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Research Article

Pharmacological analysis of the role of kisspeptin-10 in reinforcing mechanisms

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Abstract

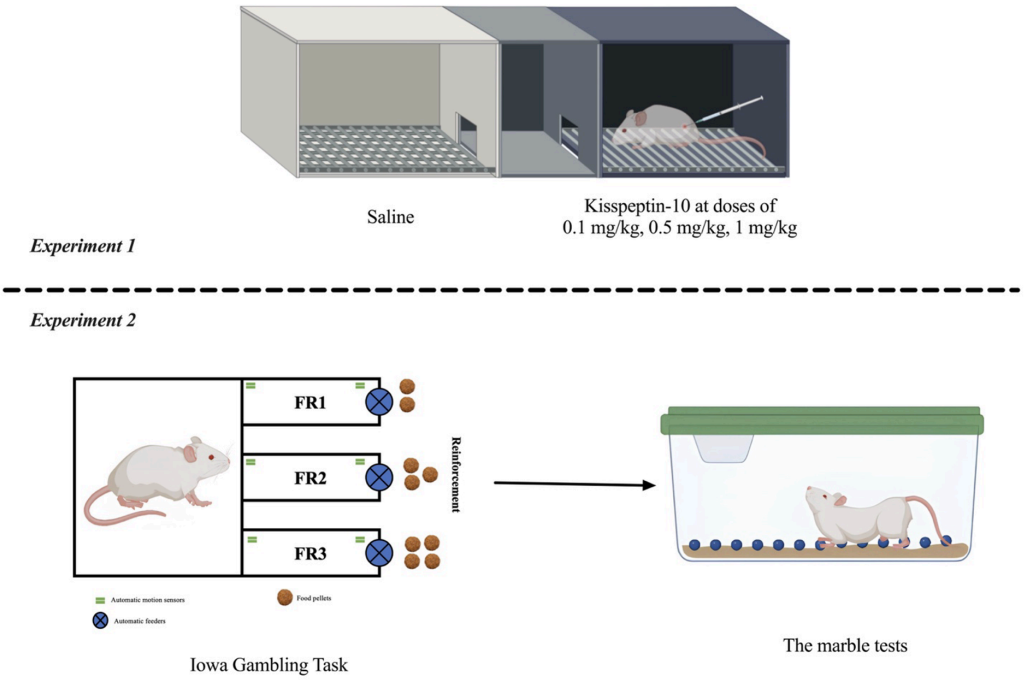
Introduction: Behavioral and substance addictions are driven by shared neurobiological mechanisms, often involving the reward system. Kisspeptin-10, a neuropeptide primarily linked to reproductive functions, has emerged as a potential modulator of reward-related behaviors and decision-making. This study explores the effects of kisspeptin-10 on impulsivity, compulsivity, and reinforcement mechanisms.

Materials and Methods: Male Wistar rats were used to assess the effects of kisspeptin-10 on behavior. A conditioned place preference (CPP) test evaluated reinforcement effects at doses of 0.1 mg/kg, 0.5 mg/kg, and 1 mg/kg. A modified Iowa Gambling Task analyzed decision-making and impulsivity under variable reinforcement schedules. The marble-burying test was employed to assess compulsive behaviors. Statistical analysis included one-way ANOVA and Tukey's post-hoc test.

Results and Discussion: Kisspeptin-10 at 1 mg/kg induced a significant CPP response, suggesting reinforcing properties. In the gambling task, kisspeptin-10 enhanced impulsive choices by increasing preference for riskier reinforcement schedules, contrasting with the stabilizing effects of paroxetine. In the marble-burying test, kisspeptin-10 increased compulsive behavior compared to paroxetine, underscoring its modulatory role in compulsivity. These effects likely reflect kisspeptin-10's interaction with dopaminergic and serotonergic systems, extending its influence beyond reproductive functions.

Conclusion: Kisspeptin-10 dose 1 mg/kg significantly modulates impulsive and compulsive behaviors, as well as reinforcing mechanisms, highlighting its potential as a therapeutic target for conditions characterized by dysregulated decision-making and compulsivity.

Graphical abstract



Keywords

kisspeptin-10, impulsivity, compulsivity, reinforcement, conditioned place preference, behavioral addiction

Introduction

Addiction, whether to substances or behaviors, poses a major challenge for public health, with substantial social and economic implications (Lebedev et al. 2023). Behavioral addictions, such as gambling disorder, share core features with substance use disorders, including compulsive engagement, loss of control, and persistent behavior despite negative consequences (Dighton et al. 2022). These similarities suggest overlapping neurobiological mechanisms involving the brain's reward system. Understanding the molecular and neural circuits underlying behavioral addictions is crucial for developing effective therapeutic strategies.

Kisspeptin, a neuropeptide primarily known for its role in reproductive regulation via the hypothalamic-pituitary-gonadal axis, has emerged as a potential modulator of reward and emotional behaviors (Mills et al. 2018). Recent studies indicate that kisspeptin and its receptor (KISS1R) are expressed in brain areas implicated in reward processing, including the hypothalamus, amygdala, and ventral tegmental area (Seminara et al. 2023). This raises the intriguing possibility that kisspeptin may influence reinforcement mechanisms, making it a candidate for modulating addictive behaviors. Kisspeptin is a hypothalamic neuropeptide, the peptide product of the KISS-1 gene, and an endogenous agonist of the Kiss1 receptor (Kiss-R). Centrally, kisspeptin stimulates the secretion of gonadotropin-releasing hormone (GnRH). It interacts with other neuropeptides to generate GnRH and also plays a role in the regulation of sexual behavior (Heitman et al. 2008). Kisspeptin is derived from a peptide consisting of 145 amino acids (preprokisspeptin), which is then transformed into its immediate precursor, kisspeptin-54. From kisspeptin-54, shorter peptides such as kisspeptin-14, kisspeptin-13, and kisspeptin-10 are subsequently synthesized (Aquino et al. 2019).

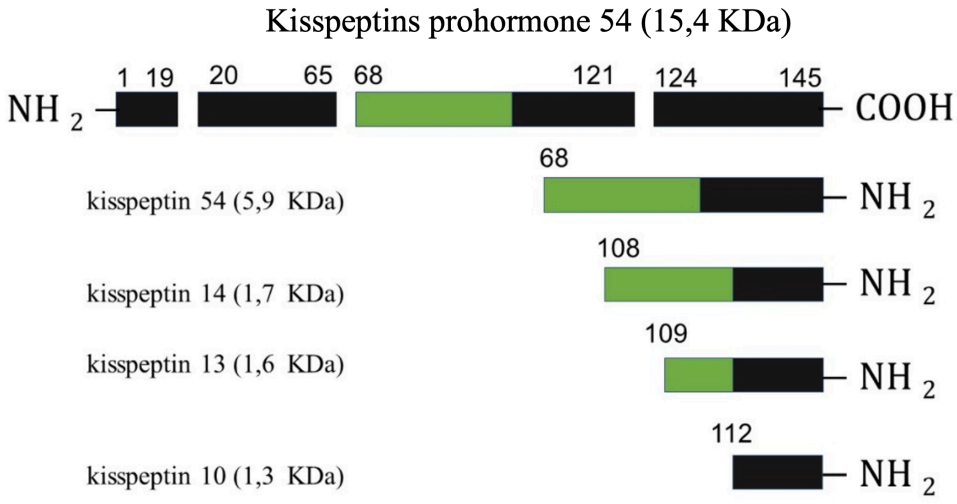


Figure 1. Main structural features of kisspeptins formed as a result of post-stranding modification of prohormone.

Recent studies suggest that kisspeptin also interacts with the dopamine system in both fish and mammals, contributing to its multifaceted effects on behavior and physiology (Lehman et al. 2013; Aquino et al. 2019). Kisspeptin can influence dopaminergic neurons, particularly those in the hypothalamus, which play a pivotal role in the regulation of reproductive and motivated behaviors. Kisspeptin neurons are located close to dopaminergic populations in the arcuate nucleus and preoptic area, facilitating direct or indirect interactions (Mills et al. 2019). Dopaminergic neurons in the tuberoinfundibular system (TIDA) are critical for inhibiting prolactin secretion. Kisspeptin's modulation of these neurons could influence prolactin levels, integrating reproductive and metabolic cues (Aquino et al. 2019). This positions kisspeptin as a potential mediator of reinforcement mechanisms associated with both physiological and pathological states.

The CPP model provides a robust framework for investigating whether kisspeptin administration can elicit rewarding effects through environmental conditioning. By associating a specific context with kisspeptin exposure, this paradigm can reveal its ability to influence place preference, shedding light on its role in reward perception. Concurrently, gambling addiction models simulate risk-based decision-making and reward sensitivity, offering a platform to assess how kisspeptin modulates compulsive behaviors tied to uncertain rewards.

Furthermore, behavioral addictions are often accompanied by alterations in stress and emotion regulation, systems also influenced by kisspeptin (Csabafi et al. 2023). By interacting with the hypothalamic-pituitary-adrenal (HPA) axis and stress-sensitive brain regions, kisspeptin may indirectly impact behaviors driven by heightened stress or anxiety, which frequently co-occur with compulsive gambling and other behavioral addictions (Ibos et al. 2021; Tissen et al. 2023).

Materials and Methods

Animals

Male rats Wistar with aged 6-7 weeks old and weighing 200-250 g were used in this study. Rats were obtained from the breeding nursery of laboratory animals were from the "«Rappolovo"», Leningrad region (Russia). The rats were acclimatized for 14 days under the standard condition consisting of a constant temperature (25±1°C) and a 12-hour light/dark cycle. In addition, food and water were given ad libitum. The study has been designed to reduce the number of animals. The animal was only used once and was not involved in another study. All treatments were designed to minimize the animal suffering. The study plan, standardized operating procedures, and the accompanying documentation were subjected to ethical review by the local ethical committee at St. Petersburg State

Pediatric Medical University, Minutes №17/05 dated 14.10.2022, Ministry of Health Care of the Russian Federation.

Conditioned Place Preference (CPP) test

To establish a CPP response to kisspeptin-10 in rats, a two-chamber apparatus with smooth and grid floors was used. During the conditioning phase, animals were sequentially placed in the two chambers, separated by a partition, for 30 minutes each, with a 1-hour interval between placements, over the course of four days. During the 1-hour interval, rats were kept in their home cage. Prior to being placed in the first chamber, the rats received an intraperitoneal injection of saline. Before being placed in the second chamber, they were administered an intraperitoneal injection of kisspeptin-10 at the doses of 0.1 mg/kg, 0.5 mg/kg, or 1 mg/kg. The control group received saline injections in the second chamber as well. To evaluate the development of CPP to kisspeptin-10, on the sixth day of the experiment, the time the animals spent in each compartment was recorded over a 15-minute period under free movement conditions within the apparatus (Tissen et al. 2021). The following groups were formed: rats receiving saline acting as control (n=11) three groups for three doses of the drug (n=10).

A variant of the Iowa Gambling Task test of "reinforcement probabilities and magnitudes"

The food reinforcement setup included a starting platform (33 × 50 × 35 cm) and 3 arms (50 × 15 ×35 cm) (Fig. 2). At the end of each arm was an automatically controlled feeder. Food reinforcement was provided when the feeder was reached in each arm of the three-arm maze. When the animal exited the arm to the starting area, the next reinforcement was given. Training was performed each day. Runs to the feeder and returns to the starting chamber were tested for 10 min, and no additional cues were given. Animals were fed daily, with feeding time limited to 4 h, and free access to water was provided (Lebedev et al. 2023). Food deprivation was maintained before each experiment for 20 h. Animals were trained in a three-arm maze for 21 days. A sunflower seed served as reinforcement. A training regimen of food reinforcement was used during the first days of the experiment. At each choice of arm 1, animal received one seed. At each choice of arm 2, two seeds were given, and at each choice of arm 3, and three seeds were given. The training regimen of food reinforcement feeding lasted for 5 days. No experiments were performed for the next two days (Lebedev et al. 2022). On the 8th day of training, the mode of food reinforcement was changed. Two seeds were fed in arm 1 (reinforcement mode FR1_2). At the same time, each reach of the feeder was reinforced with food. In arm 2, three seeds were presented in FR2_3 mode, and every second run to the feeder was reinforced with food; in arms 3, 4, seeds were presented in FR3_4 mode (i.e. only every 3rd run to the feeder was reinforced with food). Thus, 1/2 of the runs to arm 2 and 2/3 of the runs to arm 3 of the mazes remained without reward. Rats were trained for 2 weeks in this regimen. Rats that did not enter the maze arms were removed from the experiment (no more than 15%) (Pyurveev et al. 2024). The following groups were formed: rats receiving saline acting as control (n=10); rats receiving the antidepressant paroxetine (n=8) and rats receiving kisspeptin-10 (n=8).

The marble burying test

The animals were examined to quantify their status of anxiety, obsessive compulsive behavior, or repetitive behavior. A 5-cm layer of sawdust was placed in into a 20 × 25 × 17-cm cage, and 1-cm -diameter glass beads were placed equidistantly. The rat was placed in the cage for 30 min. After which, the number of balls covered by sawdust by more than 2/3 was counted. The number of buried balls per experiment was determined. In this experiment, each animal was tested thrice (Pyurveev et al. 2024). The following groups were formed: rats receiving saline acting as control (n=10); rats receiving the antidepressant paroxetine (n=8) and rats receiving kisspeptin-10 (n=8).

Drugs

To establish a conditioned place preference (CPP) response, kisspeptin-10 (Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH2) (Sigma, USA) was used. Kisspeptin-10 was administered intraperitoneally at the doses of 0.1 mg/kg, 0.5 mg/kg, or 1 mg/kg during the acquisition of the CPP response. The control group received an equivalent volume of 0.9% sodium chloride solution.

For the tests of "reinforcement probabilities and magnitudes" and "marble test", we used course administration (7 days) of the drugs. Kisspeptin-10 was administered intraperitoneally at a dose of 1 mg/kg 40 minutes before the start of the experiment. Paroxetine, provided by Ozon Pharmaceuticals (Russia), served as a comparison drug. Paroxetine was administered intraperitoneally dissolved in distilled water and administered at a dose of 1 mg/kg.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 10 (GraphPad Software Inc., USA). The Shapiro-Wilk test was used to assess the normality of data distribution. Group comparisons were conducted using one-way ANOVA followed by Tukey's post-hoc test for comparisons with the control group. Data are presented as "mean±standard deviation". Differences were considered statistically significant at $p < 0.05$.

Results

In the first experiment, we investigated which dose of kisspeptin-10 could induce the formation of a conditioned place preference. During the CPP assessment, rats that received intraperitoneal injections of 0.5 mL of saline did not exhibit place preference, spending approximately equal amounts of time in both chambers. On average, they spent 436.6 ± 11.75 seconds in the chamber associated with saline administration. One-way ANOVA revealed statistically significant differences between groups ($F(3,37) = 4.525$, $p = 0.0084$). Subsequent post hoc analysis using Tukey's test showed that only intraperitoneal administration of kisspeptin-10 at a dose of 1 mg/kg significantly increased the time spent in the chamber associated with drug administration ($p < 0.004$, Fig. 2). In contrast, intraperitoneal administration of kisspeptin-10 at the doses of 0.1 mg/kg and 0.5 mg/kg did not lead to a statistically significant increase in time spent in the chamber associated with the drug. The obtained results demonstrated that kisspeptin-10 at a dose of 1 mg/kg exhibits pronounced reinforcing properties, as evidenced by an increase in the time spent by rats in the drug-paired chamber during the CPP test. Lower doses (0.1 mg/kg and 0.5 mg/kg), however, did not elicit significant behavioral changes compared to the control group, indicating a dose-dependent effect.

Thus, our findings suggest a potential role for kisspeptin-10 in modulating reinforcing behavior, possibly through its impact on neurotransmitter systems involved in positive reinforcement.

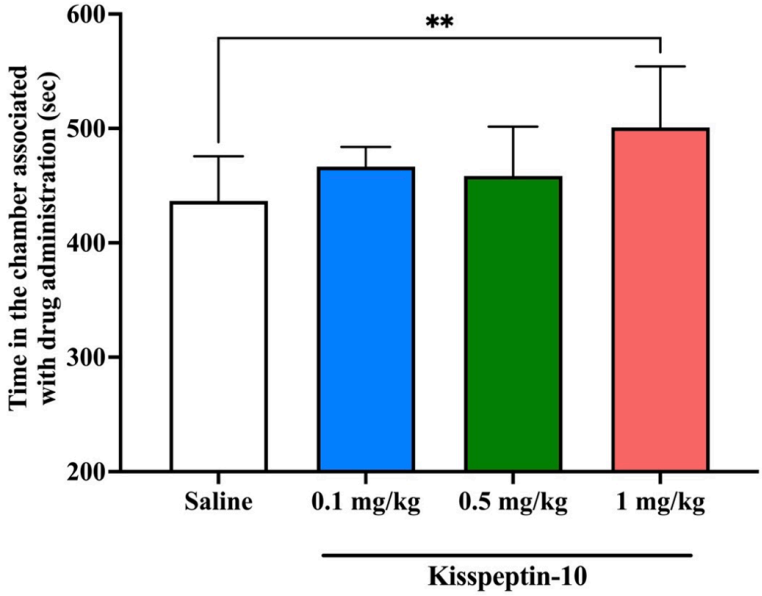


Figure 2. Conditioned site preference response to intraperitoneal injection of kisspeptin-10 at doses of 0.1 mg/kg, 0.5 mg/kg, and 1 mg/kg. Data are presented as arithmetic mean ± error of the mean. ***Note:*** ** – $p < 0.01$ – relative to the group receiving saline. One-way ANOVA and Tukey"s test for multiple comparisons of mean.

In our modified version of the IOWA test, which evaluates reinforcement magnitude and probability, we assessed the number of entries into each arm of a maze under variable-probability reinforcement conditions in groups receiving intraperitoneal injections of physiological saline, the selective serotonin reuptake inhibitor paroxetine at 1 mg/kg, and kisspeptin-10 at 1 mg/kg.

To analyze the effect of paroxetine at a dose of 1 mg/kg on impulsivity-like behavior, a one-way analysis of variance (ANOVA) was performed, revealing significant differences in the percentage of arm entries in the setup ($F(2, 21) = 9.701$, $p = 0.001$, Fig. 3). Subsequent *post hoc* analysis using Tukey's test showed that animals receiving paroxetine injections significantly preferred the less risky option with the FR1 reinforcement schedule ($p = 0.04$).

To assess the effect of kisspeptin-10 at a dose of 1 mg/kg on impulsivity-like behavior, another one-way ANOVA was conducted, also demonstrating significant differences in the percentage of arm entries ($F(2, 21) = 13.55$, $p = 0.0002$). The post hoc Tukey's test revealed that animals injected with kisspeptin-10 significantly more often preferred the riskier option with the FR3 reinforcement schedule ($p = 0.03$).

ANOVA analysis also showed significant differences ($F(2, 23) = 4.26$, $p = 0.02$) in the percentage of entries into the riskier arm with the FR3 reinforcement schedule between animals injected with kisspeptin-10 and those injected with paroxetine ($p = 0.003$).

These findings indicate that paroxetine and kisspeptin-10 exert opposing effects on the regulation of impulsive choices. Paroxetine reduces risk-taking behavior, while kisspeptin-10 increases the propensity to select risky reinforcement options. These results underscore the potential role of kisspeptin-10 in modulating decision-making mechanisms and its possible involvement in processes associated with heightened impulsivity.

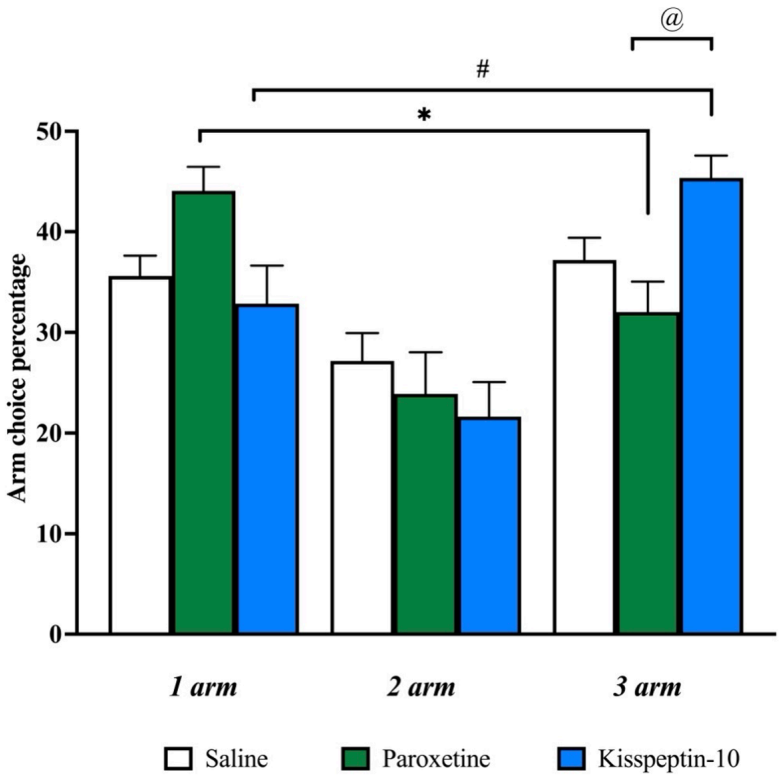


Figure 3. Behavior of experimental animals in behavioral tests. The influence of drugs on the behavior of rats in a situation of choosing the probability and strength of food reinforcement in a three-arm maze. Data are presented as arithmetic mean ± error of the mean. *Note*: * – $p \leq 0.05$ intragroup difference of entries into different arms of the three-arm maze in animals receiving paroxetine; # – $p \leq 0.05$ intragroup differences of entries into different arms of the three-arm maze in animals receiving kisspeptin-10; @ – $p \leq 0.05$ intergroup comparison of entries into the third arm of the three-arm maze in animals receiving paroxetine and kisspeptin-10. One-way ANOVA and Tukey's test for multiple comparisons of mean.

On being placed in a cage containing 20 evenly spaced glass marbles, a rat generally approached a marble within 60 seconds. Typically, it would sniff one or more marbles before proceeding to grasp one with its forepaws and push it around with the snout, forepaws or hindlimbs. These episodes alternated with bouts of exploration of the cage floor, walls and roof. When it returned to the marbles, the rats would repeat the process or include variations such as pushing sawdust towards marbles with the snout or forelimbs, or rats diged holes in the sawdust and pushed marbles. Again, these bouts alternated with general exploration, or with periods of quite resting or grooming.

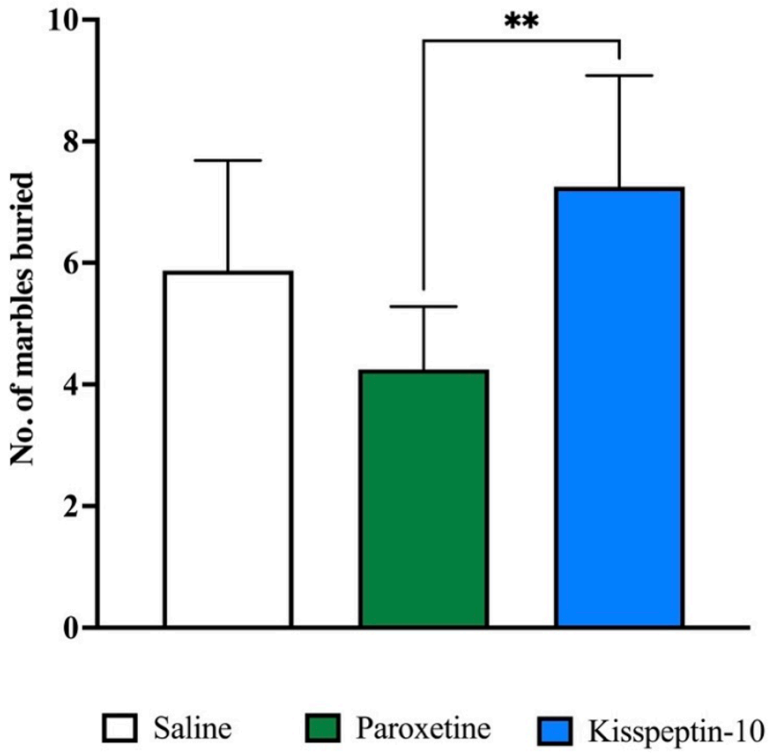


Figure 4. Behavior of experimental animals in behavioral tests. The effect of drugs on compulsive behavior in the balloon marble test. Data are presented as arithmetic mean ± error of the mean. ***Note*:** ** – $p \leq 0.001$ intergroup comparison of the number of burying marbles in animals treated with paroxetine and kisspeptin-10. One-way ANOVA and Tukey's test for multiple comparisons of mean.

A one-way ANOVA revealed statistically significant differences in the number of marbles buried more than two-thirds deep following drug administration ($F(2, 21) = 7.03$, $p = 0.004$, Fig. 4). Subsequent *post hoc* analysis using Tukey's test showed that animals receiving an injection of kisspeptin-10 exhibited a significant increase in the number of buried marbles compared to the paroxetine-treated group ($p = 0.003$). However, no significant differences were identified between the other groups. Thus, the results of the analysis demonstrated that kisspeptin-10 administration induces a significant increase in the number of buried marbles, which may indicate an enhancement of compulsive behavior in animals. This effect was statistically significantly higher compared to the paroxetine-treated group, known for its properties in reducing anxiety-related and compulsive responses, as evidenced by the absence of heightened activity in this group.

The lack of significant differences between the kisspeptin-10 and control (saline-treated) groups may suggest that the effect of kisspeptin-10 on this behavioral model is specific and not comparable to baseline animal behavior under control conditions. Additionally, the absence of significant differences between the paroxetine and control groups supports the hypothesis that paroxetine stabilizes compulsive behavior at levels observed in the control group.

Discussion

The current study aimed to investigate the effects of kisspeptin-10 on reward-associated behaviors, impulsive choice, and compulsive tendencies, with a comparative analysis against saline and the selective serotonin reuptake inhibitor paroxetine. Our findings provide novel insights into the behavioral modulation associated with kisspeptin-10, a neuropeptide primarily implicated in the regulation of reproduction and sexual behavior, highlighting its broader influence on impulsivity and compulsivity.

In the conditioned place preference test, kisspeptin-10 at a dose of 1 mg/kg significantly increased the time spent in the drug-paired chamber, while lower doses (0.1 mg/kg and 0.5 mg/kg) did not elicit significant effects. This dose-dependent response suggests that kisspeptin-10 exerts reinforcing properties akin to other reward-associated stimuli. In our previous work, it was shown for the first time that repeated intranasal injections of kisspeptin-10 induced the production of URPM in rats (Tissen et al. 2021). This suggests that kisspeptin-10 is able to activate the reward system or brain regions related to this system, which ultimately leads to the formation of an emotional-positive state. Given the established role of kisspeptin in stimulating gonadotropin-releasing hormone (GnRH) release and activating reward pathways in the brain, such as the ventral tegmental area (VTA) and nucleus accumbens, these results align with its proposed role in modulating reward-related behaviors. These findings highlight the capacity of kisspeptin-10 to influence neural circuits underlying reinforcement, extending its role beyond reproductive functions (Gibula-Tarlowska et al. 2019; Tissen et al. 2021).

The results from the modified IOWA test reveal that kisspeptin-10 promotes impulsive-like behavior, as evidenced by a preference for the riskier FR3 reinforcement schedule. This effect contrasts with that of paroxetine, which reduced risk-taking behavior and increased preference for the less risky FR1 schedule. Impulsivity, a hallmark of several psychiatric conditions, is closely associated with dopaminergic activity in brain regions such as the prefrontal cortex and striatum. The observed effects of kisspeptin-10 may be mediated through its modulation of dopamine pathways, which are also involved in sexual motivation and arousal (Aquino et al. 2019). Previous research has demonstrated that kisspeptin-10 enhances sexual behavior, a phenomenon that may be partially driven by its ability to amplify risk-taking tendencies and diminish inhibitory control (Tissen et al. 2023).

In the marble-burying test, an established model of compulsive-like behavior, kisspeptin-10 significantly increased the number of buried marbles compared to paroxetine. This effect suggests that kisspeptin-10 may enhance compulsive tendencies, a finding consistent with its impulsivity-enhancing properties. The lack of significant differences between the kisspeptin-10 and control groups warrants further investigation but may indicate that kisspeptin-10's effects are context-dependent and influenced by specific behavioral paradigms. Notably, the stabilizing effect of paroxetine on compulsive behaviors, demonstrated by its similarity to control levels, underscores its efficacy in mitigating anxiety-driven responses (Chakhava et al. 2010; Himanshu et al. 2020).

The dual enhancement of impulsivity and compulsivity by kisspeptin-10 could be linked to its role in sexual behavior (Franssen et al. 2018; Mills et al. 2019). Both impulsivity and compulsivity are integral to mating strategies in animal models, with impulsivity facilitating risk-taking and pursuit of potential mates, and compulsivity ensuring sustained attention to mating-related stimuli (Seminara et al. 2003; Putteerak et al. 2016). Kisspeptin-10's effects on these behaviors may reflect an evolutionary adaptation that prioritizes reproductive success, potentially at the expense of inhibitory control in other domains. Mood and emotions play a crucial role in maintaining optimal reproductive health. Research indicates that mood disorders in individuals are often linked to reduced sexual desire and lower fertility rates. Given the complex interactions between reproduction, mood, and emotions, it is reasonable to suggest that they may be governed by similar hormonal processes (Putteerak et al. 2016). The antidepressant-like effects of kisspeptins have been observed in male mice through a modified forced swimming test. In this experiment, rodents are placed in a water-filled container and their behaviors are evaluated for active actions (such as swimming and climbing) and passive behaviors (like immobility), which indicate antidepressant and depressant effects, respectively. The findings showed that administering kisspeptin directly into the brain ventricles enhanced active behaviors (increased climbing and swimming) while decreasing the time spent immobile (Tanaka et al. 2013).

Intracranial administration of kisspeptin in zebrafish results in a greater number of top-to-bottom transitions during a novel tank diving test, indicating improved exploratory behavior and lower anxiety levels (Lebedev et al. 2022). It was shown, mammalian kisspeptin analogs Kiss1 reduce anxiety-phobic responses to novelty in *Danio rerio*.

Data on the unidirectional effects of mammalian kisspeptin analogs and serotonin-type antidepressants support the potential role of Kiss1 in modulating serotonin-dependent behaviours in *Danio rerio*. The data obtained support the hypothesis that kisspeptin may be involved in the regulation of anxiety-phobic states, apparently to maintain the emotional aspects of reproductive behavior, such as sexual motivation and arousal (Lebedev et al. 2022). Studies have shown that social isolation in *Danio rerio* fish reduces communicative behavior. Mammalian kisspeptin analogs, teleost kisspeptin Kiss1, and oxytocin normalize fish communicative behavior after a period of social isolation to the level of the control group (Goltz et al. 2023; Goltz et al. 2024).

Additionally, a recent study examined the effects of central administration of the octapeptide kisspeptin-8 on anxiety responses in rodents. In this research, adult male rats exhibited anxiogenic effects, as evidenced by reduced time spent in the open arm of an elevated plus maze (EPM) and elevated corticosterone levels (Ibos et al. 2021).

Conclusion

The findings from this study demonstrate that kisspeptin-10 at a dose of 1 mg/kg significantly influences impulsive and compulsive behaviors, likely through its modulation of reward and decision-making circuits. These results provide valuable insights into the neurobehavioral effects of kisspeptin-10, emphasizing its potential role beyond reproduction. Future studies should investigate the specific neural mechanisms underlying these effects, including the involvement of dopamine and serotonin systems, and explore whether these findings translate to human models. Additionally, understanding the interaction between kisspeptin-10 and environmental factors, such as stress or prior reinforcement history, could further elucidate its role in regulating complex behaviors.

Additional information

Conflict of interest

The authors declare no conflict of interests.

Ethical statement

The study plan, standardized operating procedures, and the accompanying documentation were subjected to ethical review by the local ethical committee at St. Petersburg State Pediatric Medical University, Minutes №17/05 dated 14.10.2022, Ministry of Health Care of the Russian Federation.

Funding

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Data availability

All of the data that support the findings of this study are available in the main text.

References

- Aquino NSS, Kokay I.C, Perez CT, Ladyman SR, Henriques PC, Silva JF, Broberger C, Grattan DR, Szawka RE (2019) Kisspeptin stimulation of prolactin secretion requires Kiss1 receptor but not in tuberoinfundibular dopaminergic neurons. Endocrinology 160(3): 522–533. https://doi.org/10.1210/en.2018-00932 [PubMed]
- Chakhava VO, Budtueva FS, Borukaev RR (2010) Efficacy of adepress (paroxetin) in generalized anxiety disorder. Korsakov Journal of Neuropathology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova] 110(8): 25–29. [PubMed] [in Russian]
- Csabafi K, Ibos KE, Bodnár É, Filkor K, Szakács J, Bagosi ZA (2023) Brain region-dependent alteration in the expression of vasopressin, corticotropin-releasing factor, and their receptors might be in the background of Kisspeptin-13-induced hypothalamic-pituitary-adrenal axis activation and anxiety in rats. Biomedicines 11(9): 2446. https://doi.org/10.3390/biomedicines11092446 [PubMed] [PMC]
- Dighton G, Kitchiner N, Larcombe J, Rogers D. et al (2022) Gambling problems among United Kingdom armed forces veterans: Associations with gambling motivation and posttraumatic stress disorder. International Gambling Studies 23(12): 1-22. https://doi.org/10.1080/14459795.2022.20

- Franssen D, Tena-Sempere M (2018) The kisspeptin receptor: A key G-protein-coupled receptor in the control of the reproductive axis. Best practice & research. Clinical Endocrinology & Metabolism 32(2): 107–123. https://doi.org/10.1016/j.beem.2018.01.005 [PubMed]
- Gibula-Tarlowska E, Grochecki P, Silberring J, Kotlinska JH (2019) The kisspeptin derivative kissorphin reduces the acquisition, expression, and reinstatement of ethanol-induced conditioned place preference in rats. Alcohol (Fayetteville, N.Y.) 81: 11–19. https://doi.org/10.1016/j.alcohol.2019.04.001 [PubMed]
- Golts VA, Lebedev AA, Blazhenko AA, Lebedev VA, Bayramov AA, Khokhlov PP, Bychkov ER, Pyurveev SS, Kazakov SV, Shabanov PD (2023) Comparison of anxiolytic effects of mammalian and bony fish kisspeptins in Danio rerio. Psychopharmacology and Biological Narcology 14(2): 85–96. https://doi.org/10.17816/phbn501442 [in Russian]
- Goltz VA, Lebedev AA, Eresko SO, Airapetov MI, Pyurveev SS, Bychkov ER, Bayramov AA, Lebedev VA, Shabanov PD (2024) Kiss1 kisspeptin of bony fish and mammalian kisspeptin analogs enhance the communicative behavior of *Danio rerio* induced by social isolation. Reviews on Clinical Pharmacology and Drug Therapy 22(2): 191–203. https://doi.org/10.17816/RCF625892 [in Russian]
- Heitman LH, Ijzerman AP (2008) G protein-coupled receptors of the hypothalamic-pituitary-gonadal axis: a case for Gnrh, LH, FSH, and GPR54 receptor ligands. Medicinal Research Reviews 28(6): 975–1011. https://doi.org/10.1002/med.20129 [PubMed]
- Himanshu D, Deepa Sarkar N (2020) A review of behavioral tests to evaluate different types of anxiety and anti-anxiety effects. Clinical Psychopharmacology and Neuroscience: the official scientific journal of the Korean College of Neuropsychopharmacology 18(3): 341–351. https://doi.org/10.9758/cpn.2020.18.3.341 [PubMed] [PMC]
- Ibos KE, Bodnár É, Bagosi Z, Bozsó Z, Tóth G, Szabó G, Csabafi K (2021) Kisspeptin-8 induces anxiety-like behavior and hypolocomotion by activating the HPA axis and increasing GABA release in the nucleus accumbens in rats. Biomedicines 9(2): 112. https://doi.org/10.3390/biomedicines90201121 [PubMed] [PMC]
- Pyurveev SS, Lebedev AA, Bychkov ER, Shabanov PD (2024) Intranasal administration of ghrelin receptor antagonist [D-Lys-3]-GHRP-6 reduces the manifestations of impulsivity and compulsivity induced by maternal deprivation in rats. Research Results in Pharmacology. 10(2): 97–106. https://doi.org/10.18413/rrpharmacology.10.448
- Lebedev AA, Blazhenko AA, Goltz VA, Devyashin AS, Lebedev VA, Kazakov SV, Bayramov AA, Khokhlov PP, Bychkov ER, Shabanov PD (2022) Effects of kisspeptin analogues on the behavior of Danio rerio. Reviews on Clinical Pharmacology and Drug Therapy 20(2): 201–210. https://doi.org/10.17816/RCF202201-210
- Lebedev AA, Purveev SS, Sexte E.A, Reichardt BA, Bychkov ER Shabanov PD (2023) Studying the involvement of ghrelin in the mechanism of gambling addiction in rats after exposure to psychogenic stressors in early ontogenesis. Journal of Evolutionary Biochemistry and Physiology 59: 1402–1413. https://doi.org/10.1134/S1234567823040316
- Lehman MN, Hileman SM, Goodman RL (2013) Neuroanatomy of the kisspeptin signaling system in mammals: comparative and developmental aspects. Advances in Experimental Medicine and Biology 784: 27–62. https://doi.org/10.1007/978-1-4614-6199-9_3 [PubMed] [PMC]
- Mills EGA, Dhillo WS, Comninos AN (2018) Kisspeptin and the control of emotions, mood and reproductive behaviour. The Journal of Endocrinology 239(1): R1–R12. https://doi.org/10.1530/JOE-18-0269 [PubMed]
- Mills EGA, O'Byrne KT, Comninos AN (2019) Kisspeptin as a behavioral hormone. Seminars in Reproductive Medicine 37(2): 56–63. https://doi.org/10.1055/s-0039-3400239 [PubMed]
- Pastuszak AW, Badhiwala N, Lipshultz LI, Khera M (2013) Depression is correlated with the psychological and physical aspects of sexual dysfunction in men. International Journal of Impotence Research 25(5): 194–199. https://doi.org/10.1038/ijir.2013.4 [PubMed]
- Putteeraj M, Soga T, Ubuka T, Parhar IS (2016) A "timed" kiss is essential for reproduction: lessons from mammalian studies. Frontiers in Endocrinology 7: 121. https://doi.org/10.3389/fendo.2016.00121 [PubMed] [PMC]
- Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JS, Jr, Shagoury JK, Bo-Abbas Y, Kuohung W, Schwinof KM, Hendrick AG, Zahn D, Dixon J, Kaiser UB, Slaugenhaupt SA, Gusella JF, O'Rahilly S, Carlton MB, Crowley WF, Jr Aparicio SA, Colledge WH (2003) The GPR54 gene as a regulator of puberty. The New England Journal of Medicine 349(17): 1614–1627. https://doi.org/10.1056/NEJMoa035322 [PubMed]
- Sivalingam M, Parhar IS (2022) Hypothalamic kisspeptin and kisspeptin receptors: Species variation in reproduction and reproductive behaviours. Frontiers in Neuroendocrinology 64: 100951. https://doi.org/10.1016/j.yfrne.2021.100951 [PubMed]
- Tanaka, M, Csabafi K, Telegdy G (2013) Neurotransmissions of antidepressant-like effects of kisspeptin-13. Regulatory Peptides 180: 1–4. https://doi.org/10.1016/j.regpep.2012.08.017 [PubMed]
- Tissen IY, Lebedev AA, Tsikunov SG, Shabanov PD (2023) Kisspeptin reduces sexual dysfunction in a rat model of posttraumatic stress disorder. Psychopharmacology & Biological Narcology 14(4): 237–244. https://doi.org/10.17816/phbn623033 [in Russian]
- Tissen IY, Chepik PA, Lebedev AA, Magarramova LA, Bychkov ER, Shabanov PD (2021) Conditioned place preference of kisspeptin-10. Reviews on Clinical Pharmacology and Drug Therapy 19(1): 47–53. https://doi.org/10.17816/RCF19147-53 [in Russian]

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