques with a denser core than the control groups [33]. There is a hypothesis that dense-

core plaques have a restriction mechanism, possibly similar to tuberculosis granulomas. With its help, microglia protect the brain from degeneration associated with AD. Highly polymerized and compacted A β in the nuclei has a less damaging effect and limits the spread of A β oligomers and protofibrils throughout the brain [38].

Since one of the symptoms of AD is increased anxiety, the presence of an anxiolytic effect in OXT makes this neuropeptide even more interesting. The effect of OXT on anxiety levels was studied using the light / dark box test. When the neuropeptide was administered into the PVN of male Wistar rats, a decrease in anxiety was observed. Preliminary infusion of the transient receptor potential channel antagonist SKF96365 into PVN blocked the anxiolytic effect of OXT [39].

Vasopressin and Alzheimer's disease

AVP is known to regulate water balance and blood pressure. It is also a neurotransmitter involved in the modulation of social communication, spatial memory and influencing memory consolidation and retrieval. One of the characteristic symptoms of AD is impaired spatial memory and social recognition memory, which manifest in the form of disorientation and inability to recognize familiar faces. As the results of the study showed, intranasal use of AVP (4–8) for 4 weeks (the main metabolic fragment of AVP, differing in chemical structure, but having a similar effect) significantly improved working and long-term memory in mice with a model of AD (APP/PS1 line), which was proven in the Y-maze test. In addition, a decrease in the latency period was found in the Morris water maze test, which indicates an improvement in spatial memory [40].

The study by C.J. Finton et al. shows the importance of the duration of AVP therapy for a significant effect on spatial memory. The significance of the effect on spatial memory depends on the duration of AVP therapy. Chronic intranasal administration of the neuropeptide showed a positive effect on spatial memory, while a single administration of AVP before testing had no significant effect [41].

The effect of a V1aR antagonist was studied to confirm the relationship between the AVP level and spatial memory. Intraperitoneal administration of SR49059 to Wistar rats prior to the Morris water maze test revealed the effect of AVP on spatial memory and learning. The results of Western blotting and ELISA showed a significant decrease in the expression of

AVP and V1aR, which confirms the association between the level of the neuropeptide and spatial memory [42].

In addition to its ability to restore impaired spatial memory, AVP is also important for normal social recognition and formation of social memory. Studies show that blocking AVP receptors, as well as a decrease in the level of this neuropeptide, cause social memory impairment. Thus, mice with OXTR and AVPR1b knockout in hippocampal CA2 pyramidal neurons have impairments of social memory and impaired detection of social novelty [43]. When tested in AVP knockout rats (Brattleboro strain), impairments in recognition of new objects and conditional learning, as well as a decrease in the ability to social discrimination are observed [44].

The hippocampus is one of the key structures associated with learning, memory, and thinking, the activity of which depends on the rate of excitation of neurons in this part of the brain. The neuropeptide is able to modulate the electrophysiological changes caused by A β . AVP-induced changes in spontaneous discharges in the hippocampus in the CA1 region may help protect synaptic plasticity and cognitive functions, the impairment of which underlies many neurodegenerative diseases [45].

Social memories are formed partly as a result of information encoding by the hippocampus. The CA2 region of the hippocampus and in particular the AVPR1b expressed there are required for memory formation. In behavioral testing, mice (GENSAT QZ27 line) injected with adeno-associated virus (AAV) and wild-type mice were exposed to an unfamiliar female and re-exposed to the original or new female after a 2-hour retention interval. At the same time, optical stimulation of the nerve endings of PVN neurons innervating CA2 was present or absent in the tests. Optical stimulation during initial contact (memory acquisition) improved social recognition, i.e. the olfactory exploration of the female decreased upon repeated exposure. However, optical stimulation had no effect on the sociability of the mice. Stimulation during subsequent contact (memory recall) did not cause improvement. Administration of the AVPR1b antagonist to CA2 blocked the enhancement of social recognition. This suggests that the AVP^{PVN→CA2} pathway, which depends on AVPR1b signaling, promotes the acquisition of new memories, enhancing social memory. The authors of the study suggested that targeted therapy with AVPR1b agonists could become potential treatment for patients with dementia who have reduced social memory [46].

Neuropeptide S and Alzheimer's disease

Neuropeptide S (NPS) is an endogenous peptide in the central nervous system that selectively binds and activates NPS receptors. NPSR mRNA expression occurs throughout the central nervous system, with significant amounts expressed in the olfactory nuclei, thalamus, anterior and posterior hypothalamus, as well as the cortex, amygdala, and hippocampus. The NPS / NPSR system regulates many physiological and pathological functions, including arousal, wakefulness, learning and memory, anxiety, food intake and energy balance, drug addiction and pain. During experiments, it was found that in animals this neuropeptide promotes learning, improves memory, and also reduces anxiety [47].

Mice with AD (APP/PS1 line) showed a noticeable decrease in NPSR in the hippocampal region compared with wild-type mice. It can be assumed that the basis of AD symptoms is a lack of NPS effects, caused by a decrease in the amount of NPSR [48].

Increased anxiety is one of the symptoms of AD. NPS has a powerful anxiolytic effect, which makes it possible to consider it as a potential substance for the treatment of diseases accompanied by anxiety. Characteristic phenotypic features of NPS precursor knockout mouse models include learning and memory deficits, as well as increased anxiety [49]. NPS promotes anxiolysis in the amygdala and its mechanism of action depends on NPSR-mediated phospholipase C signaling. This ability of the neuropeptide is confirmed by the administration of a phospholipase C inhibitor (U73122), which prevents NPS-induced anxiolysis [50].

Scientists have found that the effects of NPS in the PVN are mediated by actions on local OXT neurons. NPS activates a subpopulation of OXT neurons in the PVN, which is confirmed by an increase in the intracellular concentration of Ca^{2+} ions in neurons of this subpopulation and an increase in the release of OXT by somatodendrites in the PVN. In turn, the activated OXT-PVN subpopulation mediates the anxiolytic effect of NPS, which is confirmed by the results of behavioral testing. Pre-administration of an OXTR antagonist blocks NPS-induced anxiolysis [51].

To study the effect of NPS on memory, this neuropeptide was administered once into the lateral ventricle of male Swiss Kunming mice 5 minutes after training. When tested on day 3 after training, the test group spent significantly more time with the

new non-social object than the control group. Thus, the introduction of NPS made it possible to prolong object recognition memory.

As is known, AD is accompanied by a progressive decline in memory; when A β 1–42 was administered to test mice, a significant impairment in object recognition memory was observed. The progression of this condition was eliminated by the administration of NPS [52]. Research by R.W. Han et al. showed that infusion of NPS into the basolateral amygdala of Kunming mice after training improved long-term non-social object recognition memory, which was reduced by intraperitoneal administration of propranolol [53].

NPS plays a key role in the regulation of memory and learning in rodents [54]. Inhibition of NPSR activation causes impairment of olfactory spatial memory. Endogenous NPS plays an important role in the regulation of olfactory spatial memory, possibly due to the activation of NPSR-bearing neurons in the olfactory cortex and subicular complex of the hippocampus, but the precise mechanisms involved in olfactory spatial memory impaired by NPSR antagonists have yet to be determined [55].

P. Zhao et al. proved the influence of NPS on the key pathogenetic links of AD. The effect of NPS was analyzed in both wild-type mice and mice (APP/PS1 line) with a genetic model of AD. Eight-month-old mice were continuously injected intravenously with NPS for 2 weeks, and then hippocampal ELISA was performed. According to the results of the analysis, a decrease in the intensity of formation and subsequent deposition of A β plaques was observed due to a decrease in γ -secretase activity and APP phosphorylation at Thr668 compared to the ELISA results of the control group of mice that were intravenously injected with normal saline. Moreover, when performing the Morris water maze test, a gradual decrease in the latency period was noted during the five days of training. This suggests that NPS can not only improve spatial memory in wild-type mice, but also effectively restore cognitive impairment and significantly increase the number of active neurons in the hippocampus in mice.

The neuropeptide normalized the expression of synapsin I and PSD95 in the hippocampus, suggesting that NPS probably restores memory deficits by reversing impairments in hippocampal synaptic plasticity [48]. Together, these experimental data make it possible to consider NPS as a potential candidate for the treatment of AD.

CONCLUSION

All studies discussed in this review article have shown a relationship between the action of neuropeptides and the pathogenesis of AD. The exact mechanism of the potential therapeutic effect of neuropeptides has yet to be revealed, but the trend in the scientific field and the number of modern and fairly large publications suggest that this may happen in the nearest future.

When studying such a complex issue, it is important to conduct not one, but a series of studies, to compare the effects of treatment with neuropeptides and drugs that are currently included in clinical guidelines for the treatment of AD. It is also necessary to conduct a battery of behavioral tests for a more thorough understanding of the condition of the test animals and to perform tests at different periods of time with the possibility of further comparison of previously obtained and newer results with each other to determine the delayed effects of treatment.

REFERENCES

- Lane C.A., Hardy J., Schott J.M. Alzheimer's disease. *Eur. J. Neurol.* 2018;25(1):59–70. DOI: 10.1111/ene.13439.
- Athar T., Al Balushi K., Khan S.A. Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. *Mol. Biol. Rep.* 2021;48(7):5629–5645. DOI: 10.1007/s11033-021-06512-9.
- Brejijeh Z., Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules.* 2020;25(24):5789. DOI: 10.3390/molecules25245789.
- Mantzavinos V., Alexiou A. Biomarkers for Alzheimer's disease diagnosis. *Curr. Alzheimer Res.* 2017;14(11):1149–1154. DOI: 10.2174/1567205014666170203125942.
- Grossberg G.T., Tong G., Burke A.D., Tariot P.N. Present algorithms and future treatments for Alzheimer's disease. *J. Alzheimers Dis.* 2019;67(4):1157–1171. DOI: 10.3233/JAD-180903.
- Briggs R., Kennelly S.P., O'Neill D. Drug treatments in Alzheimer's disease. *Clin. Med. (Lond.)*. 2016;16(3):247–253. DOI: 10.7861/clinmedicine.16-3-247.
- Bordt E.A., Smith C.J., Demarest T.G., Bilbo S.D., Kingsbury M.A. Mitochondria, oxytocin, and vasopressin: unfolding the inflammatory protein response. *Neurotoxicity Res.* 2019;36(2):239–256. DOI: 10.1007/s12640-018-9962-7.
- Szczepanska-Sadowska E., Wsol A., Cudnoch-Jedrzejewska A., Czarzasta K., Żera T. Multiple aspects of inappropriate action of renin-angiotensin, vasopressin, and oxytocin systems in neuropsychiatric and neurodegenerative diseases. *J. Clin. Med.* 2022;11(4):908. DOI: 10.3390/jcm11040908.
- Caldwell H.K. Oxytocin and vasopressin: powerful regulators of social behavior. *Neuroscientist.* 2017;23(5):517–528. DOI: 10.1177/1073858417708284.
- Dumais K.M., Veenema A.H. Vasopressin and oxytocin receptor systems in the brain: Sex differences and sex-specific regulation of social behavior. *Front. Neuroendocrinol.* 2016;40:1–23. DOI: 10.1016/j.yfrne.2015.04.003.
- McCormack S.E., Blevins J.E., Lawson E.A. Metabolic Effects of oxytocin. *Endocr. Rev.* 2020;41(2):121–145. DOI: 10.1210/endrev/bnz012.
- Kerem L., Lawson E.A. The effects of oxytocin on appetite regulation, food intake and metabolism in humans. *Int. J. Mol. Sci.* 2021;22(14):7737. DOI: 10.3390/ijms22147737.
- Ludwig M., Apps D., Menzies J., Patel J.C., Rice M.E. Dendritic release of neurotransmitters. *Compr. Physiol.* 2016;7(1):235–252. DOI: 10.1002/cphy.c160007.
- Johnson Z.V., Young L.J. Oxytocin and vasopressin neural networks: Implications for social behavioral diversity and translational neuroscience. *Neurosci. Biobehav. Rev.* 2017;76(Pt.A):87–98. DOI: 10.1016/j.neubiorev.2017.01.034.
- Abramova O., Zorkina Y., Ushakova V., Zubkov E., Morozova A., Chekhonin V. The role of oxytocin and vasopressin dysfunction in cognitive impairment and mental disorders. *Neuropeptides.* 2020;83:102079. DOI: 10.1016/j.npep.2020.102079.
- Cilz N.I., Cymerblit-Sabba A., Young W.S. Oxytocin and vasopressin in the rodent hippocampus. *Genes Brain Behav.* 2019;18(1):e12535. DOI: 10.1111/gbb.12535.
- Carter C.S., Kenkel W.M., MacLean E.L., Wilson S.R., Perkeybile A.M., Yee J.R. et al. Is oxytocin “nature's medicine”? *Pharmacol. Rev.* 2020;72(4):829–861. DOI: 10.1124/pr.120.019398.
- Pekarek B.T., Kochukov M., Lozzi B., Wu T., Hunt P.J., Tepe B. et al. Oxytocin signaling is necessary for synaptic maturation of adult-born neurons. *Genes Dev.* 2022;36(21-24):1100–1118. DOI: 10.1101/gad.349930.122.
- Bidzan L., Bidzan M., Pąchalska M. Aggressive and impulsive behavior in Alzheimer's disease and progression of dementia. *Med. Sci. Monit.* 2012;18(3):CR182–189. DOI: 10.12659/msm.882523.
- Cárdenas J., Blanca M.J., Carvajal F., Rubio S., Pedraza C. Emotional processing in healthy ageing, mild cognitive impairment, and Alzheimer's disease. *Int. J. Environ. Res. Public Health.* 2021;18(5):2770. DOI: 10.3390/ijerph18052770.
- Duan Y., Lu L., Chen J., Wu C., Liang J., Zheng Y. et al. Psychosocial interventions for Alzheimer's disease cognitive symptoms: a Bayesian network meta-analysis. *BMC Geriatr.* 2018;18(1):175. DOI: 10.1186/s12877-018-0864-6.
- Caldwell H.K., Albers H.E. Oxytocin, vasopressin, and the motivational forces that drive social behaviors. *Curr. Top Behav. Neurosci.* 2016;27:51–103. DOI: 10.1007/7854_2015_390.
- Lin Y.T., Hsieh T.Y., Tsai T.C., Chen C.C., Huang C.C., Hsu K.S. Conditional deletion of hippocampal CA2/CA3a oxytocin receptors impairs the persistence of long-term social recognition memory in mice. *J. Neurosci.* 2018;38(5):1218–1231. DOI: 10.1523/JNEUROSCI.1896-17.2017.
- Raam T., McAvoy K.M., Besnard A., Veenema A.H., Sahay A. Hippocampal oxytocin receptors are necessary for discrimination of social stimuli. *Nat. Commun.* 2017;8(1):2001. DOI: 10.1038/s41467-017-02173-0.
- Takahashi J., Yamada D., Ueta Y., Iwai T., Koga E., Tanabe M. et al. Oxytocin reverses Aβ-induced impairment of hippocampal synaptic plasticity in mice. *Biochem. Bio-*

- phys. Res. Commun.* 2020;528(1):174–178. DOI: 10.1016/j.bbrc.2020.04.046.
26. Takahashi J., Ueta Y., Yamada D., Sasaki-Hamada S., Iwai T., Akita T. et al. Intracerebroventricular administration of oxytocin and intranasal administration of the oxytocin derivative improve β -amyloid peptide (25–35)-induced memory impairment in mice. *Neuropsychopharmacol. Rep.* 2022;42(4):492–501. DOI: 10.1002/npr2.12292.
 27. Tanaka A., Furubayashi T., Arai M., Inoue D., Kimura S., Kiriya A. et al. Delivery of oxytocin to the brain for the treatment of autism spectrum disorder by nasal application. *Mol. Pharm.* 2018;15(3):1105–1111. DOI: 10.1021/acs.molpharmaceut.7b00991.
 28. Quintana D.S., Lischke A., Grace S., Scheele D., Ma Y., Becker B. Advances in the field of intranasal oxytocin research: lessons learned and future directions for clinical research. *Mol. Psychiatry.* 2021;26(1):80–91. DOI: 10.1038/s41380-020-00864-7.
 29. El-Ganainy S.O., Soliman O.A., Ghazy A.A., Allam M., Elbahnasi A.I., Mansour A.M. et al. Intranasal oxytocin attenuates cognitive impairment, β -amyloid burden and tau deposition in female rats with Alzheimer's disease: interplay of ERK1/2/GSK3 β /caspase-3. *Neurochem. Res.* 2022;47(8):2345–2356. DOI: 10.1007/s11064-022-03624-x.
 30. Lemke G., Huang Y. The dense-core plaques of Alzheimer's disease are granulomas. *J. Exp. Med.* 2022;219(8):e20212477. DOI: 10.1084/jem.20212477.
 31. Simpson D.S.A., Oliver P.L. ROS generation in microglia: understanding oxidative stress and inflammation in neurodegenerative disease. *Antioxidants (Basel).* 2020;9(8):743. DOI: 10.3390/antiox9080743.
 32. Edler M.K., Mhatre-Winters I., Richardson J.R. Microglia in Aging and Alzheimer's Disease: A Comparative Species Review. *Cells.* 2021;10(5):1138. DOI: 10.3390/cells10051138.
 33. Selles M.C., Fortuna J.T.S., de Faria Y.P.R., Siqueira L.D., Lima-Filho R., Longo B.M. et al. Oxytocin attenuates microglial activation and restores social and non-social memory in APP/PS1 Alzheimer model mice. *iScience.* 2023;26(4):106545. DOI: 10.1016/j.isci.2023.106545.
 34. Gorina Ya.V., Salmina A.B., Kuvacheva N.V., Komleva Yu.K., Morozova G.A., Demko I.V., Petrova M.M. Neuroinflammation and insulin resistance in Alzheimer's disease. *Sibirskmedobozr.* 2014;4:11–19 (in Russ.).
 35. Inoue T., Yamakage H., Tanaka M., Kusakabe T., Shimatsu A., Satoh-Asahara N. Oxytocin suppresses inflammatory responses induced by lipopolysaccharide through inhibition of the eIF-2-ATF4 pathway in mouse microglia. *Cells.* 2019;8(6):527. DOI: 10.3390/cells8060527.
 36. Roth C.L., D'Ambrosio G., Elfers C. Activation of nuclear factor kappa B pathway and reduction of hypothalamic oxytocin following hypothalamic lesions. *J. Syst. Integr. Neurosci.* 2016;2(1):79–84. DOI: 10.15761/JSIN.1000114.
 37. Yuan L., Liu S., Bai X., Gao Y., Liu G., Wang X. et al. Oxytocin inhibits lipopolysaccharide-induced inflammation in microglial cells and attenuates microglial activation in lipopolysaccharide-treated mice. *J. Neuroinflammation.* 2016;13(1):77. DOI: 10.1186/s12974-016-0541-7.
 38. Huang Y., Happonen K.E., Burrola P.G., O'Connor C., Hah N., Huang L. et al. Microglia use TAM receptors to detect and engulf amyloid β plaques. *Nat. Immunol.* 2021;22(5):586–594. DOI: 10.1038/s41590-021-00913-5.
 39. Van den Burg E.H., Stindl J., Grund T., Neumann I.D., Strauss O. Oxytocin stimulates extracellular Ca²⁺ influx through TRPV2 channels in hypothalamic neurons to exert its anxiolytic effects. *Neuropsychopharmacology.* 2015;40(13):2938–2947. DOI: 10.1038/npp.2015.147.
 40. Zhang X., Zhao F., Wang C., Zhang J., Bai Y., Zhou F. et al. AVP(4–8) Improves cognitive behaviors and hippocampal synaptic plasticity in the APP/PS1 mouse model of Alzheimer's disease. *Neurosci. Bull.* 2020;36(3):254–262. DOI: 10.1007/s12264-019-00434-0.
 41. Finton C.J., Ophir A.G. Developmental exposure to intranasal vasopressin impacts adult prairie vole spatial memory. *Psychoneuroendocrinology.* 2022;141:105750. DOI: 10.1016/j.psyneuen.2022.105750.
 42. Yang C., Zhang X., Gao J., Wang M., Yang Z. Arginine vasopressin ameliorates spatial learning impairments in chronic cerebral hypoperfusion via V1a receptor and autophagy signaling partially. *Transl. Psychiatry.* 2017;7(7):e1174. DOI: 10.1038/tp.2017.121.
 43. Cymerblit-Sabba A., Walsh C., Duan K.Z., Song J., Holmes O., Young W.S. Simultaneous knockouts of the oxytocin and vasopressin 1b receptors in hippocampal CA2 impair social memory. *BioRxiv.* 2023;2023. DOI: 10.1101/2023.01.30.526271.
 44. Varga J., Klausz B., Domokos Á., Kálmán S., Pákási M., Szűcs S. et al. Increase in Alzheimer's related markers precedes memory disturbances: studies in vasopressin-deficient Brattleboro rat. *Brain Res. Bull.* 2014;100:6–13. DOI: 10.1016/j.brainresbull.2013.10.010.
 45. Pan Y.F., Jia X.T., Wang X.H., Chen X.R., Li Q.S., Gao X.P. et al. Arginine vasopressin remolds the spontaneous discharges disturbed by amyloid β protein in hippocampal CA1 region of rats. *Regul. Pept.* 2013;183:7–12. DOI: 10.1016/j.regpep.2013.03.003.
 46. Smith A.S., Williams Avram S.K., Cymerblit-Sabba A., Song J., Young W.S. Targeted activation of the hippocampal CA2 area strongly enhances social memory. *Mol. Psychiatry.* 2016;21(8):1137–1144. DOI: 10.1038/mp.2015.189.
 47. Lukas M., Neumann I.D. Nasal application of neuropeptide S reduces anxiety and prolongs memory in rats: social versus non-social effects. *Neuropharmacology.* 2012;62(1):398–405. DOI: 10.1016/j.neuropharm.2011.08.016.
 48. Zhao P., Qian X., Nie Y., Sun E., Wang Z., Wu J. et al. Neuropeptide S ameliorates cognitive impairment of APP/PS1 transgenic mice by promoting synaptic plasticity and reducing A β deposition. *Front. Behav. Neurosci.* 2019;13:138. DOI: 10.3389/fnbeh.2019.00138.
 49. Liu X., Si W., Garau C., Jüngling K., Pape H.C., Schulz S., Reinscheid R.K. Neuropeptide S precursor knockout mice display memory and arousal deficits. *Eur. J. Neurosci.* 2017;46(1):1689–1700. DOI: 10.1111/ejn.13613.
 50. Grund T., Neumann I.D. Neuropeptide S induces acute anxiolysis by phospholipase C-dependent signaling within the medial amygdala. *Neuropsychopharmacology.* 2018;43(5):1156–1163. DOI: 10.1038/npp.2017.169.

51. Grund T., Goyon S., Li Y., Eliava M., Liu H., Charlet A. et al. Neuropeptide S activates paraventricular oxytocin neurons to induce anxiolysis. *J. Neurosci.* 2017;37(50):12214–12225. DOI: 10.1523/JNEUROSCI.2161-17.2017.
52. Han R.W., Zhang R.S., Xu H.J., Chang M., Peng Y.L., Wang R. Neuropeptide S enhances memory and mitigates memory impairment induced by MK801, scopolamine or A β ₁₋₄₂ in mice novel object and object location recognition tasks. *Neuropharmacology.* 2013;70:261–267 .DOI: 10.1016/j.neuropharm.2013.02.002.
53. Han R.W., Xu H.J., Zhang R.S., Wang P., Chang M., Peng Y.L. et al. Neuropeptide S interacts with the basolateral amygdala noradrenergic system in facilitating object recognition memory consolidation. *Neurobiol. Learn Mem.* 2014;107:32–36. DOI: 10.1016/j.nlm.2013.10.010.
54. Li C., Wu X.J., Li W. Neuropeptide S promotes maintenance of newly formed dendritic spines and performance improvement after motor learning in mice. *Peptides.* 2022;156:170860. DOI: 10.1016/j.peptides.2022.170860.
55. Wang C., Xin L., Cai C.C., Cong C.Y., Xie J.F., Kong X.P. et al. Neuropeptide S displays as a key neuromodulator in olfactory spatial memory. *Chem. Senses.* 2020;45(3):195–202. DOI: 10.1093/chemse/bjaa003.

Authors' contribution

Avliyakulyeva A.M., Kindyakova E.K. – search and analysis of articles, manuscript design, creation of figures. Kuzmina S.V. – discussion of the concept of the article, final editing of the manuscript for publication. Gorina Ya.V., Lopatina O.L. – concept development, article search, manuscript editing.

Authors' information

Avliyakulyeva Aylar M. – Teaching Assistant, Department of Biological Chemistry with a Course in Medical, Pharmaceutical and Toxicological Chemistry, Junior Researcher, Laboratory of Social Neuroscience, V.F. Voyno-Yasenetsky KrasSMU, Krasnoyarsk, ailara@bk.ru, <https://orcid.org/0009-0009-8457-4581>

Kindyakova Ekaterina K. – Teaching Assistant, Department of Biological Chemistry with a Course in Medical, Pharmaceutical and Toxicological Chemistry, Junior Researcher, Laboratory of Social Neuroscience, V.F. Voyno-Yasenetsky KrasSMU, Krasnoyarsk, kindyakova13@mail.ru, <https://orcid.org/0009-0008-3803-1490>

Kuzmina Svetlana V. – Dr. Sci. (Med.), Associate Professor, Professor, Department of Psychiatry and Medical Psychology, Kazan State Medical University, Kazan, skouzmina21@list.ru, <https://orcid.org/0000-0002-7330-1213>

Gorina Yana V. – Dr. Sci. (Biology), Associate Professor, Department of Biological Chemistry with a Course in Medical, Pharmaceutical and Toxicological Chemistry, Senior Researcher, Laboratory of Social Neuroscience, V.F. Voyno-Yasenetsky KrasSMU; Associate Professor, Department of Biophysics, Institute of Fundamental Biology and Biotechnology, Siberian Federal University, Krasnoyarsk, yana_20@bk.ru, <https://orcid.org/0000-0002-3341-1557>

Lopatina Olga L. – Dr. Sci. (Biology), Associate Professor, Professor, Department of Biological Chemistry with a Course in Medical, Pharmaceutical and Toxicological Chemistry, Head of the Laboratory of Social Neuroscience, V.F. Voyno-Yasenetsky KrasSMU; Professor of the Department of Biophysics, Institute of Fundamental Biology and Biotechnology, Siberian Federal University, Krasnoyarsk, ol.lopatina@gmail.com, <https://orcid.org/0000-0002-7884-2721>

(✉) Avliyakulyeva Aylar M., ailara@bk.ru

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