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INVOLVEMENT OF NORADRENALINE, SEROTONIN AND BRAIN NEUROTROPHIC FACTOR IN THE ANALGETIC EFFECTS OF VASOPRESSIN IN THE THERMAL TAIL IMMERSION TEST IN RATS

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Abstract. The study of the role of the neuroendocrine system in the modulation of pain remains relevant. The analgesic properties of arginine vasopressin (AVP) are known, but the mechanisms underlying these effects are poorly understood. The aim of the study was to evaluate the effect of vasopressin receptor agonist type 2, 1-deamino-8-D-arginine-vasopressin, DDAVP, on pain sensitivity and the content of norepinephrine (NE), serotonin (5-HT), dopamine (DA) and brain neurotrophic factor (BDNF) in the parietal cortex and spinal cord in the test of thermal immersion of the tail in rats. The study was conducted on male Wistar rats. The animals were divided into 4 groups: group 1 — intact rats; group 2 — received saline solution; Group 3 — received DDAVP in a single dose of 2 ng and a cumulative dose of 10 ng; group 4 — received DDAVP in a single dose of 2 μg and a cumulative dose of 10 μg. DDAVP was administered intranasally once a day for 5 days. The saline solution was administered according to the peptide application scheme. The content of corticosterone in blood serum was determined by enzyme immunoassay. The content of NE, 5-HT, DA and their metabolites in the brain was assessed using high-performance liquid chromatography. BDNF levels were assessed using enzyme immunoassay. DDAVP in different doses reduced pain sensitivity in rats. When DDAVP was administered in small doses, the content of NE decreased in the parietal cortex; NE levels increased and 5-HT content decreased in the spinal cord. After administration of the peptide in large doses, the content of NE decreased in the parietal cortex, and the levels of 5-HT decreased in the spinal cord. DDAVP in different doses increased the content of BDNF in the parietal cortex and spinal cord. Thus, it was found that DDAVP-induced analgesia is associated with the modulatory effect of the peptide on the exchange of NE, 5-HT and BDNF at the supraspinal and spinal levels.

Keywords: vasopressin, pain, corticosterone, norepinephrine, serotonin, dopamine, brain neurotrophic factor

ВОВЛЕЧЕНИЕ НОРАДРЕНАЛИНА, СЕРОТОНИНА И НЕЙРОТРОФИЧЕСКОГО ФАКТОРА МОЗГА В АНАЛГЕТИЧЕСКИЕ ЭФФЕКТЫ ВАЗОПРЕССИНА В ТЕСТЕ ТЕПЛОВОЙ ИММЕРСИИ ХВОСТА У КРЫС

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Резюме. Сохраняет свою актуальность изучение роли нейроэндокринной системы в модуляции боли. Известны аналгетические свойства аргинин-вазопрессина (АВП), но механизмы, лежащие в основе этих эффектов, изучены мало. Целью исследования была оценка влияния агониста рецепторов вазопрессина 2-го типа, 1-дезамино-8-D-аргинин-вазопрессина (ДДАВП) на болевую чувствительность и содержание норадреналина (NE), серотонина (5-HT), дофамина (DA), нейротрофического фактора мозга (BDNF) в теменной коре и спинном мозге в тесте тепловой иммерсии хвоста у крыс. Исследование проведено на самцах крыс линии Вистар. Животных разделили на 4 группы: 1-я группа — интактные крысы; 2-я — получившие физиологический раствор; 3-я — получившие ДДАВП в однократной дозе 2 нг и кумулятивной дозе 10 нг; 4-я — получившие ДДАВП в однократной дозе 2 мкг и кумулятивной дозе 10 мкг. ДДАВП вводили интраназально 1 раз в день в течение 5 дней. Физиологический раствор вводили по схеме применения пептида. Содержание кортикостерона в сыворотке крови определяли с помощью иммуноферментного анализа. Оценивали содержание NE, 5-HT, DA и их метаболитов в мозге с использованием высокоэффективной жидкостной хроматографии; уровни BDNF — с применением иммуноферментного анализа. ДДАВП в разных дозах снижал болевую чувствительность у крыс. При введении ДДАВП в малых дозах в теменной коре снизилось содержание NE; в спинном мозге повысились уровни NE, снизилось содержание 5-HT. После введения пептида в больших дозах в теменной коре уменьшилось содержание NE, в спинном мозге — уровни 5-HT. ДДАВП в разных дозах увеличивал содержание BDNF в теменной коре и спинном мозге. Таким образом, было установлено, что вызванная ДДАВП аналгезия связана с модуляторным влиянием пептида на обмен NE, 5-HT и BDNF на супраспинальном и спинальном уровнях.

Ключевые слова: вазопрессин, боль, кортикостерон, норадреналин, серотонин, дофамин, нейротрофический фактор мозга

INTRODUCTION

Exploring mechanisms that cause pain and searching for new ways of its reduction remains actual. Recently, there has been considerable interest in analogs of endogenous neuropeptides, especially through their intranasal administration in clinical practice. One of such substances is arginine vasopressin (AVP), which exhibits peripheral and central properties [3, 4, 9]. AVP realizes its effects by activation of three types of receptors: V1aR, V1bR and V2R [9]. The involvement of V1aR in pain modulation has been established [4, 20]. The role of V2R in this process is poorly understood. The neurochemical mechanisms of the analgesic effects of AVPs are practically unknown.

It was previously shown that AVP and the V2R agonist, 1-desamino-8-D-arginine-vasopressin (DDAVP), caused analgesia in rats in models of acute and chronic pain, under different types of exposure (thermal, mechanical, chemical), and during central and peripheral administration of the peptide [4]. It is known that AVP is involved in modulating stress-responsiveness, and stress can induce analgesia [6, 17]. Clinical trials have shown that DDAVP reduced the severity of tension headaches, renal colic, and pain caused by orthopedic interventions and degenerative-dystrophic spine diseases when administered intranasally [1, 11, 24, 25].

The involvement of noradrenergic, serotoninergic and dopaminergic systems, brain-derived neurotrophic factor (BDNF) in pain modulation is well known [4, 13, 16]. According to the literature, administration of AVP and DDAVP caused changes in the levels of norepinephrine (NE), serotonin (5-NT), dopamine (DA), and BDNF in brain and blood in rats [2, 4, 30]. There are no data on the effect of DDAVP on pain sensitivity, BDNF content and monoamine neurotransmitters in the model of acute thermal pain in rats.

AIM

The aim of the research was to evaluate the effect of 1-desamino-8-D-arginine-vasopressin when administered intranasally. Pain sensitivity and brain content of norepi-

nephrine, serotonin, dopamine and their metabolites, brain neurotrophic factor were examined using the thermal tail immersion test in rats.

MATERIALS AND METHODS

30 sexually mature male Wistar rats were analyzed (Rappolovo nursery, initial body weight 220±25 g), all rats were kept under standard vivarium conditions. All animals were divided into 4 groups by the method of block randomization: Group 1 included 8 intact rats (control group, CG); Group 2 — 7 animals that received saline solution; Group 3 — 7 rats that received DDAVP in a single dose of 2 ng and cumulative dose of 10 ng; Group 4 — 8 animals that received DDAVP in a single dose of 2 μg and cumulative dose of 10 μg. Rats were injected with synthetic analog of AVP, water solution of DDAVP, Ferring s.p.a., Italy, intranasally once a day for 5 days. Saline solution was administered according to the scheme of DDAVP administration.

Thermal irritation of tail skin was performed by immersing it in a container with water heated to a temperature of 52.0±0.1 °C [5]. To determine the nociceptive response threshold (NRT), tail retraction time in seconds was recorded. Mean NRP values were determined in each animal using 6-fold measurements. The percentage of analgesia (% A) was calculated using the formula:

$$A = (P – D) / (15 – D) – 100\%,$$

where A is the percentage of analgesia or the percentage of maximum possible effect; P is the latent period of reaction in seconds after administration of DDAVP or saline solution; D is the latent period before drug administration; 15 s is the maximum time of heat exposure in seconds [20].

Following the last latency measurement, all animals were euthanized by decapitation, mixed arteriovenous blood was obtained, and the brain and spinal cord with L_5–S_2 spinal roots were extracted. After blood was collected, a tube was placed in a thermostat (37°C) and incubated for 30 min until clot formation, then the clot was gently separated from the tube walls, the sample was centrifuged for 10 min at 200 g and the supernatant (serum) was collected. Blood corticosterone content was estimated in the serum collected after euthanasia using a commercial reagent kit by Enzo № ADI-900-097 ELISA kit. All manipulations were performed in exact accordance with the instructions.

In order to determine the content of neurotransmitters and their metabolites, brain tissue samples were homogenized in 0.1 H perchloric acid, centrifuged for 30 min at 10,000 g and 4 °C, and the supernatant was collected. The levels of NE, 5-HT, DA and their metabolites (3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5HIAA)) were determined by using high-performance liquid chromatography according to the technique [31].

To determine BDNF content, brain tissue samples were homogenized with a hand homogenizer in lysis buffer (20 mM Tris, 150 mM NaCl, 0.1% Triton X-100, 5 mM EDTA, 1 mM FMSF, pH 7.6). Then the samples were centrifuged for 20 min at 4 °C, 5000 g and the supernatant was collected. The samples were stored at –70 °C. The concentration of BDNF in tissue homogenates was determined by enzyme-linked immunosorbent assay using a commercial reagent kit Rat BDNF ELISA Kit (ab213899); the procedure was performed according to the manufacturer's instructions.

Statistical analysis was performed using STATISTICA 8.0 program (StatSoft, USA). Normality of distribution was checked by the Shapiro-Wilk test. All data were expressed as mean values ± standard deviation. Statistical differences were tested using Student's criterion for independent samples or analysis of variance (for dependent or independent samples) followed by Tukey's post-hoc test. $p < 0.05$ was regarded as statistically significant.

RESULTS

There were no differences in pain sensitivity in the CG and the rest of the groups before administration of saline and

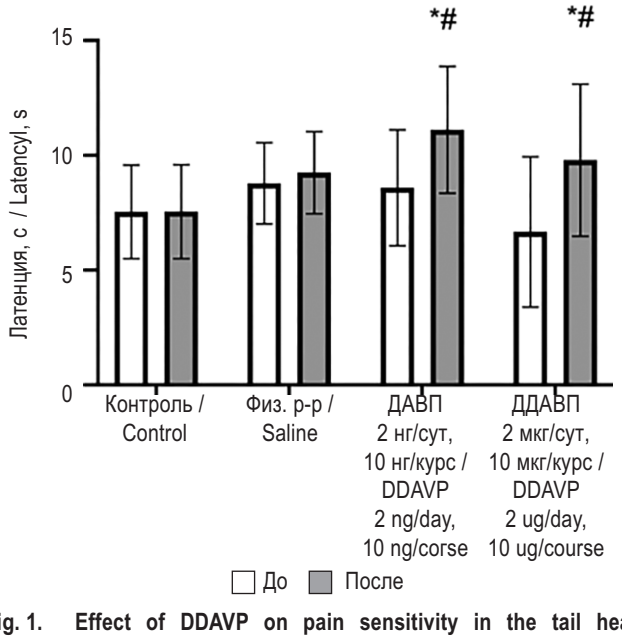

Fig. 1. Effect of DDAVP on pain sensitivity in the tail heat immersion test in rats (M±SEM, s). * — difference from control group at p <0.05; # — difference before and after administration of DDAVP at p <0.05

Рис. 1. Влияние ДДАВП на болевую чувствительность в тесте тепловой иммерсии хвоста у крыс (M±SEM, с). * — отличие от КГ при p <0,05; # — отличие до и после введения ДДАВП при p <0,05

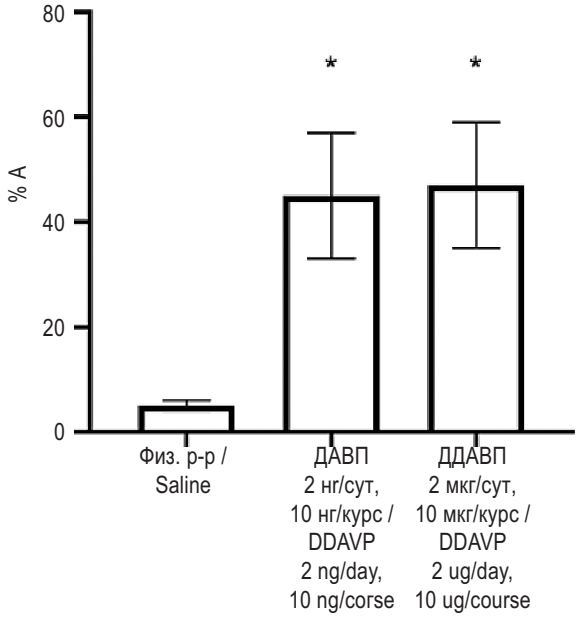

Fig. 2. Percentage of analgesia upon administration of DDAVP in the tail heat immersion test in rats. * — difference from the introduction of saline solution at p <0.05

Рис. 2. Процент аналгезии при введении ДДАВП в тесте тепловой иммерсии хвоста у крыс. * — отличие от введения физиологического раствора при p <0,05

Table 1

Serum corticosterone content in rats after administration of DDAVP (M±SEM, ng/ml) in the tail heat immersion test in rats

Таблица 1

Содержание кортикостерона в сыворотке у крыс после введения ДДАВП (M±SEM, нг/мл) в тесте тепловой иммерсии хвоста у крыс

Группы животных / Groups of animals	Содержание кортикостерона, нг/мл / Corticosterone content, ng/ml
Контрольная группа / Control group (n=8)	256±23
Физиологический раствор / Saline (n = 7)	269±23
ДДАВП (2 нг/сут, 10 нг/курс; n=7)/ DDAVP (2 ng/day, 10 ng/course; n=7)	325±40
ДДАВП (2 мкг/сут, 10 мкг/курс; n=8) / DDAVP (2 μg/day, 10 μg/course; n=8)	355±34

Table 2

Effect of DDAVP on the content of BDNF, neurotransmitters and their metabolites in the parietal cortex of rats

Таблица 2

Влияние ДДАВП на содержание BDNF, нейромедиаторов и их метаболитов в теменной коре у крыс

Показатель / Indication	Контроль / Control (n=5)	Физиологический раствор / Saline (n=7)	ДДАВП / DDAVP	
			2 нг/сут, 10 нг/курс / 2 ng/day, 10 ng/course (n=7)	2 мкг/сут, 10 мкг/курс / 2 μg/day, 10 μg/course (n=7)
BDNF, пг/мг / BDNF, pg/mg	20,6±1,62	25,60±1,69	39,80±6,58*	29,63±4,28*
NE, нг/мг белка / NE, ng/mg protein	2,42±0,64	1,80±1,18	0,32±0,20*	0,26±0,14*
DA, нг/мг белка / DA, ng/mg protein	0,29±0,20	0,30±0,17	0,74±0,23	0,46±0,21
DOPAC, нг/мг белка / DOPAC, ng/mg protein	0,33±0,17	0,30±0,18	0,32±0,13	0,47±0,14
HVA, нг/мг белка / HVA, ng/mg protein	0,26±0,16	0,16±0,09	0,23±0,13	0,26±0,10
5-HT, нг/мг белка / HVA, ng/mg protein	0,27±0,18	1,78±1,10	1,43±0,54	1,36±1,12
5-HIAA, нг/мг белка / 5-HIAA, ng/mg protein	2,98±1,26	3,91±1,52	1,78±0,51	3,19±0,81

Note: * — differences compared to control group at p <0.05
Примечание: * — отличия по сравнению с контрольной группой при p <0,05.

Table 3

Effect of DDAVP on the content of BDNF, neurotransmitters and their metabolites in the spinal cord of rats (M±SEM, units)

Таблица 3

Влияние ДДАВП на содержание BDNF, нейромедиаторов и их метаболитов в спинном мозге у крыс (M±SEM, единицы)

Показатель / Indication	Контроль / Control (n=5)	Физиологический раствор / Saline (n=7)	ДДАВП / DDAVP	
			2 нг/сут, 10 мкг/курс / 2 ng/day, 10 μg/course (n=7)	2 мкг/сут, 10 мкг/курс / 2 μg/day, 10 μg/course (n=7)
BDNF, пг/мг / BDNF, pg/mg	17,7±1,6	25,8±1,36	29,0±1,87*	40,6±3,3*#&
NE, нг/мг белка / NE, ng/mg protein	0,68±0,07	0,9±0,56	1,60±0,28*	0,43±0,12
DA, нг/мг белка / DA, ng/mg protein	0,46±0,1	0,67±0,19	0,64±0,13	0,57±0,09
DOPAC, нг/мг белка / DOPAC, ng/mg protein	0,32±0,10	0,56±0,05	0,50±0,11	0,43±0,16
HVA, нг/мг белка / HVA, ng/mg protein	0,10±0,07	0,05±0,05	0,13±0,05	0,09±0,04
5-HT, нг/мг белка / HVA, ng/mg protein	5,07±1,53	4,35±0,59	2,86±0,56#	1,97±0,46*
5-HIAA, нг/мг белка / 5-HIAA, ng/mg protein	1,57±0,64	1,25±0,34	0,66±0,12	1,19±0,23

Note: * — differences compared to the control group at p <0.05; # — difference compared to the introduction of saline at p <0.05; & — differences when administering small and large doses of the peptide.
Примечание: * — отличия по сравнению с контрольной группой при p <0,05; # — отличие по сравнению с введением физиологического раствора при p <0,05; & — отличия при введении малых и больших доз пептида.

DDAVP at different doses (Fig. 1). DDAVP at low and high doses increased PNR in rats (Tukey's criterion, p=0.00001, p=0.00001, respectively) (Fig. 1). PNRs were higher after administration of low- and high-dose DDAVP compared with CG (F(3,26)=12.95, p=0.00002; Tukey's criterion, p=0.01, p=0.04, respectively).

When DDAVP was administered, % A amounted to 45.3±12.0% at low doses and 45.5±11.4% at high doses, which was higher compared to saline administration (F(2,19)=4.6, p=0.023, Tukey's criterion, p=0.04, p=0.03, respectively) (Figure 2), it did not affect serum corticosterone content in different doses (Table 1).

After low-dose DDAVP administration, NE levels decreased in parietal cortex compared to CG (F(3,21)=3.78; p=0.02; Tukey's criterion, p=0.04); BDNF levels increased (F(3,21)=3.78; p=0.02; Tukey's criterion, p=0.04) (Table 2). Low-dose DDAVP in the spinal cord decreased 5-NT levels (F(3,21)=3.58; p=0.03); increased BDNF levels (F(3,16)=28.47, p=0.0001; Tukey's criterion, p=0.01) (Table 3).

After high-dose DDAVP administration, NE levels decreased in parietal cortex compared to CG (F(3,21)=3.78; p=0.02; Tukey's criterion, p=0.04); BDNF levels increased (F(3,16)=3.89; p=0.029; Tukey's criterion, p=0.04) (Table 2). High-dose DDAVP in the spinal cord decreased 5-NT levels (F(3,21)=3.45; p=0.03); increased BDNF levels compared to CG, saline and low-dose peptide administration compared to CG (F(3,19)=14.78, p=0.00003; Tukey's criterion, p=0.0001; p=0.0002; p=0.0004, respectively) (Table 3).

Thus, DDAVP reduced pain sensitivity in the thermal tail immersion test in rats, when administered intranasally at different doses. Analgesia was associated with similar changes in NE, 5-NT and BDNF content in the brain regardless of administered doses of DDAVP. Low-dose dDAVP decreased NE content in parietal cortex, increased NE levels, and decreased 5-NT content in the spinal cord. DDAVP at high doses decreased NE content in parietal cortex and decreased 5-NT levels in the spinal cord. DDAVP at different doses increased BDNF content in cortex and spinal cord.

DISCUSSION

This work revealed an analgesic effect of V2R agonist, DDAVP, when administered intranasally in the tail heat immersion test in rats for the first time. The obtained results are comparable to the data acquired with intraventricular administration of AVP [14].

To date, the exact mechanisms of peptide penetration into the brain during intranasal administration remain poorly understood. At the same time, it is believed that under these conditions the central and peripheral effects of AVPs are due to both its direct penetration into the central nervous system and its non-direct penetration through the systemic

bloodstream [28]. The research showed that different doses of DDAVP did not affect the content of corticosterone in blood, hence, did not cause stress-induced analgesia.

It is known that AVP induces analgesia by activating mainly its own receptors. According to the literature, AVP-induced analgesia at the supraspinal level is caused by activation of V1aR and V2R in the brain nuclei [26, 27, 29]; whereas the spinal cord and spinal ganglia are affected by V1aR [19].

Впервые показано участие норадренергической и серотDDAVP was proved to exercise analgesic effects on noradrenergic and serotoninergic systems, as well as BDNF for the first time. It is known that the tail thermal immersion test is accomplished at the spinal level through supraspinal influences [15]. Analgesia induced by administration of DDAVP at different doses was induced by changes in NE content at supraspinal and spinal levels, 5-HT — at the spinal level. It is known that conductors containing NE and 5-HT at the supraspinal level constitute the descending antinociceptive system [7, 10, 12, 18]. At the spinal level, NE-induced analgesia is caused by activation of α2-adrenoreceptors; 5-HT-related analgesia is caused by 5-NT1A and 5-HT3 receptors [7, 17, 18].

BDNF content in parietal cortex and spinal cord increased after peptide administration at different doses. According to the literature, BDNF-induced analgesia at the supraspinal level is associated with increased activity of the serotoninergic system and release of endogenous opioid peptides [21–23]. At the spinal level, it is associated with increased GABA- and glycinergic transmission in neurons of the posterior horns of the spinal cord [8]. There is reason to believe that the identified analgesic effects of DDAVP associated with NE, 5-HT and BDNF could be caused by different molecular mechanisms at different levels of the nervous system.

CONCLUSION

1. The V2R agonist, 1-desamino-8-D-arginine-vasopressin, DDAVP, reduced pain sensitivity in rats in the tail thermal immersion test when administered intranasally at different doses.

2. Analgesia induced by DDAVP at different doses was associated with the involvement of noradrenergic system and BDNF at supraspinal and spinal levels, as well as with the involvement of serotoninergic system at the spinal cord level.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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All procedures complied with ethical standards approved by legal acts of the Russian Federation, international regulations (Directive 2010/63/EU of the European Parliament and the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes), and the recommendations of the Bioethics Committee of FSBSI "IEM" (protocol No. 6/20 of October 21, 2020).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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Все процедуры соответствовали этическим стандартам, утвержденным правовыми актами РФ, международными правилами (Директивой 2010/63/EU Европейского парламента и Совета Европейского союза от 22 сентября 2010 года по охране животных, используемых в научных целях), рекомендациям комитета по биоэтике ФГБНУ «ИЭМ» (протокол № 6/20 от 21.10.2020 г).

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