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Research Article

A new ghrelin receptor antagonist agrelax participates in the control of emotional-explorative behavior and anxiety in rats

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BACKGROUND: Currently, no study has investigated on the role of ghrelin in the reinforcing system and emotional behavior. Previously, we examined the properties of GHSR1A antagonist [D-Lys3]-GHRP-6 to reduce negative emotional states caused by stress.

AIM: To study the involvement of a new peptide antagonist of the GHSR1A receptor agrelax in the control of emotional–exploratory behavior and anxiety in rats.

MATERIALS AND METHODS: Experiments were performed on 42 male Wistar rats. The behavior of rats was observed; agrelax 1 μg/mL (or water) with a volume of 20 μL (10 μl in each nostril) was administered intranasally. A battery of behavioral tests was used: an elevated plus maze, an open field, a marble test, an intruder–resident test, and an anxiety-phobic state assessment (FS).

RESULTS: In the elevated plus maze test, the time spent in the light arm and the number of hangings from the open arm increased in the test animals compared with animals that did not receive the drug ($p < 0.05$). After the administration of agrelax, the number of balloons buried and the number of elevations supported by the wall of the chamber in the marble test decreased compared with that in animals that did not receive the drug ($p < 0.05$). In the open field, agrelax-infected rats showed a decrease in the number of sniffs ($p \leqslant 0.01$). In the FS test after the agrelax administration, the time of descent from the platform decreased compared with the control ($p \leqslant 0.05$). In the "intruder–resident" test, individual behavior ($p \leqslant 0.01$) and protective behavior ($p \leqslant 0.05$) decreased after agrelax administration.

CONCLUSION: A new peptide antagonist of the GHSR1A receptor agrelax is involved in the control of emotional–exploratory behavior in rats. Agrelax reduced anxiety levels and exploratory activity. The results provide grounds for the development of new approaches to the treatment of phobic spectrum disorders using drugs that modulate ghrelin regulation.

Keywords: ghrelin; GHSR1A antagonist; agrelax; anxiety.

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Научная статья

Новый антагонист рецепторов грелина агрелакс участвует в контроле эмоционально-исследовательского поведения и уровня тревожности у крыс

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Актуальность. В настоящее время ощущается дефицит работ, посвященных роли системы грелина в механизмах подкрепления и эмоционального поведения. Ранее нами были изучены свойства антагониста GHSR1A [D-Lys3]-GHRP-6 снижать отрицательные эмоциональные состояния, вызванные стрессом.

Цель — изучение участия нового пептидного антагониста рецепторов GHSR1A агрелакса в механизмах контроля эмоционально-исследовательского поведения и уровня тревожности у крыс.

Материалы и методы. Опыты выполнены на 42 крысах-самцах линии Вистар. Интраназально за 10 мин до тестирования поведения вводили агрелакс 1 мкг/мл (или воду) объемом 20 мкл (по 10 мкл в каждую ноздрю). Использовали батарею поведенческих тестов: приподнятый крестообразный лабиринт, открытое поле, закапывание шариков, чужак — резидент, оценка тревожно-фобического состояния (ТФС).

Результаты. В тесте «приподнятый крестообразный лабиринт» время нахождения в светлом рукаве и число свешиваний с открытого рукава увеличивались по сравнению с животными, не получавшими препарат ($p < 0,05$). В тесте закапывания шариков число число подъемов с опорой на стенку камеры и число закопанных шариков снижались после введения агрелакса по сравнению с животными, не получавшими препарат ($p < 0,05$). В тесте «открытое поле» у крыс, которым вводили агрелакс, снижалось число обнюхиваний ($p \leqslant 0,01$). В тесте ТФС у крыс после введения агрелакса снижалось время спуска с платформы по сравнению с контролем ($p \leqslant 0,05$). В тесте «чужак — резидент» после введения агрелакса снижалось число актов индивидуального поведения ($p \leqslant 0,01$) и число актов, относящихся к защитному поведению ($p \leqslant 0,05$).

Заключение. Новый пептидный антагонист рецепторов GHSR1A агрелакс участвует в механизмах контроля эмоционально-исследовательского поведения у крыс. Агрелакс снижает уровень тревожности и исследовательскую активность. Полученные сведения дают основания для разработки новых подходов к лечению расстройств фобического спектра с использованием препаратов, модулирующих грелиновую регуляцию.

Ключевые слова: грелин; антагонист GHSR1A; агрелакс; тревожность.

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BACKGROUND

Ghrelin, a peptide hormone discovered in the late twentieth century [1], is produced in the gastric and intestinal mucosa, consists of 28 amino acids, and includes three isoforms, i.e., acylated ghrelin, non-acylated (desacyl-ghrelin), and obestatin [2]. The ghrelin receptor has two molecular forms, GHSR1A and GHSR1B, and only GHSR1A is associated with biological activity. GHSR1A receptors are located mostly in pancreatic islets, adrenal glands, thyroid gland, myocardium, and brain structures such as the anterior lobe of the pituitary gland, arcuate nucleus of the hypothalamus, hippocampus, substantia nigra, and ventral tegmental area [3]. Most studies have shown that ghrelin is involved in appetite regulation [4], controls the search behavior of finding psychostimulants [5] and alcohol [6], and participates in the brain's physiological response to stress [7]. Corticoliberin-producing neurons of the paraventricular nucleus of the hypothalamus and certain extrahypothalamic structures of the extended amygdala (central nucleus of the amygdala, nucleus accumbens, bed nucleus of the stria terminalis, and substantia innominata) mediating reinforcement and dependence mechanisms are considered possible targets of ghrelin involvement in stress response [8]. Studies have demonstrated that peripheral and central administration of ghrelin activates corticoliberin neurons [9] and, consequently, the hypothalamus–pituitary–adrenal system [10]. The activation of this system is important if ghrelin may have a protective role against the development of depressive symptoms in chronic stress [11].

Currently, only a few studies have focused on the role of the extrahypothalamic system of ghrelin in emotional research activity, and the mechanisms of influence of ghrelin receptors on reinforcement and emotional behavior under various environmental influences are quite unclear. Previously, peripheral and central administration of ghrelin activated corticoliberin neurons and, consequently, the hypothalamus–pituitary–adrenal system [12]. Researchers emphasize that ghrelin plays a protective role against the development of depressive symptoms under stress [13].

Agrelax, a peptide antagonist of ghrelin active against GHSR1A ghrelin receptors, was created at the Institute of Experimental Medicine [14]. Previously, the properties of the GHSR1A antagonist [D-Lys3]-GHRP-6 were examined to reduce stress-related negative emotional states [11].

The *study* aimed to investigate the involvement of a new peptide antagonist of the GHSR1A receptor agrelax in the control of emotional and exploratory behavior, and anxiety in rats.

MATERIALS AND METHODS

Experiments were conducted on 42 male Wistar rats weighing 200–220 g. They were kept in groups of 8–9 individuals in cages (53 × 32 × 19 cm) under 12-h artificial light and temperature of 22°C ± 2°C. Behavior was tested in rats sequentially (24–48 h apart), and agrelax, a ghrelin receptor antagonist, was administered intranasally at a concentration of 1 μg/mL (or water) for 20 μL (10 μL in each nostril) 10 min before testing [11]. A battery of behavioral tests was employed: open-field, elevated plus maze, marble test, "intruder–resident" test, and phobic anxiety assessment (PAA). Each group included at least 8–10 rats. The obtained data were processed statistically using Student's t-test and the analysis of variance. Differences were considered statistically significant at $p < 0.01$.

"Open-field" behavior of rats

The free motor activity of animals was investigated in the classical "open-field" test, which is a circular area with a diameter of 80 cm, bounded on the circumference by opaque boards with a height of 30 cm and having 16 holes (burrows) with a diameter of 3 cm each. The open field was illuminated by 100 lux. One experiment took three min. Horizontal and vertical motor activities, grooming reactions, and number of defecation boluses and urinations characterizing emotionality were recorded.

Aggression in the "intruder–resident" test

In the cage, a smaller animal was placed with a sexually mature male. The total number of behavioral acts of aggression, defense, and other behavioral displays were recorded.

Behavior in the elevated plus maze

A maze consisted of two 50 × 10 cm open arms and two 50 × 10 cm closed arms, with the top open and arranged perpendicularly to each other. The height was 1 m from the floor. The animal was placed in the center of the maze. The time spent in closed and open arms, time hanging in open arms, and number of peeks out of closed arms was recorded. The test was completed in five min.

Phobic anxiety in rats

In rats, phobic anxiety was investigated by species-specific reactions to a series of ethologically acceptable test stimuli provoking anxiety and fear in a special setup, as described by Lebedev et al. [15]. Test scores were summarized and then compared between different groups of animals.

Marble test

This obsessive–compulsive disorder model involves compulsive ideas and actions. Sawdust was placed in a 20 × 25 × 17 cm cage with a 5-cm layer and 20 glass marbles with a diameter of 1 cm were placed equidistantly on top. Rats were placed in the cage for 30 min. Then, the number of buried marbles covered by more than $^2/_3$ of sawdust was counted. In this experiment, each animal was tested three times [16, 17].

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Table 1. Animal behavior in the elevated cruciform maze test after the intranasal administration of agrelax (*M* ± *m*)
Таблица 1. Поведение животных в тесте «приподнятый крестообразный лабиринт» после интраназального введения агрелакса (*M* ± *m*)

Time of staying in separate maze compartments, s	Control animals (H_2O)	Animals after agrelax administration
Center	16.61 ± 7.00	5.31 ± 1.66*
Open arm	8.33 ± 6.55	23.97 ± 1.54*
Hanging up	5.45 ± 2.28	28.68 ± 7.85*
Open arm + hanging up	13.78 ± 7.77	30.65 ± 7.23
Closed arm	208.26 ± 12.56	184.43 ± 7.57
Peeking out	61.36 ± 13.99	0.63 ± 0.53**
Closed arm + peeking out	269.62 ± 11.65	264.06 ± 7.99
Number of arm-to-arm transitions	22.13 ± 3.07	11.75 ± 2.57*

*$p < 0.05$; **$p < 0.01$ between the compared groups of rats.

Statistical processing

GraphPad Prism version 5 and SPSS SigmaStat 3.0 were used for statistical data analysis. The Kolmogorov–Smirnov test was used to assess the conformity of the distributions of random variables. To compare the control and experimental groups, the non-parametric Wilcoxon test for pairwise comparisons and the one-factor analysis of variance, followed by multiple intergroup comparisons using the Newman–Keuls criterion, were applied. Data were presented as arithmetic mean ± standard deviation.

RESULTS AND DISCUSSION

The anxiolytic activity of the ghrelin antagonist was assessed in the elevated plus maze test. The time in the light and dark arms, grooming, and the number of hang-ups and runs were recorded. In the control group, the time in the light arm and the number of hang-ups from the open arms were 8.33 ± 6.55 and 5.45 ± 2.28 s, respectively. In the group receiving the ghrelin receptor antagonist agrelax intranasally, the time in the light arm and the number of hang-ups increased to 28.68 ± 7.85 and 28.68 ± 7.85 s ($p < 0.05$), respectively, compared with the group not receiving the drug ($p < 0.05$). After agrelax administration, the animals had decreased time to peek out ($p < 0.01$), were in the center of the maze ($p < 0.05$), and had fewer arm-to-arm transitions ($p < 0.05$) (Table 1).

In the marble test, the behavior of rats the agrelax-treated group differed from that of the control group (Table 2). In the agrelax-treated group, the number of buried marbles and the number of lifts with support on the chamber wall decreased compared with the control group ($p < 0.05$).

In the open-field test (Table 3), the agrelax-treated group had increased running time ($p < 0.01$), whereas the number of squares crossed did not change. In addition, the time, number, and probability of sniffing and the number and time of sniffing around were significantly reduced ($p < 0.01$) in animals that received agrelax compared with rats given water ($p < 0.01$). The total number of acts per experiment in the agrelax-treated group was significantly lower than that in the control group ($p < 0.05$).

In the total score, the PAA of the agrelax-treated group did not differ from that of the control group (Table 4). However, the time in descending the platform in the agrelax-treated group and, accordingly, the mean score decreased in test 1 compared with the control group ($p \leqslant 0.05$).

In the "intruder–resident" test, communicative behavioral acts, acts of aggression, and total number of movements were determined (Table 5). The number of acts of individual behavior ($p < 0.01$) and the total number of acts per experiment ($p < 0.01$) decreased in the aggrelax-treated group compared

Table 2. Animal behavior in the balloon burial test after the intranasal administration of agrelax (*M* ± *m*)
Таблица 2. Поведение животных в тесте закапывания шариков после интраназального введения агрелакса (*M* ± *m*)

Indices	Control animals (H2O)	Animals after agrelax administration
Number of buried marbles, *n*	11.38 ± 0.90	9.88 ± 0.04*
Number of lifts supported on the chamber wall, *n*	7.12 ± 0.56	5.45 ± 0.13*

*$p < 0.05$.

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with that in the control group. The agrelax-treated group had decreased number of defensive behavioral patterns compared with the control group intranasally injected with water ($p < 0.05$).

Thus, in the elevated plus maze test, agrelax showed moderate anxiolytic activity, increasing the time spent in the light arm compared with control animals and the number of peeks out of the closed arm and arm-to-arm transitions. Moreover, in the marble test, the number of buried marbles decreased after the administration of agrelax, which may be associated with a decrease in obsessive–compulsive disorder. In addition, a decrease in the latent time of descending the platform was observed in the PAA test. This is consistent with experimental and clinical evidence that the blockade of ghrelin receptors with the [D-Lys3]-GHRP-6 antagonist reduced manifestations of anxiety and fear after social isolation stress [18]. Furthermore, the results of the present experiments are in agreement with our previous results of intranasal course (7 days) administration of the ghrelin receptor antagonist [D-Lys3]-GHRP-6 after the presentation of a vital stressor [18]. The results of the intruder-resident test did not demonstrate a pronounced effect of agrelax on intraspecific communication activity, which is consistent with the data of Shabanov et al. [19]. The analysis of the open-field test scores showed that the number of sniffing, on-the-spot movements, and sums of all acts during the experiment were significantly reduced with agrelax administration. This is consistent with literature findings that antidepressants block the activation of ghrelin-induced behaviors. In this case, ghrelin penetrates from the

Table 3. Animal behavior in the open field test after the intranasal administration of agrelax ($M \pm m$)
Таблица 3. Поведение животных в тесте «открытое поле» после интраназального введения агрелакса ($M \pm m$)

Patterns		Control animals (H_2O)	Animals after agrelax administration
Locomotion	*n*	19.00 ± 2.51	17.63 ± 2.64
	p	0.130 ± 0.014	0.138 ± 0.017
	t	16.60 ± 1.98	40.84 ± 6.22**
Sniffing	*n*	67.63 ± 2.69	55.00 ± 2.28**
	p	0.472 ± 0.005	0.348 ± 0.009*
	t	115.17 ± 4.62	85.94 ± 5.99**
On-the-spot movement	*n*	39.25 ± 2.41	25.75 ± 1.77**
	p	0.277 ± 0.020	0.216 ± 0.024
	t	23.35 ± 2.29	14.26 ± 1.92**
Grooming	*n*	1.63 ± 0.53	3.13 ± 0.55
	p	0.012 ± 0.004	0.026 ± 0.005
	t	9.27 ± 3.34	14.40 ± 2.62
Vertical racks	*n*	2.13 ± 1.04	4.63 ± 1.61
	p	0.014 ± 0.007	0.036 ± 0.011
	t	1.90 ± 1.20	5.68 ± 1.93
Racks with a stop	*n*	4.75 ± 1.18	5.75 ± 1.49
	p	0.033 ± 0.007	0.044 ± 0.010
	t	5.29 ± 1.08	6.21 ± 1.57
Mink behavior	*n*	8.75 ± 1.09	11.25 ± 2.05
	p	0.060 ± 0.006	0.089 ± 0.014
	t	7.50 ± 0.55	11.65 ± 2.42
Freezing	*n*	0	0
	p	0	0
	t	0	0
Rest	*n*	0.13 ± 0.12	0.25 ± 0.24
	p	0.002 ± 0.001	0.003 ± 0.002
	t	0.92 ± 0.90	1.04 ± 1.01
Total of all acts		143.25 ± 5.38	123.38 ± 6.20*
Crossed squares	*n*	39.00 ± 4.55	38.38 ± 6.34
Number of boluses		1.75 ± 0.37	1.00 ± 0.38

p, probability of an act, *n*, number of acts; *t*, time of the act *$p < 0.05$; **$p < 0.01$ между between the compared groups of rats.

Table 4. Assessment of the anxiety-phobic state in male rats after agrelax administration (*M* ± *m*)
Таблица 4. Оценка тревожно-фобического состояния у самцов крыс после введения агрелакса (*M* ± *m*)

Tests	Control animals (H_2O)	Animals following agrelax administration
Test 1. Descending the platform	2.25 ± 0.49	1.01 ± 0.50*
Test 2. Passing through the hole	0.13 ± 0.08	0.38 ± 0.18
Test 3. Exiting the "house"	3.38 ± 0.08	3.31 ± 0.09
Test 4. Exiting the center of the "open field"	0.13 ± 0.12	0.13 ± 0.12
Test 5. Backward walking in the "open field"	0	0
Test 6. Backward walking on the hand movement	0.88 ± 0.29	0.88 ± 0.29
Test 7. Hiding	0.25 ± 0.24	0.35 ± 0.25
Test 8. Vocalization	0.38 ± 0.18	0.25 ± 0.16
Test 9. Pinching the ears	0.13 ± 0.12	0.13 ± 0.12
Score	7.50 ± 0.79	7.31 ± 0.70

* $p < 0.05$ между сравниваемыми группами крыс.

bloodstream through the blood–brain barrier, accumulates in hippocampal neurons, increasing animal activity, and acts directly on GHSR-1A receptors [20]. The 1A receptor is located in extrahypothalamic brain structures, i.e., in the hippocampus and other emotiogenic structures, namely, the amygdala, ventral tegmental area, and nucleus accumbens [21]. The wide distribution of ghrelin receptors in the brain suggests its involvement in various physiological functions, including the organization of emotions and motivations [22]. In addition, ghrelins, which are realized through the hypothalamus, control eating behavior, metabolism, and energy [23]. The 1A receptor is expressed in neurons of the arcuate nucleus of the hypothalamus, where neuropeptide Y, regulating food intake and satiety feeling, is localized [24].

CONCLUSIONS

Therefore, agrelax, a new OX1R antagonist, exhibits anxiolytic properties and reduces exploratory activity. Previously, the ghrelin antagonist [D-Lys3]-GHRP-6 was found to have anxiolytic properties but after chronic social isolation stress [18]. In intact animals, [D-Lys3]-GHRP-6 did not induce anxiolytic effects. The obtained data provide a basis for the development of new pharmacological approaches to the treatment of phobic spectrum disorders using drugs modulating ghrelin regulation.

ADDITIONAL INFORMATION

Authors 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. The contribution of each author: V.V. Lukashkova, A.G. Pshenichnaya, E.R. Bychkov, V.A. Lebedev, V.V. Rusanovsky — manuscript drafting, writing and pilot data analyses; A.A. Lebedev, P.D. Shabanov — general concept discussion.

Table 5. Behavior of rats in the "stranger–resident" test after the intranasal administration of agrelax
Таблица 5. Поведение крыс в тесте «чужак — резидент» после интраназального введения агрелакса (*M* ± *m*)

Behavior		Control animals (H_2O)	Animals following agrelax administration
Individual behavior	*n*	47.63 ± 2.86	28.00 ± 2.50**
	p	0.610 ± 0.018	0.513 ± 0.044
Communicative behavior	*n*	21.75 ± 2.77	18.88 ± 2.95
	p	0.274 ± 0.025	0.332 ± 0.030
Protective behavior	*n*	8.75 ± 1.96	7.88 ± 2.17
	p	0.105 ± 0.018	0.134 ± 0.028
Aggressive behavior	*n*	0.88 ± 0.39	1.13 ± 0.58
	p	0.011 ± 0.005	0.021 ± 0.009
Score	*n*	79.00 ± 6.11	55.89 ± 5.06**

n — количество актов за опыт, *p* — вероятность; *$p < 0.05$; **$p < 0.01$ между сравниваемыми группами крыс.

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

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