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Agrelax reduces conditioned place preference of ethanol and compulsive behavior in rats during its withdrawal

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ABSTRACT. ***Introduction***. Among the orexigenic peptides that mediate the emotional effects of psychoactive substances, the peptide hormone ghrelin attracts attention. It was shown that the ghrelin receptor antagonist agrelax, synthesized at the Institute of Experimental Medicine, reduced the manifestations of compulsive overeating and impulsivity in a model of gambling addiction. ***Aim***. To study the effect of agrelax on the conditioned place preference of ethanol and compulsive behavior against the background of its withdrawal in male rats. ***Materials and methods.*** A conditioned place preference of ethanol was developed in male rats in a two-chamber setup, over a period of eight days, for two hours per day. In the first hour, the rats were placed in the first chamber and administered saline solution. Then, ethanol (0.5 g/kg) was administered intraperitoneally and the rats were placed in the second compartment of the setup for 1 hour. On the 9th day, the doors between the compartments were opened, and the rat test groups were administered either agrelax (10μg in 20μL) intranasally, naloxone (1mg/kg) intraperitoneally, or simple saline, and the animal was placed in the setup for 10 min. Then, place preference extinction was carried out for seven days, which consisted of daily testing without the introduction of alcohol and other drugs. On the 11th day of the experiment, compulsive behavior was recorded by burying marbles in the marble test after the introduction of each of the substances. On the 18th day of the experiment, ethanol was administered and the resumption of the conditioned place preference reaction was recorded. Some animals were administered agrelax or naloxone 5 minutes before the introduction of ethanol to determine the effect on the resumption of the conditioned place preference reaction. ***Results.*** After the introduction of saline on the 8th day of the experiment, the animals spent 71% of the time in the chamber associated with the introduction of ethanol. In rats given agrelax or naloxone, a decrease in staying in the chamber associated with ethanol was observed, respectively, to 45% ($p < 0.05$) and 39% ($p < 0.01$). Naloxone caused a blockade of the renewal of preference for the ethanol chamber, which was manifested by a 26% decrease in the time spent in the preferred chamber associated with the introduction of ethanol. The ghrelin receptor antagonist agrelax (10μg in 20μl, intranasally) did not cause a decrease in the reproduction of the conditioned reaction of preference for the ethanol chamber. On the 10th day of the experiment, after the introduction of saline, the animals buried 17.2±2.3 marbles in the marble test. Agrelax and naloxone reduced the number of buried marbles against the background of ethanol withdrawal to 13±3.5 ($p < 0.05$) and 11±2.4 ($p < 0.05$), respectively. ***Conclusion.*** Agrelax reduces the manifestation of the conditioned reaction of ethanol place preference and compulsive behavior in rats against the background of its withdrawal, which is comparable to the effect of naloxone. At the same time, unlike naloxone, agrelax did not cause a decrease in the resumption of ethanol place preference. Thus, we demonstrate the important role of the ghrelin system in the mechanisms of the reinforcing effect of alcohol, which invites further investigation into the use of new ghrelin antagonists in the correction of pathological craving.

Keywords: ghrelin, agrelax, conditioned reaction of place preference, alcohol, compulsivity

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Оригинальная статья
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Агрелакс снижает условную реакцию предпочтения места этанола и компульсивное поведение крыс на фоне его отмены

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РЕЗЮМЕ. ***Введение.*** Среди орексигенных пептидов, опосредующих эмоциональные эффекты психоактивных веществ, привлекает внимание пептидный гормон грелин. Показано, что антагонист рецептора грелина агрелакс, синтезированный в ФБГНУ «Институт экспериментальной медицины», снижал проявления компульсивного переедания и импульсивности в модели игровой зависимости. ***Цель.*** Изучить влияние агрелакса на условную реакцию предпочтения места введения этанола и компульсивное поведение на фоне его отмены у самцов крыс. ***Материалы и методы.*** У самцов крыс вырабатывали условную реакцию предпочтения места введения этанола в двухкамерной установке. В течение 8 дней вводили физиологический раствор и помещали животное в отсек установки на 1 ч. Через 2 ч вводили этанол (0,5 г/кг внутрибрюшинно) и производили посадку в другой отсек установки на 1 ч. На 9-й день открывали дверцы между отсеками, вводили вещество (агрелакс 10 мкг в 20 мкл интраназально или вещество сравнения налоксон 1 мг/кг внутрибрюшинно) или физиологический раствор и помещали животное в установку на 10 мин. Затем производили угашение предпочтения места в течение 7 дней, которое заключалось в ежедневном его тестировании без введения алкоголя и иных препаратов. На 11-й день эксперимента регистрировали компульсивное поведение по закапыванию шариков после введения веществ. На 18-й день эксперимента производили введение этанола и регистрировали возобновление условной реакции предпочтения места. Части животных вводили агрелакс или налоксон за 5 мин до введения этанола для определения влияния на возобновление условной реакции предпочтения места. ***Результаты.*** После введения физиологического раствора в 8-й день эксперимента животные проводили в ассоциированной с введением этанола камере 71% времени. У крыс, получавших агрелакс или налоксон, наблюдали снижение времени пребывания в камере, ассоциированной с этанолом, до 45% ($p < 0,05$) и 39% ($p < 0,01$) соответственно. Налоксон вызывал блокаду возобновления предпочтения места введения этанола, что проявлялось уменьшением на 26% времени нахождения в предпочитаемой камере, ассоциированной с введением этанола. Антагонист рецепторов грелина агрелакс (10 мкг в 20 мкл, интраназально) не вызывал снижения воспроизведения условной реакции предпочтения места введения этанола. На 10-й день эксперимента после введения физиологического раствора животные закапывали 17,2±2,3 шарика в marble-тесте. Агрелакс и налоксон снижали число закопанных шариков на фоне отмены этанола до 13±3,5 ($p < 0,05$) и 11±2,4 ($p < 0,05$) соответственно. ***Заключение.*** Агрелакс снижает проявление условной

реакции предпочтения места введения этанола и компульсивное поведение крыс на фоне его отмены, что сравнимо с действием налоксона. В то же время в отличие от налоксона агрелакс не вызывает снижения возобновления предпочтения места введения этанола. Таким образом, показана важная роль системы грелина в механизмах подкрепляющего действия алкоголя и перспектива использования новых антагонистов грелина в коррекции патологического влечения.

Ключевые слова: грелин, агрелакс, условная реакция предпочтения места, алкоголь, компульсивность

Источник финансирования. Исследование выполнено в рамках государственного задания 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».

INTRODUCTION

Among the neuropeptides mediating the emotional effects of psychoactive substances [1], the peptide hormone ghrelin, discovered in the late XX century, has attracted considerable attention [2]. Ghrelin is produced in the gastric mucosa, consists of 28 amino acids, and exists in three isoforms: acylated ghrelin, unacylated (desacyl-ghrelin), and obestatin [3, 4]. The ghrelin receptor has two molecular forms; however, biological activity is attributed exclusively to the first form, GHSR1A. The ghrelin receptor is localized in the pancreas, adrenal glands, thyroid gland, myocardium, as well as in brain structures including the anterior pituitary, arcuate nucleus of the hypothalamus, hippocampus, substantia nigra, and ventral tegmental area [5]. Ghrelin has been shown to increase food intake via its action on the hypothalamus, which has led to its designation as a “hunger hormone” [6]. Furthermore, ghrelin stimulates appetite, thereby participating in the regulation of food motivation [7, 8].

In recent years, ghrelin has also been demonstrated to participate in the reinforcement mechanisms underlying the development of alcohol and drug dependence [7]. Thus, following ghrelin administration, ethanol intake in alcohol-experienced rats increased extracellular dopamine levels in the ventral tegmental area [9]. Food restriction, which elevates ghrelin levels [10], has also been shown to increase amphetamine- and cocaine-induced locomotor activity, enhance cocaine-seeking behavior, and elevate cocaine and amphetamine self-administration in rats [11]. Intracerebroventricular and intra-VTA administration of ghrelin increased alcohol consumption in mice [12, 13].

Ghrelin is involved in stress mechanisms, as corticotropin-releasing hormone (CRH) is considered one of the potential targets of ghrelin in the stress response. Ghrelin has been shown to activate CRH neurons in mice [14]. Extrahypothalamic targets directly affected by ghrelin include the extended amygdala circuitry — a stress-responsive brain system that mediates reinforcement and addiction mechanisms [15]. Ghrelin administration has been demonstrated to activate CRH neurons and, consequently, the hypothalamic-pituitary-adrenal (HPA) axis [16]. Activation of this axis is essential when ghrelin exerts a protective role against the development of depressive symptoms under chronic stress [17].

AIM

The aim of this study was to investigate the involvement of ghrelin and its receptor antagonist [D-Lys3]-GHRP-6 in the mechanisms of conditioned reinforcement in rats with long-term ethanol consumption.

MATERIALS AND METHODS

Animals. A total of 46 male Wistar rats obtained from the Rappolovo laboratory animal nursery (Leningrad Region) were used in the study. The animals were housed in standard plastic cages, 8–10 individuals per cage, with free access to food and water under an inverted light cycle from 8:00 to 20:00 at a temperature of 22±2 °C. All experiments were conducted during the autumn–winter period.

Conditioned place preference pest. To establish conditioned place preference (CPP) for ethanol administration in rats, a two-compartment apparatus with distinct floor textures (smooth vs. grid) was used. During CPP acquisition, animals were sequentially placed into two compartments separated by a partition for 30 min each, with a 2 h interval between sessions, over 8 consecutive days. During the 1 h interval between sessions, rats were kept in their home cages. Prior to placement into the first compartment, rats received an intraperitoneal injection of 0.9% sodium chloride solution (saline); prior to placement into the second compartment, animals were injected intraperitoneally with ethanol at a dose of 0.5 g/kg. The control group received saline intraperitoneally in the second compartment. To control for potential effects of floor texture on the acquisition of ethanol-induced CPP, experimental animals were divided into two subgroups. Rats in the first subgroup were initially placed into the compartment with a grid floor, and those in the second subgroup — into the compartment with a smooth floor. To assess the acquisition of ethanol-induced CPP, on day 9 of the experiment, the time spent in compartments with different floor textures was recorded over 15 min under conditions of free movement within the two-compartment apparatus. The data were expressed as the percentage of time spent in the ethanol-paired compartment relative to the total test duration. In subsequent experiments, only animals that spent more than 60% of the time

in the alcohol-paired compartment (chamber preference criterion) were used. Such animals constituted approximately half of all rats in which CPP acquisition was attempted. On day 9 of the experiment, these animals received a single intranasal administration of the ghrelin receptor antagonist Agrelax at a dose of 10 μg in 20 μL, or intraperitoneal naloxone at a dose of 1 mg/kg, without ethanol administration, to evaluate the effects of these substances on CPP expression. Control animals under the same experimental conditions received an equivalent dose of saline intranasally or intraperitoneally. Place preference extinction was then conducted over 7 days, which consisted of daily testing without ethanol or any drug administration. On day 11 of the experiment, compulsive behavior was assessed using the marble-burying test following drug administration. By day 7 of extinction, CPP was no longer observed, i.e., animals spent approximately equal time in both compartments. On day 18 of the experiment, ethanol was administered and reinstatement of conditioned place preference was assessed. Ethanol (0.5 g/kg) was administered intraperitoneally, the animal was placed into the apparatus for 10 min, and CPP reinstatement (spending more than 60% of time in the ethanol-paired compartment) was recorded. Some animals received Agrelax or naloxone 5 min prior to ethanol administration to determine their effects on the reinstatement of conditioned place preference. A subset of animals (9 rats) received a single additional intranasal administration of the ghrelin receptor antagonist Agrelax (10 μg) 5 min prior to ethanol administration, another subset (10 rats) received intraperitoneal naloxone (1 mg/kg), and another subset (9 rats) received 20 μL of saline, to assess their effects on CPP reinstatement.

Pharmacological substances. The ghrelin receptor antagonist Agrelax, synthesized at the Institute of Experimental Medicine, was used in the study. It was dissolved in distilled water at a concentration of 0.5 mg/mL and administered intranasally at a dose of 10 μg in 20 μL (10 μL per nostril). Naloxone (Tocris, England) was dissolved in distilled water and administered intraperitoneally at a dose of 1 mg/kg. Control animals received an equivalent volume (20 μL) of 0.9% sodium chloride solution.

Statistical significance was assessed using SPSS SigmaStat 3.0 and GraphPad Prism 6 software by one-way analysis of variance (ANOVA). One-way ANOVA was used to compare the control and experimental groups. The nonparametric Kruskal–Wallis test was applied for group comparisons. Differences were considered statistically significant at $p < 0.05$. Data are presented as mean ± standard error of the mean (SEM).

RESULTS

A total of 52 rats from the same delivery were included in the experiment. Eight animals comprised the control group, which received 0.9% sodium chloride solution instead of ethanol during CPP acquisition. Animals with established ethanol-induced CPP were divided into three groups: 8 animals received intranasal administration of 20 μL of 0.9% sodium chloride solution during testing, 8 animals received naloxone (1 mg/kg) as a reference drug, and 8 animals received intranasal administration of Agrelax solution at a dose of 20 μg in 20 μL. The data presented below are from animals used to assess the anti-alcohol effects of ghrelin peptides and the reference compound naloxone. Control animals receiving intranasal 20 μL of saline spent 81.5±5.7% of the total time in the CPP chamber ($p < 0.05$ vs. control). The opioid receptor antagonist naloxone reduced the time spent in the CPP chamber (to 55.8±6.9% of the total time), while the ghrelin receptor antagonist Agrelax reduced the time spent in the CPP chamber (to 63.8±4.7% of the total time) (Fig. 1). Thus, naloxone significantly affected

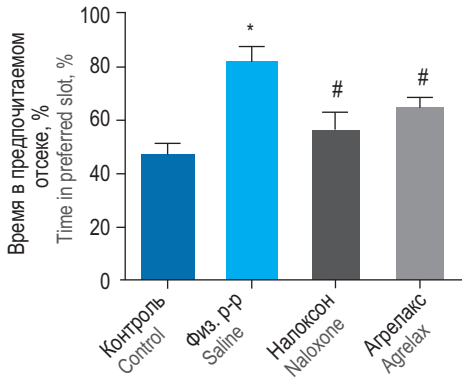

Fig. 1. Expression of conditioned place preference response (CPPR) of ethanol. * — p <0.05 in relation to the control; # — p <0.05 in relation to the group with the production of CPPR with ethanol (drawing by the authors)

Рис. 1. Экспрессия условной реакции предпочтения места (УРПМ) введения этанола. * — p <0,05 по отношению к контролю; # — p <0,05 по отношению к группе с выработкой УРПМ введения этанола (рисунок авторов)

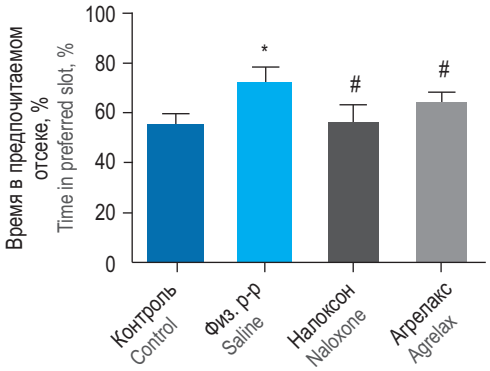

Fig. 2. **Reinstatement conditioned place preference response (CPPR) with ethanol. * — p <0.05 in relation to the control; # — p <0.05 in relation to the group with the production of CPPR with ethanol (drawing by the authors)**

Рис. 2. Возобновление условной реакции предпочтения места (УРПМ) введения этанола. * — p <0,05 по отношению к контролю; # — p <0,05 по отношению к группе с выработкой УРПМ введения этанола (рисунок авторов)

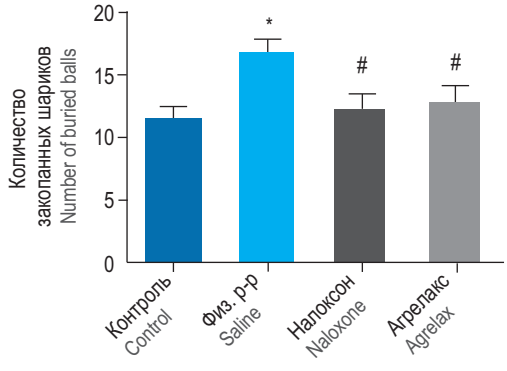

Fig. 3. **Number of buried marbles in marble test after ethanol withdrawal. * — p <0.05 in relation to the control; # — p <0.05 in relation to the group with the production of conditioned place preference responsewith ethanol (drawing by the authors)**

Рис. 3. Число закопанных шариков в marble-тесте на фоне отмены этанола. * — p <0,05 по отношению к контролю; # — p <0,05 по отношению к группе с выработкой условной реакции предпочтения места введения этанола (рисунок авторов)

CPP expression, while the ghrelin antagonist Agrelax blocked the expression of the response, manifested as a decrease in the time spent in the preferred chamber associated with ethanol administration.

The ethanol CPP extinction test revealed that animals spent 55.1±4.2% of the total time in the ethanol-paired chamber, indicating that CPP was not expressed and did not reach the 60% preference criterion. Following ethanol administration (priming), rats demonstrated reinstatement of CPP, spending on average 72.1±5.7% of the total time in the alcohol-paired chamber ($p < 0.05$). The ghrelin receptor antagonist Agrelax (10 μg in 20 μL, intranasally) did not reduce the reinstatement of ethanol-induced CPP following ethanol challenge. Naloxone blocked the reinstatement of ethanol-induced place preference, manifested as a decrease in the time spent in the preferred ethanol-paired chamber to 52.9±11.2% (Fig. 2).

In the marble-burying test on day 10 of the experiment, following saline administration, animals buried 16.6±±1.3 marbles. Naloxone and Agrelax reduced the number of marbles buried during ethanol withdrawal to 12.2±1.2 ($p < 0.05$) and 12.7±1.4 ($p < 0.05$), respectively (Fig. 3).

DISCUSSION

The present study demonstrated that intranasal administration of the peptide ghrelin antagonist Agrelax delayed the acquisition of ethanol-induced CPP in rats. However, expression of ethanol-induced CPP following extinction was not reduced by Agrelax administration. A similar effect was previously shown by our group following administration of the ghrelin receptor antagonist [D Lys3]-GHRP-6 on ethanol-induced place preference in intact rats. However, unlike Agrelax, [D Lys3]-GHRP-6 reduced CPP expression and its reinstatement after extinction [17]. Agrelax reduced the expression of ethanol-induced conditioned place preference and compulsive behavior during ethanol withdrawal, an effect comparable to that of naloxone. However, unlike naloxone, Agrelax did not reduce the reinstatement of ethanol-induced place preference. These findings are generally consistent with the literature regarding the potential involvement of the ghrelin system in reinforcement mechanisms [18]. In particular, several studies have shown that the central ghrelin system is important for intracranial reinforcement processes activated by addictive substances [19,20]. For example, administration of the ghrelin receptor antagonist [D Lys3]-GHRP-6 significantly reduced the reinforcing properties of amphetamine as well as the psychomotor stimulant cocaine. Of interest are our previously reported data [17] demonstrating that intraperitoneal administration of ethanol at doses of 0.5, 0.75, and 1.5 g/kg may possess both reinforcing and aversive properties, and that the re-

inforcing effects do not always increase with increasing ethanol dose. Low doses of ethanol (0.5–0.75 g/kg) typically exhibit a clear reinforcing effect, in this case associated with the preferred CPP chamber. This appears to be related to individual differences among animals within the heterogeneous study population.

The present study demonstrates the involvement of the central ghrelin system in the mechanisms of pathological alcohol craving and the potential utility of ghrelin receptor antagonists for reducing reinforcement activated by this system. Studies on the ghrelin system reported in the scientific literature have primarily focused on the regulation of feeding behavior [21]. In particular, it has been shown that food restriction, which elevates ghrelin levels [22], also increases amphetamine- or cocaine-induced locomotor activity, enhances cocaine-seeking behavior, and elevates cocaine and amphetamine self-administration in rats [13].

Our findings are also consistent with other experiments using the ghrelin receptor antagonist [D Lys3]-GHRP-6, which is structurally a fragment of substance P, the main representative of the neurokinins involved in the regulation of alcohol and psychoactive substance consumption.

A significant reduction in the reinforcing properties of ethanol has been demonstrated, as measured by dopamine levels in the nucleus accumbens and behavioral parameters (locomotor activity and conditioned place preference). The study of the physiological role of ghrelin and its receptors in the mechanisms of reinforcement and dependence on psychoactive substances, as well as the effects of ghrelin ligands on emotional, exploratory, and motor activity during alcohol exposure and stress, represents a relevant problem for both physiology and neuropharmacology. Indeed, the ghrelin system is increasingly considered a target for pharmacological intervention [13]. However, no studies have been conducted to date examining the regulation of emotional, exploratory, and motor activity during chronic alcohol exposure by ghrelin or components of its system (desacyl-ghrelin, obestatin).

In contrast, intracerebroventricular or local administration of ghrelin into the ventral tegmental area increased alcohol consumption in mice [13]. Furthermore, the effect of ghrelin was shown to be most pronounced in rodents with prior alcohol experience, as peripheral ghrelin administration to alcohol-naive rats only marginally increased alcohol intake [13,23]. Thus, ghrelin and its GHSR1A receptors may regulate the level of consumption and seeking of addictive substances. This suggests that treatment of patients with alcohol dependence using pharmacological agents targeting the ghrelin system may represent a promising direction in modern psychopharmacology and biological addiction medicine.

CONCLUSION

Thus, the novel ghrelin receptor antagonist Agrelax reduced the expression of ethanol-induced conditioned place preference and compulsive behavior in rats during ethanol withdrawal, an effect comparable to that of naloxone. However, unlike naloxone, Agrelax did not reduce the reinstatement of ethanol-induced place preference. This study demonstrates the important role of the ghrelin system in the mechanisms underlying the reinforcing effects of alcohol and the potential of novel ghrelin receptor antagonists for the correction of pathological craving.

ADDITIONAL INFORMATION

Authors' contribution. 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.

Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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