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Analysis of Melanocyte-Stimulating Hormone Role in Regulation of Emotional and Exploratory Behavior in Rats

Sarng S. Pyurveev, Andrei A. Lebedev, Eugeny R. Bychkov, Anna G. Pshenichnaya, Maksim E. Abrosimov, Viktor A. Lebedev, Ivan A. Balagansky, Petr D. Shabanov

Institute of Experimental Medicine, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: Animals' emotions and exploratory behavior are significant markers of its cognitive and neurobiological health.

AIM: To investigate the effect of a melanocortin-stimulating hormone antagonist on the emotional and exploratory behavior of male rats.

METHODS: A series of experiments included a group of 20 male Wistar rats, with a baseline weight of 200–220 grams. A behavioral test battery was used, including Open-Field test, Elevated Plus Maze test, Resident-Intruder test, and Porsolt Forced Swim test. The sample size was fixed at 10 animals per group. ML-00253764, a melanocortin receptor 4/α-melanocyte-stimulating hormone receptor antagonist, diluted in distilled water at 1 mg/mL was administered intranasally at 20 μg (10 μ/mL in each nostril) 15 minutes prior to the behavior testing. Additionally, 0.9% sodium chloride solution was administered in a similar dose to serve as a control.

RESULTS: Intranasal administration of the MC4R antagonist ML-00253764 has been demonstrated to reduce anxiety, enhance research activity, and produce antidepressant effects. In the Open-Field and Elevated Plus Maze tests, an increase in the number of locomotor responses, exploratory activities, and time in open arms was observed, suggesting the activation of exploratory behavior and the anxiolytic effect of the compound. In the Porsolt Forced Swim test, a decrease in immobilization time was documented, which is indicative of the antidepressant effect The Resident-Intruder test demonstrated a decrease in aggressive and defensive behaviors, thereby indicating a normalized social behavior.

CONCLUSION: The study findings highlight the significance of the melanocortin system in the regulation of emotional and cognitive functions, thereby offering novel insights into the potential therapeutic benefits of MC4R antagonists for the treatment of anxiety and depression.

Keywords: melanocortin-stimulating hormone; ML-00253764; behavior; MC4R.

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Исследование роли меланоцитстимулирующего гормона в организации эмоционального и исследовательского поведения у крыс

С.С. Пюрвеев, А.А. Лебедев, Е.Р. Бычков, А.Г. Пшеничная, М.Е. Абросимов, В.А. Лебедев, И.А. Балаганский, П.Д. Шабанов

Институт экспериментальной медицины, Санкт-Петербург, Россия

АННОТАЦИЯ

Обоснование. Эмоциональное состояние и исследовательское поведение животных — важные индикаторы их когнитивного и нейробиологического статуса.

Цель — изучение действия антагониста меланокортинстимулирующего гормона на эмоциональное и исследовательское поведение самцов крыс.

Материалы и методы. Опыты выполнены на 20 крысах-самцах линии Вистар с начальной массой 200–220 г. Использовали батарею поведенческих тестов: «открытое поле», «приподнятый крестообразный лабиринт», «чужак – резидент», тест Порсолта. Выборка для каждой группы животных составляла по 10 крыс. Для анализа использовали антагонист рецепторов MC4R α-MSH ML-00253764, разведенный в дистиллированной воде 1 мг/мл, который вводили интраназально в дозе 20 мкг (по 10 мкг/мкл в каждую ноздрю) за 15 мин до исследования поведения в тестах. В качестве контроля использовали введение аналогичной дозы 0,9 % раствора хлорида натрия.

Результаты. Было показано, что интраназальное введение антагониста MC4R ML-00253764 вызывает снижение тревожности, увеличение исследовательской активности и проявляет антидепрессивное действие. В тестах «открытое поле» и «приподнятый крестообразный лабиринт» отмечались повышение числа локомоций, исследовательских актов и времени пребывания в открытых рукавах, что указывает на активацию исследовательского поведения и анксиолитический эффект препарата. В тесте Порсолта наблюдалось снижение времени иммобилизации, свидетельствующее об антидепрессивном эффекте. В тесте «чужак – резидент» уменьшение актов агрессии и защитного поведения указывает на нормализацию социального поведения.

Заключение. Полученные результаты подчеркивают значимость меланокортиновой системы в регуляции эмоциональных и когнитивных функций, а также открывают перспективы применения антагонистов MC4R для терапии тревожных и депрессивных расстройств.

Ключевые слова: меланокортинстимулирующий гормон; ML-00253764; поведение; MC4R.

Как цитировать

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ЭКО•ВЕКТОР

BACKGROUND

The emotional state and exploratory behavior of animals are important indicators of their cognitive and neurobiological status. Peptides involved in appetite regulation, such as anorexigenic (appetite-suppressing) and orexigenic (appetite-stimulating) compounds, play a central role not only in maintaining energy balance, but also in modulating emotional and cognitive functions [1]. These neuropeptides are widely distributed throughout the central nervous system, where they modulate the function of the hypothalamic-pituitary-adrenal axis, dopaminergic reward system, and stress responsiveness [2, 3]. Among the anorexigenic peptides, particular attention is given to proopiomelanocortin (POMC) and leptin, which are associated with the regulation of anxiety and depression. Orexigenic peptides such as ghrelin and neuropeptide Y (NPY) influence motivational and exploratory behavior [4, 5].

POMC is a large precursor polypeptide synthesized in the pituitary gland, which gives rise to several biologically active metabolites involved in the regulation of various physiological functions, including stress control, energy homeostasis, skin pigmentation, and immune responses [6, 7].

The melanocortin system was first identified in 1961 during studies on the regulation of skin pigmentation in humans. Its primary regulators are melanocyte-stimulating hormones (MSH), a group of polypeptides derived from the proteolytic processing products of POMC [8]. These peptides are involved in regulating endocrine, cardiovascular, and reproductive functions, as well as feeding behavior, energy metabolism, and insulin sensitivity [9]. This functional diversity is due to the tissue-specific post-translational cleavage of their precursor, POMC, which gives rise to multiple MSH isoforms such as α-MSH, γ-MSH, and β-MSH, all containing the conserved His-Phe-Arg-Trp sequence. The biological effects of MSH are mediated through their interaction with melanocortin receptors (MCRs), of which five subtypes are known: MC1R to MC5R [8, 10]. MC1R is primarily expressed in skin melanocytes, MC2R in adipocytes and adrenal glands, and MC5R in exocrine glands and certain peripheral tissues, whereas MC3R and MC4R are predominantly expressed in the central nervous system (CNS) [9, 10]. This localization of MC3R and MC4R suggests their involvement in the regulation of autonomic and neuroendocrine functions. MC3R and MC4R are most commonly found in hypothalamic structures.

Structurally, MCRs belong to the G protein-coupled receptor (GPCR) superfamily. They consist of variable extracellular domains, including three extracellular loops (ECL1–ECL3) and an N-terminal domain, three cytoplasmic loops, an intracellular C-terminal domain, and seven highly conserved hydrophobic transmembrane segments that form a transmembrane channel. MC3R and MC4R share a similar primary structure, showing 58% identity and 76% similarity in their amino acid sequences [11, 12]. Despite their high degree of similarity in primary structure, regulatory properties, and intracellular signaling cascades, MC3R and MC4R differ in tissue distribution and pharmacological profiles.

The principal ligand for MC1R through MC4R is α-MSH. MC4R has high affinity for γ-MSH and lower affinity for both α- and β-MSH. Although MC4R primarily interacts with α-MSH, it can also be activated, albeit less effectively, by β-MSH and γ-MSH [13]. The varying affinities of different MCR types for their agonists are determined by the specific conformation of the ligand-binding site within the transmembrane channel and the structure of their extracellular domains [14].

The uniqueness of the melanocortin system lies in the fact that its activity can be inhibited by two endogenous antagonists, agouti protein and agouti-related peptide (AgRP), which exhibit different selectivity toward melanocortin receptors (MCRs) [14].

Among the various functions of the melanocortin system, its role in maintaining energy homeostasis and regulating feeding and sexual behavior is the most thoroughly studied. The CNS-localized MC3R and MC4R play a key role in sustaining energy balance and controlling feeding behavior. Both receptors exhibit constitutive activity, which can vary considerably depending on the binding of different ligands. In addition, MC3R functions as an autoreceptor, modulating MC4R-dependent cascades through a negative feedback mechanism [13]. The canonical signaling pathway of MC3R and other MCRs is coupled to G_s proteins, leading to activation of adenylate cyclase, an increase in intracellular cyclic adenosine monophosphate, and subsequent activation of protein kinase A [14]. Agonist binding to MC3R and MC4R can also activate the mitogen-activated protein kinase cascade via stimulation of phosphoinositide 3-kinase, which is associated with ERK1/2 kinases [15, 16]. Hormone-activated MC3R and MC4R can stimulate phospholipase C activity [14]. Thus, MCRs interact with multiple signaling pathways and effectors.

It is known that a decrease in leptin levels directly affects the expression of genes encoding POMC and AgRP in the hypothalamus, leading to a reduction in the concentrations of MC3R and MC4R agonists and an increase in endogenous AgRP levels [11]. In contrast, leptin administration results in increased POMC mRNA expression and MC4R activation. Importantly, leptin resistance and a reduction in leptin's effects on the functional state of the melanocortin system have been reported in obese mice [17].

Thus, decreased functional activity and impaired regulation of MC3R- and MC4R-mediated pathways in the brain lead to disrupted feeding behavior and energy

metabolism, reduced insulin sensitivity in peripheral tissues, and, ultimately, morbid obesity, metabolic syndrome, and type 2 diabetes mellitus [17].

This work aimed to assess the effect of a melanocortin-stimulating hormone antagonist on the emotional and exploratory behavior of male rats.

METHODS

Experimental Animals

The study was conducted in accordance with the legislation of the Russian Federation and the technical standards of the Eurasian Economic Union on Good Laboratory Practice (GOST R53434–2009, GOST R51000.4–2011). The overall study design, protocols of each experimental procedure, selection of pharmacological agents, individual animal observation records, and sacrifice method were approved by the Local Ethics Committee of Saint Petersburg State Pediatric Medical University.

Twenty male Wistar rats weighing 200–220 g at baseline were used. The animals were housed in groups of five per cage under artificial 12-hour light/dark cycles at a temperature of 22±2°C. All animals had ad libitum access to water and standardized dry feed. The study used a battery of behavioral tests, including the open field test, elevated plus maze test, resident–intruder test, and Porsolt forced swim test. The sample size was 10 animals per group.

Behavioral Tests

Open field test. The spontaneous locomotor activity of rats was assessed using the open field test, which consisted of a circular arena with a diameter of 80 cm enclosed by opaque walls 30 cm high. A total of 16 evenly spaced holes (burrows) with a diameter of 3 cm were distributed across the field's surface to evaluate the species-specific component of exploratory behavior in rodents (hole exploratory behavior). The illumination level in the open field was set at 100 lux. Each test session lasted 3 minutes. A series of elementary motor acts and postures, which collectively characterize the rats' overall behavior in the open field, were selected based on a behavioral atlas for rodents. For observation and statistical analysis, each elementary act was assigned a specific numerical code: 0=locomotion (forward movement of the body in the horizontal plane); 1=sniffing (head movements and orienting responses without substantial displacement of the body in horizontal or vertical planes). This act may be performed in either a sitting or standing position, which are difficult to distinguish without compromising its core biological meaning; therefore, no distinction was made during recording based on the position in which it occurred; 2=rearing (standing on hind legs in the center of the open field); 3=grooming (all forms of grooming behavior); 4=immobility (resting or sitting, visually defined as a lack of movement, typically in a sitting position with limbs tucked under the body and a hunched back); 5=in-place movement (head and trunk movements within a notional circle centered on the hind legs, with coordinates remaining largely unchanged. Typically achieved by stepping with the forelegs whereas the hind legs remain stationary); 6=hole-poking (hole exploratory behavior); 7=wall-rearing (rearing with forelegs resting against the wall of the arena).

Elevated plus maze test. The behavior of rats in the elevated plus maze was assessed using an apparatus consisting of two open arms (50×10 cm) and two closed arms (50×10 cm) with open tops, arranged perpendicularly. The maze was elevated 1 meter above the floor. Each animal was placed in the center of the maze. By pressing a key of an ethograph connected to a computer, the following parameters were recorded: time spent in open and closed arms, time spent hanging over the edge in open arms, and time spent peering out of closed arms. The duration of the test was 5 minutes.

Porsolt forced swim test. The forced swim test is based on the observation that when forced to swim in a water-filled cylinder, rodents (rats or mice) adopt an immobile posture (immobility). In this test, the animal's immobility is interpreted as a passive reaction to stress, indicating depressive behavior, also known as behavioral despair. Each rat was placed in a transparent cylinder 70 cm in height, filled with water at 25°C, for 6 minutes. To facilitate adaptation, each animal was exposed to the same water immersion conditions for 5–6 minutes the day before testing. On the test day, animals were placed in the water-filled cylinder in such a way that they could neither escape nor find any support, i.e., their legs could not touch the bottom. When placed in water, animals initially displayed vigorous motor activity in order to escape the aversive stressful situation, but then abandoned these attempts and floated in a characteristic posture, remaining completely motionless or making only minor movements to keep their heads above the water surface. This behavior is regarded as a manifestation of despair, suppression, or a depressive-like state. The main indicator of the severity of this condition in this test is the duration of immobility, that is, the total time of immobility episodes for each animal during the 6-minute observation period.

Resident–intruder test. The test animal ("resident," a rat weighing 220–240 g) was placed in a cage (20×36×20 cm) for 1 hour, after which a second animal ("intruder") was introduced for 5 minutes. The "intruders" were male rats weighing 170–180 g, deliberately smaller than the "residents," to create conditions that favored the resident's zoosocial dominance. The number of aggressive and defensive behavioral manifestations, as well as the total number of behavioral acts characterizing the interaction between the two rats, were recorded.

Pharmacological Agents

To assess behavioral effects, the MC_4R/α-MSH receptor antagonist ML-00253764 (Tocris, UK), diluted in distilled water to a concentration of 1 mg/mL, was administered intranasally at a dose of 20 μg (10 μg/μL per nostril) 15 minutes prior to testing in the open field test, elevated plus maze test, resident–intruder test, and Porsolt forced swim test. A 0.9% sodium chloride solution was administered in an equivalent dose as a control.

Statistical Analysis

The significance of differences was evaluated using the SPSS Statistica v.10 software package. The Student's *t*-test for independent samples was used to compare the control and experimental groups. Differences were considered significant at $p < 0.05$. Results are presented as mean±standard error of the mean (*M*±SEM).

RESULTS

In the open field test, intranasal administration of ML-00253764 led to alterations in behavioral patterns: there was a marked trend toward an increase in locomotor activity, from 18.6±3.97 acts in the control group to 27.80±6.97 acts after ML-00253764 administration, indicating enhanced motor activity. A significant increase in the number of exploratory acts was observed following intranasal administration, from 45.20±3.67 to 61.00±3.35 ($p < 0.01$), reflecting enhanced exploratory behavior (Table 1). The total number of behavioral acts after ML-00253764 administration increased from 103.80±6.61 to 145.80±7.39 ($p < 0.01$), underscoring a general activation of exploratory activity (Table 2).

Thus, ML-00253764 enhances exploratory and locomotor activity in rats while reducing anxiety. This supports the MSH antagonist's potential as a modulator of exploratory behavior.

In the elevated plus maze test, intranasal administration of ML-00253764 resulted in a significant reduction in the time spent in closed arms: from 274.38±9.13 s in the control group to 224.18±13.42 s in the experimental group ($p < 0.01$). Moreover, there was a significant increase in the number of head dips, from 5.70±2.91 in the control group to 29.64±8.67 in the experimental group ($p < 0.05$) (Table 3).

Thus, the MSH antagonist reduces anxiety and enhances exploratory behavior in rats, as evidenced by the decreased time spent in closed arms and increased frequency of head dips. These findings confirm its anxiolytic effect.

In the resident–intruder test, intranasal administration of ML-00253764 reduced the number of acts associated with defensive behavior (0 vs. 3.20±1.28 in the control group, $p < 0.05$) (Table 4).

In the Porsolt forced swim test, ML-00253764 administration in the experimental group significantly ($p < 0.05$) reduced immobility time compared to the intact control group: from 43.04±15.37 s in the control group to 7.63±6.21 s following ML-00253764 administration. There was also a significant decrease in the total number of behavioral acts: from 71.80±18.36 in the control group to 23.60±11.08 in the experimental group ($p < 0.05$) (Table 5). Thus, ML-00253764 administration is associated with a pronounced antidepressant effect, as evidenced by reduced immobility time.

DISCUSSION

The findings of the present study underscore the significance of the melanocyte-stimulating hormone and its antagonist in the regulation of emotional and exploratory behavior in rats. The results of the open field test, elevated plus maze test, resident–intruder test, and Porsolt forced swim test demonstrate that administration of an MSH antagonist has a marked influence on behavioral parameters. These observations suggest that the melanocortin system may be a promising target for the regulation of emotional states.

In the open field test, animals that received the MSH antagonist showed a marked increase in exploratory activity, as evidenced by an increase in locomotion, rearing, and sniffing episodes. These changes may be attributed

Table 1. Amino acid sequences of natural melanocortins

Таблица 1. Аминокислотные последовательности природных меланокортинов

Peptide	Amino acid sequence
ACTH	Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Asn-Gly-Ala-Glu-Asp-Glu-Ser-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe
α-MSH	Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2
β-MSH	H-Ala-Glu-Lys-Lys-Asp-Glu-Gly-Pro-Tyr-Arg-Met-Glu-His-Phe-Arg-Trp-Gly-Ser-Pro-Pro-Lys-Asp-OH
γ1-MSH	H-Tyr-Val-Met-Gly-His-Phe-Arg-Trp-Asp-Arg-Phe-NH2
γ2-MSH	H-Tyr-Val-Met-Gly-His-Phe-Arg-Trp-Asp-Arg-Phe-Gly-OH
γ3-MSH	H-Tyr-Val-Met-Gly-His-Phe-Arg-Trp-Asp-Arg-Phe-Gly-Arg-Arg-Asn-Ser-Ser-Ser-Ser-Gly-Ser-Ser-Gly-Ala-Gly-Gln-OH

Table 2. Animals' behavior in the Open-Field test after the intranasal administration of ML-00253764, *M*±SEM

Таблица 2. Поведение животных в тесте «открытое поле» после интраназального введения ML-00253764, *M*±SEM

Pattern		Control animals	Experimental animals
Locomotion	*n*	18.6±3.97	27.80±6.97
	t	12.25±2.88	23.92±6.69
Sniffing	*n*	45.20±3.67	61.00±3.35**
	t	100.03±13.07	91.88±5.73
In-place movement	*n*	28.4±4.62	36.60±4.99
	t	15.55±3.14	28.65±6.13
Grooming	*n*	2.59±1.32	5.00±2.07
	t	30.01±15.31	13.16±6.71
Rearing	*n*	1.51±0.77	2.20±1.02
	t	1.40±0.72	1.96±0.96
Wall-rearing	*n*	3.00±0.89	6.00±1.07
	t	2.88±0.74	8.10±4.06
Hole exploratory behavior	*n*	3.60±1.29	7.00±1.52
	t	8.91±4.06	9.90±2.09
Freezing	*n*	0	0
	t	0	0
Rest	*n*	1.80±0.73	0.39±0.20
	t	13.48±6.74	4.86±2.48
Total behavioral acts		103.80±6.61	145.80±7.39**
Squares crossed	*n*	18.40±2.38	33.60±8.96
Number of boli		1.80±0.20	1.40±0.24

Note. *n*, number of actions per experiment; *t*, time of the action per experiment, s. ***p* <0.01 for the control group.
Примечание. *n* — число актов за опыт; *t* — время акта за опыт, с. ***p* <0,01 к группе контроля.

Table 3. Animals' behavior in the Elevated Plus Maze test after the intranasal administration of the melanocortin-stimulating hormone antagonist ML-00253764, *M*±SEM

Таблица 3. Поведение животных в тесте «приподнятый крестообразный лабиринт» после интраназального введения антагониста меланокортинстимулирующего гормона ML-00253764, *M*±SEM

Time spent in maze arms, s	Control animals	Experimental animals
Center	5.82±2.53	14.80±6.45
Open arm	14.77±7.76	31.40±8.46
Head-dipping	0	0
Open arm + head-dipping	14.77±7.76	31.40±8.46
Closed arm	274.38±9.13	224.18±13.42**
Head-dipping	5.70±2.91	29.64±8.67*
Closed arm + head-dipping	278.8±8.68	253.82±11.53
Number of arm-to-arm transitions, *n*	8.00±2.28	13.00±3.11

Note. **p* <0.05; ***p* <0.01 for the control group.
Примечание. **p* <0,05; ***p* <0,01 к группе контроля.

Table 4. Animals' behavior in the Resident-Intruder test after the intranasal administration of the melanocortin-stimulating hormone antagonist ML-00253764, *M*±SEM

Таблица 4. Поведение животных в тесте «чужак – резидент» после интраназального введения антагониста меланокортинстимулирующего гормона ML-00253764, *M*±SEM

Behavior		Control animals	Experimental animals
Individual behavior	*n*	48.00±6.04	45.80±6.88
	p	0.767±0.05	0.881±0.05
Communicative behavior	*n*	11.80±4.49	6.00±2.41
	p	0.176±0.06	0.120±0.05
Aggressive behavior	*n*	0.39±0.20	0
	p	0.007±0.01	0
Defensive behavior	*n*	3.20±1.28	0*
	p	0.054±0.02	0*
Total behavioral acts	*n*	63.20±7.65	51.80±6.49

Note. *n*, number of actions per experiment; *p*, probability; **p* <0.05 for the control group.
Примечание. *n* — количество актов; *p* — вероятность; **p* <0,05 к группе контроля.

Table 5. Animal's behavior in the Porsolt Forced Swim test after the intranasal administration of ML-00253764, *M*±SEM

Таблица 5. Поведение животных в тесте Порсолта после интраназального введения ML-00253764, *M*±SEM

Pattern		Control animals	Experimental animals
Active swimming	*n*	33.00±9.73	10.20±4.16
	t	354.64±67.38	310.66±71.89
Passive swimming	*n*	11.40±2.50	7.00±2.23
	t	196.59±82.45	272.87±75.36
Immobility	*n*	25.40±9.78	7.63±3.89
	t	43.04±15.37	7.63±6.21*
Diving	*n*	2.00±0.32	1.90±0.96
	t	5.72±1.44	16.07±8.19
Active swimming + diving	*n*	35.00±9.96	12.00±5.06
	t	360.36±68.49	320.40±73.50
Total behavioral acts	*n*	71.80±18.36	23.60±11.08*

Note. *n*, number of actions; *t*, time of the status, s; **p* <0.05 for the control group.
Примечание. *n* — количество актов; *t* — время состояния, с; **p* <0,05 к группе контроля.

to the antagonistic effects on MCR, particularly MC3R and MC4R, which are known to play a role in the regulation of stress responsiveness and cognitive functions. Our findings confirm that the melanocortin system, through its regulation of the hypothalamic-pituitary-adrenal axis and interactions with dopaminergic pathways, modulates exploratory behavior by reducing anxiety and enhancing motivation to explore new environments. It has been demonstrated that preventive MC4R blockade using the intranasally administered antagonist HS014 modulates transcriptomic changes in the rat brain induced by a single episode of prolonged stress. An accelerated inhibition of stress-response systems (within 30 minutes) was observed, along with attenuation or prevention of aberrant gene expression associated with post-traumatic stress disorder seven days after a single episode of prolonged stress. These findings suggest a potential neuroprotective role of MC4R antagonists in relation to transcriptional disturbances associated with post-traumatic stress disorder [18, 19].

The elevated plus maze test revealed a marked reduction in anxiety levels in rats that received the MSH antagonist, as evidenced by increased time spent in open arms and a higher frequency of head dips. These findings indicate a pronounced anxiolytic effect of the compound. Activation of melanocortin receptors such as MC4R may enhance stress responsiveness, whereas their blockade by an antagonist contributes to anxiety reduction. This can be explained by decreased activation of hypothalamic pathways involved in corticosteroid secretion. In a study by Sarkar et al. [20], the effect of α-MSH on cAMP response element-binding protein (CREB) phosphorylation

was assessed in hypothalamic paraventricular nucleus neurons producing thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRH). The results demonstrated that intracerebral administration of α-MSH increased CREB phosphorylation in these neurons, suggesting a potential role of α-MSH in regulating TRH and CRH function via CREB activation [19]. Intra-structural administration of an MC4R agonist into the medial amygdala produced an anxiogenic effect, as evidenced by a reduction in both the number of entries into open arms and the time spent there in the elevated plus maze test. In contrast, injection of SHU9110 into the medial amygdala blocked the anxiogenic effect elicited by immobilization stress [20]. In the resident–intruder test, administration of the MSH antagonist reduced the number of defensive behavior acts and completely eliminated aggressive responses. This suggests a normalizing effect of the drug on social behavior, which may also be related to reduced anxiety [21]. Previous studies have demonstrated that the melanocortin system is involved in the regulation of social interactions through its influence on the amygdala and hypothalamus. MC4R antagonists are capable of reducing stress responses to social stimuli, which is consistent with our observations [22, 23].

In the Porsolt forced swim test, the experimental group demonstrated a marked reduction in immobility time and the total number of acts, indicating a pronounced antidepressant effect. These results may be attributed to the activation of dopaminergic and serotonergic systems, as previously confirmed in studies using depressive behavior models [24, 25]. MC4R antagonists exert modulatory effects on neurotransmitter pathways involved in mood regulation, suggesting that the melanocortin system may be a promising target for antidepressant therapy [26, 27].

Our findings emphasize the crucial role of the melanocortin system in regulating emotional and cognitive functions. The MSH antagonist may be considered a potential candidate for the development of novel therapies for anxiety and depressive disorders, as well as for the management of social and cognitive impairments.

CONCLUSION

The present study demonstrates that the melanocortin system affects emotional and exploratory behavior, including anxiety, depressive-like states, and exploratory activity. MSH antagonists may serve as tools for modulating these processes, thereby opening new perspectives for the development of psychotropic agents.

ADDITIONAL INFO

Author contributions. S.S. Pyurveev, A.A. Lebedev, E.R. Bychkov: writing the article, analyzing the data, conducting the experiments; A.G. Pshenichnaya, M.E. Abrosimov, V.A. Lebedev, I.A. Balagansky: conducting the experiments; P.D. Shabanov: development of the general concept. The authors approved the version for publication, and also agreed to be accountable for all aspects of the work, ensuring proper consideration and resolution of issues related to the accuracy and integrity of any part of it.

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Disclosure of interests. The authors declare the absence of relationships, activities and interests over the past three years related to third parties (commercial and non-commercial), whose interests may be affected by the content of the article.

Statement of originality. When creating this work, the authors did not use previously published information (text, illustrations, data).

Data availability statement. All data obtained in this study are available in the article.

Generative artificial intelligence. No generative artificial intelligence technologies were used in the creation of this article.

Provenance and peer-review. This work was submitted to the journal on an unsolicited basis and reviewed according to the usual procedure. The review involved two external reviewers, a member of the editorial board, and the scientific editor of the publication.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. С.С. Пюрвеев, А.А. Лебедев, Е.Р. Бычков — написание статьи, анализ данных, проведение опытов; А.Г. Пшеничная, М.Е. Абросимов, В.А. Лебедев, И.А. Балаганский — проведение опытов; П.Д. Шабанов — разработка общей концепции. Авторы одобрили версию для публикации, а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

Этическая экспертиза. Проведение исследования одобрено локальным этическим комитетом ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России (№ 17/05 от 14.10.2022).

Источник финансирования. Работа выполнена в рамках государственного задания Минобрнауки России ФГБНУ «Институт экспериментальной медицины» FGWG-2025-0020 «Поиск молекулярных мишеней для фармакологического воздействия при аддиктивных и нейроэндокринных нарушениях с целью создания новых фармакологически активных веществ, действующих на рецепторы ЦНС».

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

Доступ к данным. Все данные, полученные в настоящем исследовании, доступны в статье.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента, член редакционной коллегии и научный редактор издания.

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AUTHORS' INFO

***Sarng S. Pyurveev,** MD, Cand. Sci. (Medicine);
address: 12 Akademika Pavlova st.,
Saint Petersburg, 199022, Russia; ORCID: 0000-0002-4467-2269;
eLibrary SPIN: 5915-9767; e-mail: dr.purveev@gmail.com

Andrei A. Lebedev, Dr. Sci. (Biology), Professor;
ORCID: 0000-0003-0297-0425; eLibrary SPIN: 4998-5204;
e-mail: aalebedev-iem@rambler.ru

Eugeny R. Bychkov, MD, Cand. Sci. (Medicine);
ORCID: 0000-0002-8911-6805; eLibrary SPIN: 9408-0799;
e-mail: bychkov@mail.ru

Anna G. Pshenichnaya; eLibrary SPIN: 1324-9710;
e-mail: pscanna@mail.ru

Maksim E. Abrosimov;
e-mail: abrosimov.m.e.@mail.ru

Viktor A. Lebedev, Cand. Sci. (Biology);
eLibrary SPIN: 1878-8392; e-mail: aalebedev-iem@rambler.ru

Ivan A. Balagansky; ORCID: 0009-0002-1752-0785;
e-mail: balaganskiiivan@mail.ru

Petr D. Shabanov, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0003-1464-1127; eLibrary SPIN: 8974-7477;
e-mail: pdshabanov@mail.ru

ОБ АВТОРАХ

***Сарнг Саналович Пюрвеев,** канд. мед. наук; адрес: Россия, 199022, Санкт-Петербург, ул. Академика Павлова, д. 12;
ORCID: 0000-0002-4467-2269; eLibrary SPIN: 5915-9767;
e-mail: dr.purveev@gmail.com

Андрей Андреевич Лебедев, д-р биол. наук, профессор;
ORCID: 0000-0003-0297-0425; SPIN: 4998-5204;
e-mail: aalebedev-iem@rambler.ru

Евгений Рудольфович Бычков, д-р мед. наук;
ORCID: 0000-0002-8911-6805; eLibrary SPIN: 9408-0799;
e-mail: bychkov@mail.ru

Анна Геннадьевна Пшеничная; eLibrary SPIN: 1324-9710;
e-mail: pscanna@mail.ru

Максим Евгеньевич Абросимов;
e-mail: abrosimov.m.e.@mail.ru

Виктор Андреевич Лебедев, канд. биол. наук;
eLibrary SPIN: 1878-8392; e-mail: aalebedev-iem@rambler.ru

Иван Андреевич Балаганский; ORCID: 0009-0002-1752-0785;
e-mail: balaganskiiivan@mail.ru

Петр Дмитриевич Шабанов, д-р мед. наук, профессор;
ORCID: 0000-0003-1464-1127; eLibrary SPIN: 8974-7477;
e-mail: pdshabanov@mail.ru

* Corresponding author / Автор, ответственный за переписку