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Studies of the engagement for serotonergic system in regulation of aggressive behavior in two behavioral models on rats

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The article concerns study of the role for serotonin-modulating anticonsolidation protein (SMAP), being in linear relation with serotonin level (Mekhtiev, 2000), in regulation of aggressive behavior. The studies were carried out on aggression (induced by electroshock) and dominant (food deprivation) behavioral models, on the 5-month-old Wistar male rats. The studies were conducted in 5 series. In the 1st series of studies, undertaken on the aggression model with application of solid-phase ELISA-test, significant downregulation of SMAP ($p<0.001$) was revealed in the amygdala of the aggressive animals. In the 2nd series of studies, conducted on the aggression model, single intracerebral administration of SMAP brought to significant increase ($p<0.001$) of aggression in the animals of the experimental group, while administration of heat-inactivated SMAP to the control animals did not have any effect. In the 3rd series of studies, carried out on the dominant model, sharp downregulation of SMAP ($p<0.001$) in the amygdala of the dominant animals, though sharp upregulation of SMAP ($p<0.001$) in their platelets (corresponds to its level in the brain cortex) relatively to the intact animals were observed. In the 4th series of studies, undertaken on the dominant model, a single intracerebral administration of SMAP to the submissive animals brought to their transformation into the dominant animals ($p<0.001$), maintaining for 7-day timeframe, while inactive SMAP did not have any effect. In the 5th series of studies, conducted on the dominant model, a single intracerebral administration of rabbit polyclonal anti-SMAP antibodies to the dominant animals transformed them into the submissive animals for 1 day ($p<0.001$), while non-immune γ-globulins did not reveal any influence. On a whole, the obtained data indicate to positive regulation of aggressive behavior in the rats by SMAP and its downregulation in the amygdala of the aggressive animals in both behavioral models is, apparently, attributed to high rate of its utilization.

Keywords: *aggressive behavior, dominant behavior, Wistar male rats, serotonin-modulating anticonsolidation protein (SMAP), polyclonal anti-SMAP antibodies, indirect ELISA-test.*

INTRODUCTION

Aggressive behavior belongs to inborn behaviors. Aggressive behavior is a complex form of social behavior which advents in a context of protection or capture of resources (Nelson & Trainor, 2007). Animals demonstrate aggression to protect themselves or their progeny from the predators, to struggle for female and food and to maintain a certain hierarchic position inside the community (Popoda, 2008). Usually such behavior is characterized as undisguised behavior having goal of bringing physical damage to the other individuum (Soma et al., 2008). Some researchers define aggressive behavior as a type of agonistic behavior directed to establishment of the hierarchic dominance, getting an access to any goal or a right to any territory (Haind, 1975).

Different researchers for a long time with application of different behavioral models showed

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that aggressive behavior is triggered by neurotransmitters within the certain brain structures and the most part of such regulation is referred to neurotransmitter serotonin. The bodies of serotonergic neurons are located within the nucleus raphe in the brainstem and their axons reach each brain structure (Hornung, 2012). The most body of publications, related to the aggression studies on animal models, show that there is an inverse correlation between serotonin level in the brain structures and aggression (Carrillo et al., 2009; De Boer et al., 2009). It has been proved that upregulation of serotonergic system on account of precursors of serotonin, serotonin specific reuptake inhibitors or agonists of of receptor 5-HT_{1A} inhibit aggressive behavior (Nelson & Trainor, 2007). Furthermore, damage of nucleui raphe, being a locus of conglomeration of serotonergic neurons, brought to clearly seen downregulation of serotonin and increase of aggression in the rats: 50% of the rats, subjected to surgical damage of nuclei raphe and which had not demonstrated predatory agression prior to operation, turned to become "killers" of mice. The inverse correlation between downregulation of serotonin and increased level of aggression in the rats after damage of nuclei raphe was analyzed by administration of serotonin precursor – 5-oxytryptophan to a part of the rats after surgery, leading to suppression of aggression (Popova et al., 1978). Along with it, a number of scientists have demonstrated the existence of direct correlation between serotonin level and manifestation of aggression: in their studies 10-fold upregulation of serotonin level in the organism of the knock-out mice for tryptophan dehydrogenase synthesizing gene was accompanied with acute increase of aggression level (Shih et al., 2000).

In our earlier studies, undertaken on the conditioned shuttle-box model, the significant increase of aggression level in the rats after intracerebral administration of serotonin-modulating anticonsolidation protein (SMAP; Guseynov, Mekhtiev, 2013), being in linear relation with serotonin level (Mekhtiev, 2000), was noticed visually (biting the researcher's hand and gnawing the iron grid floor by specimens of the experimental group). Basing on these observations, the goal of the present study was the analysis of the role of SMAP in realization of aggressive behavior in the rats on two behavioral models designed for studies of aggressive behavior.

MATERIALS AND METHODS

SMAP was purified from the cow brains through the following 2-step potocol: 1) precipitation of proteins under final 40% concentration of ammonium sulfatis; 2) gel-chromatography on the column (3 X 60 cm) of Sephadex G-150 (Mekhtiev, 2000). SMAP purification was carried out under screening control of solid-phase indirect ELISA-test with application of anti-SMAP immunoglobulins.

Anti-SMAP polyclonal immunoglobulins were produced as a result of 6-month immunization of 4 rabbits with the purified SMAP always in a mixture with equal amount of Freund's complete adjuvant (Sigma, Germany). Blood samples were taken from the edge ear vein, serum was saved and immunoglobulins were precipitated by adding 100% ammonium sulfate solution to final concentration of 50% in the mixture.

Anti-SMAP polyclonal antibodies were purified from the solution of anti-SMAP immunoglobulins through immuno-affinity chromatography on the column (1 x 5 cm) of CNBr-Sepharose 4B with priorily immobilized SMAP. The elution procedure of the anti-SMAP antibodies, bound specifically to the affinity resin, was realized with application of chaotropic agent – 3 M potassium rodanide. In one cycle approximately 12 mg of anti-SMAP antibodies were purified from the column.

The studies were realized on the male Wistar rats having body mass 150-180 g. Behavioral studies were carried out on the aggression model, based on an electric shock stimulus, and on the dominant model, based on confronting for food.

In the 1st series the studies were carried out on the aggression model. In this model the aggression was triggered in the animals by applying the pulses of electric current to the the animals' limbs through the iron grid floor (Rylov, Sherstnev, 1984). Electric current was changed in a step-wise manner from 0.048 to 1.5 mA. Within each group the animals were culled into pairs and each pair of the rats were put into the experimental box daily, for 5 days. The fights between the animals, initiated by electric current of the highest value (1.5 mA), were estimated as score 1, though the fights under the lowest value of electric current (0.048 mA) – as

score 42, and the fights, initiated by the intermediate values of electric current, – by the scores within 1-42 points, deployed in an inverse order to the values of applied electric current. At the end of 5th day all animals were sacrificed and amygdala was taken off from their brains, water soluble proteins were extracted and used as antigens in solid-base indirect ELISA-test on the polystyrene plates of moderate adsorption (Sigma, Germany) at a concentration of 20 μg/mL in the Tris-HCl buffer (pH 8.6). Anti-SMAP rabbit immunoglobulins were used as the first antibodies in the buffer designed for antibodies (pH7.2), and anti-rabbit goat antibodies with conjugated horseradish peroxidase were used as the second antibodies in the same buffer. Orthophenylendiamine was used as a substrate for peroxidase. The reaction was stopped 20 min later from addition of substrate solution by pouring 50 μL of 3 M NaOH into each well. The results of the reaction were registered in the photometer for the ELISA-test "Spectra Max 250" (Molecular Devices Co., USA) on the wavelength 492 nm.

In the 2nd series the studies were carried out again on the aggression model. The pairs of animals were put into the experimental box of the aggression model for 5 days, daily and thereafter 3 groups were formed: 1) intact group (n=12); 2) control group – the animals were administered with inactive SMAP (60°C on a water bath, 35 min; n=12); 2) experimental group (SMAP; n=18). The preparations were administered once, into the brain lateral ventricle of the anesthetized rats (sodium etaminali, 40 mg/kg of body mass) at a concentration 1.5 mg/ml, in a volume 10 μL, in saline, 24 h prior to the behavioral 10-day studies, in which fighting scores, according to the schedule described above, were awarded daily to each of the rat. In this series application of electric pulses was started from the lowest values, in step-wise manner increasing them to the values that induced fighting between animals.

The studies of the 3rd series were carried out on the dominant model. The experimental box, constructed from transparent organic glass, is composed of two compartments of sizes 30 X 30 X 20 cm, connected by a narrow tunnel with a small feeder, containing sweet milk, in its center (Malatynska et al., 2007). At the beginning of the studies all the rats were culled into pairs and numbered. Prior to the beginning of the studies all rats were deprived for food for 2 days, while water was given *ad libidum.* At the end of the 5th day of the daily studies the animals were sacrificed, amygdala was removed from their brains, water soluble proteins were extracted and used as antigens in the indirect ELISA-test which was conducted as in the 1st series of studies. In parallel, blood samples were taken from the rats into the sample tubes containing 5% EDTA as anticoagulation agent, centrifuged at 1,000 g for 10 min, plasma was saved into the Eppendorf sample tubes and centrifuged at 9,000 g for 20 min for platelet precipitation, which were saved and used as antigens in the indirect ELISA-test at a concentration of 20 μg/mL.

In the 4th series the studies were carried out on the dominant model. At the beginning of the studies all the rats were culled into pairs and numbered. Prior to the beginning of the studies all rats were deprived for food for 2 days. Thereafter the paired and numbered animals were culled into 3 groups: 1) intact group (n=6); 2) control group – inactive SMAP (n=6); 3) experimental group – SMAP (n=6). During the experiment the animals of the control and experimental groups were paired only with the animals from the intact group.The preparations were administered the same way as in the 2nd series of studies. The studies were conducted for 5 min, daily, during 5 days. On the 5th day the duration of staying of each animal at the feeder was recorded.

In the 5th series the studies were realized on the dominant model. The animals were culled into 3 groups: 1) intact group (n=10); 2) control group – rabbit non-immune γ-globulins (n=10); 3) experimental group – anti-SMAP polyclonal antibodies (n=10). During the experiment the animals of the control and experimental groups were paired only with the animals from the intact group. The preparations were administered the same way as in the 2nd series of studies, except for their concentration: they were used at concentration 1.8 mg/mL.

The results of studies within each series were grouped, averaged within each group and analyzed on t-Student's criterion.

RESULTS

In the 1st series of studies in the course of 5-day experiments on the aggression model gradual increase of the minimal values of electric current (corresponds to decrease of aggression scores), submited to the iron grid floor, that induced fights between specimens within pairs, was noticed.

The observed increase of the minimal values of electric current (i.e. decrease of aggression scores), required to induce fights between the rats, reflects elevation of the threshold level of onset of aggressive behavior at the end of 5-day experiment. The results of the indirect ELISA-test showed noticeable downregulation of SMAP in the amygdala of the rats of the aggressive group relatively to the intact group (0.088±0.006 vs 0.134±0.002 optic units of extinction, $p<0.001$), though in the amygdala of the submissive animals the level of SMAP (0.126±0.002 vs. 0.134±0.002 optic units, $p<0.01$) changed less prominently (Fig. 1).

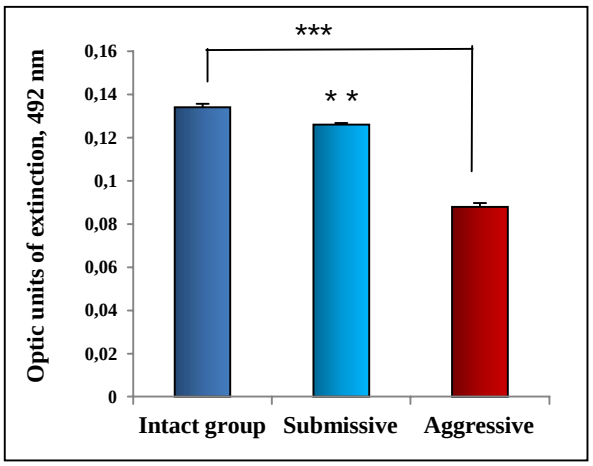

Fig. 1. Levels of SMAP in the amygdala of the rats in aggression model.**-p<0.01,***- p<0.001.

In the 2nd series of studies gradual increase of fighting scores, reflecting correspondent significant gradual decline of the threshold of aggression initiation from the score 6 prior to SMAP administration to the score 24 ($p<0.001$) on the 10th day since single intracerebral administration of SMAP was revealed (Fig. 2). At the same time no effect of inactive SMAP on the threshold of aggression initiation throughout of 10-day research was noted. These results indicate to strengthening of aggression in the rats under the effect of a single intracerebral administration of SMAP.

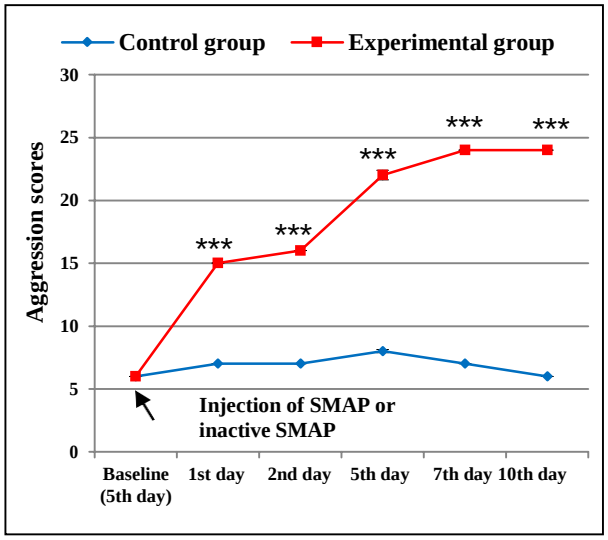

Fig. 2. Dynamics of levels of aggression after i.c. administration of SMAP. *** - p<0.001.

In the 3rd series of studies, carried out on the dominant behavioral model, the results of the indirect ELISA-test studies showed sharp downregulation of SMAP in the amygdala of the dominant animals relatively to its level of the intact animals (0.248±0.001 vs. 0.263±0.002 optic units, $p<0.001$; Fig. 3). In the amygdala of the submissive specimens downregulation of SMAP (0.253±0.001 vs. 0.263±0.002 optic units, $p<0.001$, Fig. 3), however, less pronounced than in the dominant animals, was as well observed. In the platelets of the dominant animals sharp upregulation of SMAP relatively to the intact animals was noted (0.253±0.002 vs. 0.237±0.003 optic units, $p<0.001$; Fig. 4), while in the platelets of the submissive animals not too prominent SMAP upregulation was observed (0.247±0.003 vs. 0.237±0.003 optic units, $p<0.05$).

In the 4th series of studies, undertaken on the dominant behavioral model, a single intracerebral administration of SMAP to the animals, defined as submissive ones in the preliminary studies, brought to their transformation into the dominant animals. In particular, if the staying time at the feeder of the submissive rats prior to SMAP administration made 109.8±7.3 sec, 24 h after SMAP administration it grew noticeably up to 180±1.5 sec ($p<0.001$; Fig. 5).

The observed effect of transformation of submissive animals into dominant ones lasted for 7 days and to the 8th day the values of staying time at the feeder declined to 141.7±1.9 sec ($p<0.001$ relatively to the values of the 1st day; Fig. 5).

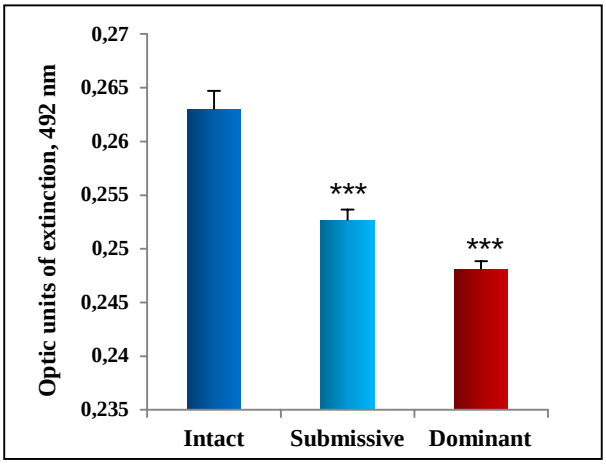

Fig. 3. Levels of SMAP in the amygdala of the rats in dominant model. *** - $p<0.001$.

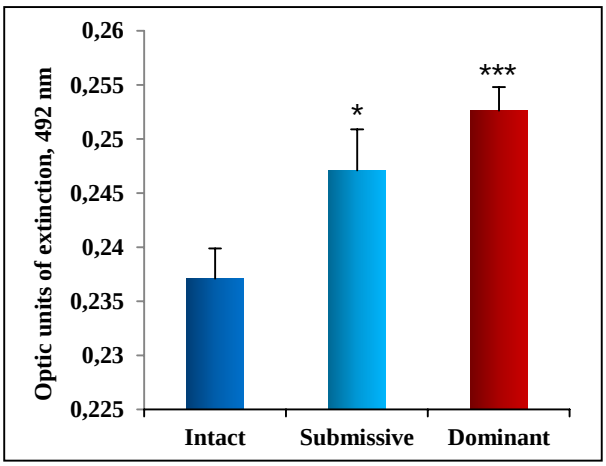

Fig. 4. Levels of SMAP in the platelets of the rats in dominant model. * - $p<0.05$; *** - $p<0.001$.

As intracerebral administration of heat-inactivated SMAP did not have strengthening effect on the original aggressive level of the submissive animals (Fig. 6), the obtained data indicate to specific effects of SMAP on animal behavior. These data support the conclusion on promoting effect of SMAP on launching aggressive behavior on the rats, noticed in the 2nd series of studies on the aggression model.

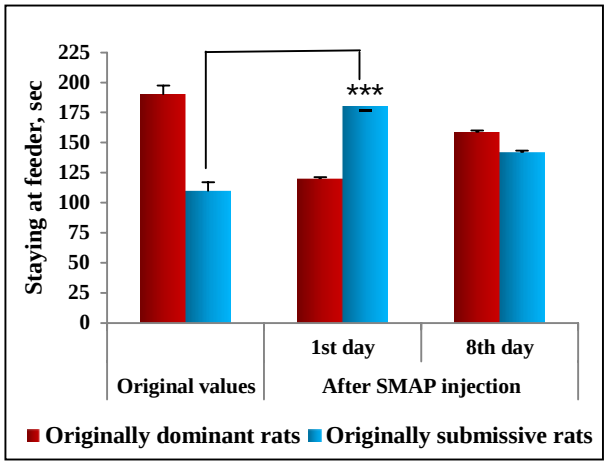

Fig. 5. Transversion of the originally submissive rats into the dominant ones after i.c. injection of SMAP in the domiunant model. *** - $p<0.001$.

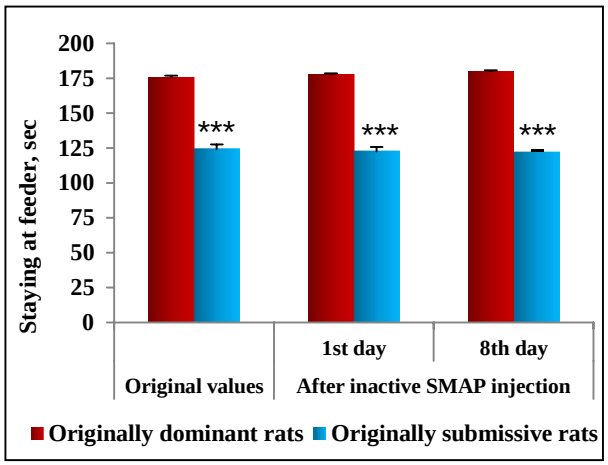

Fig. 6. Effect of i.c. injection of inactive SMAP to the originally submissive rats in the dominantg model. *** - $p<0.001$.

In the 5th series of studies on the dominant behavioral model a single intracerebral administration of anti-SMAP antibodies to the animals, defined as dominant ones in the preliminary studies, transformed them into the submissive animals. In particular, if the staying time at the feeder of the dominant rats prior to SMAP administration was 235±7.3 sec, after SMAP injection it declined drastically to 73±5.8 sec ($p<0.001$: Fig. 7). This transformation of dominant into submissive animals lasted only for 1 day, then the values of the "transformed" animals returned to the original values of staying time at the feeder, characteristic to the dominant rats (Fig. 7). At the

same time intracerebral administration of rabbit non-immune γ-globulins to the dominant animals did not change the level of their aggressiveness (not shown on the figure).

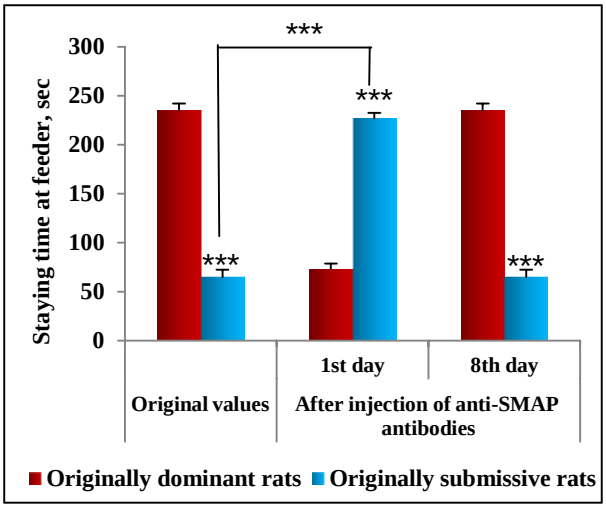

Fig. 7. Transformation of the originally dominant rats into the submissive ones after i.c. injection of anti-SMAP antibodies in the domiunant model.
*** - $p<0.001$.

Hence, the data show that both in the aggression and dominant models significant downregulation of SMAP was revealed in the amygdala and its upregulation – in the platelets of the aggressive animals. Intracerebral administration of SMAP to the rats brought to sharp increase of aggression level on the both models used in the study, especially prominent increase was noted in the dominance model under its administration to the submissive rats. Meanwhile, intracerebral administration of anti-SMAP antibodies to the dominant rats resulted in their transformation into submissive ones.

DISCUSSION

Although the role of amygdala as a pacemaker of aggressive emotions has already been proven by numerous studies, the brain structure, accepting plenty incoming afferent pathways from different brain structures including the amygdala and being the final brain structure responsible for regulation of animal's aggressive behavior, is the brain cortex. Serotonin turnover, its synthesizing and degrading enzymes and types of receptors in the platelets are similar to those in the brain cortex (Da Prada et al., 1988; Elliot & Kent, 1989; Collins et al., 2012). Basing on these grounds, the observed upregulation of SMAP in the platelets of the aggressive rats, apparently, reflects its upregulation in the brain cortex of these animals. In this relation, in our earlier studies, undertaken on the conditioned shuttle box model, noticeable upregulation of SMAP in the brain cortex of the control animals, which received acoustic stimulus (unconditioned stimulus) and electric shock (conditioned stimulus) in an uncombined, occasional order and, for this reason, got numerous unescapeable electric shocks, was observed (Guseinov, Mekhtiev, 2013). From this standpoint, intracerebral administration of SMAP to the submissive rats, whose original baseline levels of SMAP in the platelets (correspond to SMAP levels in their brain cortex) were lower than in the aggressive animals, should bring to their significant upregulation in the brain cortex and further – to elevation of aggression levels that was actually observed in the present study.

The effect of intracerebral administration of anti-SMAP antibodies on the aggressive annimals, "transforming" them for short-term timeframe (for 1 day) into the submissive ones, can reasonably be explained from standpoint of baseline upregulation of SMAP in the platelets (corresponds to its upregulation in the brain cortex) of the aggressive animals. In this case, the administered antibodies through blocking the SMAP activity bring to decline of the level of the active molecules of SMAP in the brain cortex of the submissive animals, which was manifested finally in lowering the aggression level to the one, characteristic to the submissive specimens.

The observed noticeable changes of SMAP level in the platelets of aggressive animals can be used in psychiatry as a biochemical marker of aggression in psychiatric disorders to prevent splashes of their manifestations or in revealing criminals, involved in terroristic affairs.

According to the available literature data, amygdala is the subcortical brain structure responsible for formation of aggression as emotion (Gouveia et al., 2019). From this standpoint, studies of the amygdala are very important for understanding the mechanisms of aggression formation. The revealed downregulation of SMAP in the amygdala of the aggressive animals on the both be-

havioral models, designed for the studies of aggressive behavior, is consistent with the results of the experimental studies on the animal models by other researchers, demonstrating inverse correlation between downregulation of serotonin and increased level of aggression (Popova, 2008).

Looking through the most body of publications demonstrating existence of the inverse correlation between downregulation of serotonin in the brain structures and increased level of aggression, it is important to perceive the underlying mechanism. The level of serotonin in the brain structures is defined by interplay of two types of enzymes: serotonin-synthesizing (tryptophan-hydroxylase type 2) and serotonin-degrading (monoamineoxidase A) enzymes. The found low level of serotonin in the amygdala of the aggressive animals might be due to either low activity of serotonin-synthesizing enzyme, or, otherwise, to upregulation of serotonin-degrading enzyme. In our studies downregulation of SMAP in the amygdala of the aggressive rats, apparently, is related to high rate of its utilization by the cells of this structure. This idea is based on the important role for SMAP in regulation of aggressive behavior, bringing to its mighty utilization, and supported by the observed increase of aggression level under intracerebral administration of SMAP both in the rats on the aggression model, and in the submissive rats on the dominant model. Conversely, decline of the aggression level as a result of antibody-mediated downregulation of SMAP molecules confirms its active engagement in positive regulation of aggressive behavior.

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Sıçovulların iki müxtəlif davranış modelində serotoninergik sistemın aqressiya davranışının tənzimində iştirakının tədqiqi

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Məqalə serotonin ilə düz mütənasib əlaqədə olan (Mekhtiev, 2000) serotonin-modullu antikonsolidasiya zülalının (SMAZ) aqressiya davranışının tənzimində iştirakının tədqiqinə həsr olunmuşdur. Tədqiqatlar 5 aylıq erkək Vistar siçovulları üzərində aqressiya (elektroşok ilə yaradılan) və dominant (qidadan məhrumetmə ilə yaradılan) davranış modellərində aparılmışdır. 5 seriya tədqiqatlar həyata keçirilmişdir. 1-ci seriya tədqiqatlar aqressiya davranışı modelində və bərk-fazalı ELİSA testinin tətbiqi ilə aparılmışdır, aqressiv heyvanların amiqdalasında SMAZ-ın ($p<0.001$) miqdarının nəzərəçarpacaq dərəcədə azalması müşahidə edilmişdir. 2-ci seriya tədqiqatlar aqressiya davranışı modelində aparılmışdır, SMAZ-ın eksperimental heyvanlara birdəfəlik beyindaxili yeridilməsi aqressiya səviyyəsinin əhəmiyyətli dərəcədə ($p<0.001$) yüksəlməsinə səbəb olduğu halda yüksək temperaturun təsirindən inaktivləşdirilmiş SMAZ-ın kontrol heyvanlara yeridilməsi heç bir təsir göstərməmişdir. 3-cü seriya tədqiqatlar dominant davranış modelində aparılmışdır. SMAZ-ın miqdarının dominant heyvanların amiqdalasında intakt heyvanlara nisbətən kəskin şəkildə aşağı düşdüyü ($p<0.001$) halda, onun miqdarı əksinə olaraq dominant heyvanların trombositlərində intakt heyvanlara nisbətən ciddi dərəcədə yüksəlmişdir ($p<0.001$; beyin qabığında onun miqdarını əks etdirir). 4-cü seriya tədqiqatlar dominant davranış modelində SMAZ-ın məğlub (submissiv) heyvanlara birdəfəlik beyindaxili yeridilməsi ilə həyata keçirilmiş və nəticədə bu heyvanlar dominant heyvanlara çevrilərək ($p<0.001$) və 7 gün bu üstünlüyü saxlamışdır, lakin inaktivləşdirilmiş SMAZ-ın yeridilməsindən sonra heç bir dəyişiklik müşahidə edilməmişdir. 5-ci seriya tədqiqatlar dominant davranış modelində SMAZ-a qarşı poliklonal dovşan anticisimlərinin dominant heyvanlara birdəfəlik beyindaxili yeridilməsi ilə həyata keçirilmiş və nəticədə onlar məğlub heyvanlara çevrilərək ($p<0.001$) 1 sutka ərzində bu xüsusiyyəti saxladıqları halda, qeyri-immun γ-qlobulinlərin tətbiqi heç bir təsir göstərməmişdir. Ümumilikdə əldə edilmiş nəticələr göstərir ki, SMAZ aqressiya davranışını gücləndirir və hər iki davranış modelində aqressiv hevanların amiqdalalarında SMAZ-ın miqdarının aşağı düşməsi, güman ki, onun yüksək səvviyədə utilizasiyası ilə əlaqədardır.

Açar sözlər: *Aqressiya davranışı, dominant davranış, erkək siçovullar, serotonin-modullu antikonsolidasiya zülalı (SMAZ), SMAZ-a qarşı poliklonal anticisimlər, immuno-enzim analizi*

Изучение роли серотонинергической системы в регуляции агрессивного поведения в двух поведенческих моделях у крыс

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Статья посвящена изучению роли серотонин-модулируемого антиконсолидационного белка (СМАБ), находящегося в прямой зависимости от уровня серотонина (Мехтиев, 2000), в регуляции агрессивного поведения. Исследования были выполнены на агрессивной (вызванной электрическим током) и доминантной (пищевая депривация) поведенческих моделях, на 5-месячных самцах линии Вистар. Исследования были выполнены в 5 сериях. В 1-й серии исследований, выполненной в модели агрессии, с помощью твёрдофазного иммуноферментного анализа было выявлено значительное снижение уровня СМАБ ($p<0.001$) в амигдале агрессивных животных. Во 2-й серии исследований, проведенной в модели агрессии, однократное внутримозговое введение СМАБ приводило к значительному увеличению уровня агрессивности ($p<0.001$) у животных экспериментальной группы, тогда как введение инактивированного нагреванием СМАБ контрольным животным не оказывали никакого влияния. В 3-й серии исследований, проведенной в доминантной модели, наблюдалось резкое снижение ($p<0.001$) уровня СМАБ в амигдале доминантных животных, тогда как в их тромбоцитах – значительное увеличение ($p<0.001$) его уровня (отражает его уровень в коре головного мозга) относительно значений интактных животных. В 4-й серии исследований, выполненной на доминантной модели, однократное внутримозговое введение СМАБ субмиссивным животным вызвало их трансформацию в доминантных ($p<0.001$), сохранявшуюся на протяжении 7-суточного интервала времени, в то время как инактивированный СМАБ не оказывал никакого влияния. В 5-й серии исследований, выполненной на доминантной модели, однократное внутримозговое введение кроличьих поликлональных антител к СМАБ доминантным животным приводило к их трансформации в субмиссивных животных на срок в 1 сут ($p<0.001$), тогда как неиммунные γ-глобулины не оказывали влияния. В целом, полученные результаты указывают на позитивную регуляцию агрессивного поведения со стороны СМАБ, а его снижение в амигдале агрессивных животных в обеих поведенческих моделях, вероятно, обусловлены высокой скоростью его утилизации.

Ключевые слова: *Агрессивное поведение, доминантное поведение, крысы-самцы, серотонин-модулируемый антиконсолидационный белок (СМАБ), поликлональные антитела к СМАБ, иммуноферментный анализ*