

The novel AMPA glutamate receptor antagonist zampaxidol attenuates binge eating potentiated by foot-shock stress

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Abstract

Introduction: Binge eating is linked to the brain reward system, modulated by glutamatergic projections affecting the mesolimbic dopamine pathway. This study explored AMPA receptor antagonists' effects on binge eating and stress-induced feeding behavior. **The aim** was to investigate the effects of the GluA1 AMPA receptor antagonist zampaxidol (IEM-2131) and the reference compound IEM-1460 in a binge eating model, and to demonstrate zampaxidol's antagonistic activity at AMPA receptors.

Materials and Methods: vivo experiments were performed on 42 adult male Wistar rats (250–300 g) divided into three groups (n = 14): intact control, IEM-1460 (3 mg/kg, i.p.), and zampaxidol (1 mg/kg, i.p.). In vitro experiments were conducted on 16 isolated Danio rerio neurons. Foot shock was used as stress. Antagonists' effects on kainic acid-induced ionic currents were examined via patch clamp.

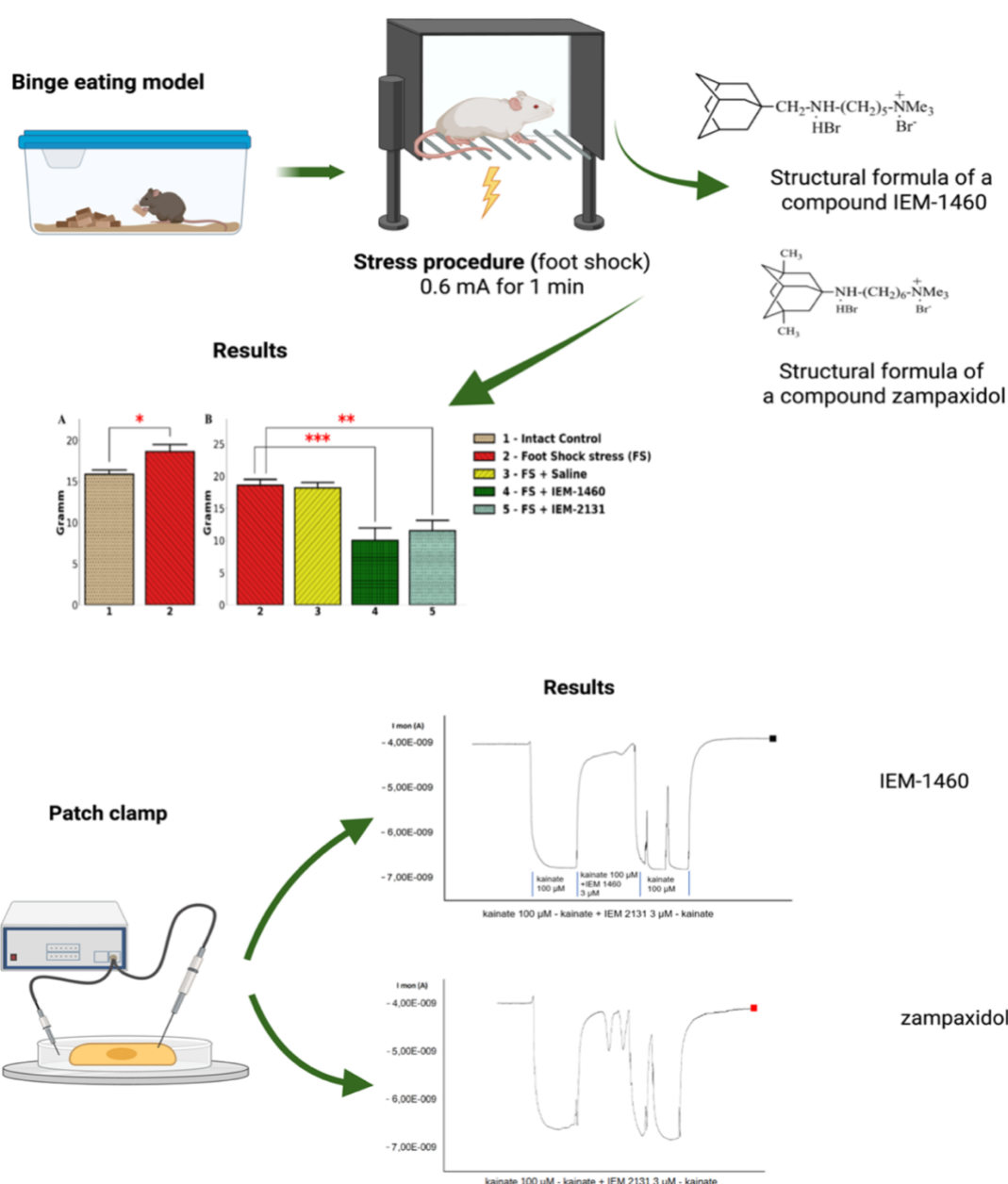
Results and Discussion: Zampaxidol and IEM-1460 reduced mean chocolate mixture consumption to 11.5 ± 1.6 g and 10.0 ± 0.9 g, respectively, significantly lower than in the no-intervention group (15.9 ± 0.5 g) and the foot-shock-only group (18.6 ± 0.9 g). Both compounds produced a pronounced blocking effect on AMPA receptors. Zampaxidol's IC₅₀ was 0.65 ± 0.27 μ M.

Conclusions: The findings highlight the essential role of GluA1 AMPA receptors in food addiction. IEM-1460 (3 mg/kg, i.p.) and zampaxidol (1 mg/kg, i.p.) demonstrated high efficacy in a rat binge eating model potentiated by foot-shock stress. AMPA receptor antagonists may be useful for treating psychogenic stress-induced binge eating.



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Graphical Abstract



Keywords

binge eating; AMPA-selective glutamate receptor 1; GluA1 protein; hyperphagia; IEM-1460; zampaxidol; patch clamp technique

Introduction

Binge eating is one of the most prevalent eating disorders (Saguy and Gruys 2010). Individuals who are diagnosed with bulimia nervosa or binge eating disorder exhibit similar patterns of compulsive overeating, neurobiological features such as dysfunctional cognitive control and food addiction, and biological and environmental risk factors (Wu et al. 2014). The majority of foods in the modern market are synthetic and therefore more palatable because of increased content of fats, sugars compared to natural ones and the presence of flavour enhancers. The

removal of fibres, water and proteins from food makes defeating faster and thereby increases the impact on the reward system (Gearhardt and Schulte 2021). Some studies show that the effect of palatable foods on a reward system analogous to addictive drugs become the key for generation of the food addiction concept (Carter et al. 2016). Furthermore, growing body of literature illustrating that those who overeat high palatable foods have similar symptoms to those who suffer from officially recognized addictions (from alcohol, drugs, etc.): the loss of control under quantity of eaten, unsuccessful attempts to give up, development of tolerance, the presence of withdrawal symptoms in the absence of addictive foods, as well as the continued eating of harmful products despite the negative consequences (Gearhardt and Schulte 2021).

The brain reward system, consisted of prefrontal cortex, amygdala, ventral tegmental area (VTA), and nucleus accumbens (NAc), and mediated for the most part with dopamine, has a substantial role in formation and maintenance of addictions (Jacques et al. 2019). It is known that stress is very important for the development of addictions. It could activate the hypothalamic-pituitary-adrenal axis, which, in turn, modulates several processes, including feeding behavior (Goeders 2003; Lebedev et al. 2023).

Dopamine cells of the VTA and the terminal area of the mesolimbic system, NAc, get glutamatergic projections from prefrontal cortex, amygdala and hippocampus (Cai and Tong 2022), which are involved in the reward assessment in addictions (Weidacker et al. 2020). Glutamatergic projections activate VTA cells and stimulate dopamine release in the NAc (Tzschentke and Schmidt 2000). The NAc dopamine release is mainly regulated by AMPA (not NMDA) receptors (Youngren et al. 1993). During the formation of addiction, the proportion of AMPA/NMDA receptor changes towards increasing AMPA receptors, leading to synaptic plasticity of the excitatory synapses of the VTA dopaminergic neurons (Van Huijstee and Mansvelder 2015). Elevation of the AMPA receptors (AMPA) activity in the postsynaptic membrane of VTA dopaminergic neurons is related to the replacement of the GluA2 subunit in existing AMPARs or the inclusion of new AMPARs containing GluA1 subunits from the cytoplasmic pool. Eventually, the augmentation of conductivity through AMPA neurons and permeability to calcium ions is observed (Morrell et al. 2008). Addictive behavior causes a growth in the number of GluA1 AMPARs and lessens the proportion of GluA2 AMPARs in the VTA and NAc decreases (Vekovischeva et al. 2001). Moreover, it was shown that in drug withdrawal, the number of GluA1 receptors in the VTA increases sharply likewise (Rasmussen 1995).

AMPA blockers are more effective in reducing the VTA and NAc activation with glutamate, stimulated in drug addiction, compared to NMDA antagonists (memantine) (Rasmussen 1995). The growing body of literature supports that AMPA blockers not only suppress sensitization, tolerance and withdrawal caused by cocaine, opiates, alcohol or amphetamine, but further prevent the relapse caused by repeated administration of these substances (Bespalov and Zvartau 2000). At the same time, AMPA blockers' anti-addictive impact is more versatile and stronger relative to both NMDA and dopamine receptor antagonists (Rasmussen 1995). The rat experiments showed that AMPAR antagonists descend self-stimulation and self-administration reactions, whereas NMDA antagonists ascend them (Ducrot et al. 2013; Potapkin et al. 2017). For many known allosteric AMPAR antagonists (talampanel, perampanel), it is characteristic to have non-selective effects, which leads to simultaneous GluA1 and GluA2 blockade (Ducrot et al. 2013). GluA2 blockade, in turn, causes suppression of cognitive functions, locomotion and exploratory activity (Yang et al. 2022). The AMPAR antagonist topiramate, which is used in the seizures treatment, is also suggested for food addiction medical maintenance. However, its use has not become widespread taking into account low efficacy and side effects (Nourredine et al. 2021). A novel selective GluA1 AMPAR antagonist IEM-2131 was synthesized in the Department of Neuropharmacology of the Institute of Experimental Medicine (St. Petersburg, Russia) and has great virtue in comparison with already known non-selective AMPA blockers (Potapkin et al. 2023). In the previous study, a potential anti-addictive effect of the first selective GluA1 AMPAR antagonist IEM-1460, which can currently be used as a reference substance to evaluate the effects of other selective AMPA blockers, was shown (Potapkin et al. 2017).

In the current study, we have explored the mechanism of AMPAR antagonists effects on binge eating. The literature devoted to AMPAR antagonists' impact on eating disorders is insufficient. There are several works in which a suppressive action of AMPA blocker topiramate on binge eating (Nourredine et al. 2021) and the extracellular dopamine level enhancement in NAc against the background of the mGluR 2/3 antagonist LY341495 (Karasawa et al. 2010) are described.

Aim

The aim of the study was to investigate the impacts of GluA1 AMPAR antagonist zampaxidol (IEM-2131) and its reference substance, GluA1 AMPAR antagonist IEM-1460, in rat binge eating model, and, besides, explore the antagonistic activity of zampaxidol towards AMPA receptors.

Materials and methods

Animals

Experiments were conducted employing 42 adult male Wistar rats weighing 250-300 g and on 16 isolated neurons obtained from 9 *Danio rerio* fishes. Wild type *Danio rerio* were received from Aqua Peter Company (Russia) at the age of 6-8 months and grown in the Federal State Budgetary Scientific Institution "Institute of Experimental Medicine" (IEM) (Russia). Rats were kept in the Federal State Budgetary Scientific Institution "Institute of Experimental Medicine" (IEM) vivarium in standard cages (40x50x20 cm). Then, according to experimental design (see below), rats were relocated in the individual cages. The access to granulated feed and water was free during all experiments. The following environmental options were used: light mode from 8.00 to 20.00 and temperature $22 \pm 2^\circ\text{C}$. All experiments were performed in accordance with the ethical principles set out in Directive 2010/63/EC of the European Parliament and of the Council of 22 September 2010, approved by the Bioethics Committee of the Institute of Experimental Medicine.

Neuronal cells

The drug's AMPAR antagonistic activity was explored on 16 isolated neurons obtained from 9 *Danio rerio* fishes. Wild type *Danio rerio* were received from Aqua Peter Company at the age of 6-8 months and grown in the IEM.

Binge eating model

The eating behavior of rats was studied with the benefit of a binge eating model (Lebedev et al. 2023). As a treat, a chocolate-feeder mixture consisting of 52% Nutella (Ferrero, Alba, Turin, Italy), 33% food pellets (4RF18; Mucedola; Settimo Milanese) and 15% water, was used. The treat was given according to a Monday-Wednesday-Friday schedule for 1 hour with the precursory 15 minutes demonstration (rats can see and smell chocolate, but not eat it). The binge eating model requires a preliminary training. At the first stage (1 week), the chocolate treat was given to groups of animals (5-6 rats). At the second stage, rats were moved in the individual cages, and the treat was given until a stable level of consumption (deviations of no more than 10%) was achieved. The second stage takes 3 weeks.

Stress procedure

As a stress exposure, an electrical foot shock (FS) was employed. FS was conducted in a specialised chamber with an electrified floor (Noldus, Behavioral research, Netherlands) with a current of 0.6 mA for 1 minute (Bali and Jaggi 2015).

Drugs

In this work, a pharmacological activity of AMPAR antagonists IEM-1431 (Fig. 1) and IEM-2161 (Fig. 2) were studied. IEM-1460 and IEM-2131 were dissolved in solution No. 1 (Brusina et al. 2024), the pH of the solution was adjusted to 7.2 with 0.1 M of NaOH. 0.5 ml of 0.9% NaCl solution served as a control.

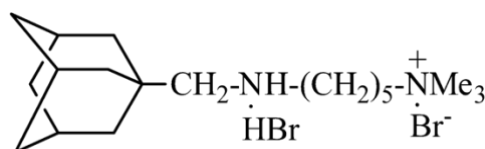


Figure 1. Structural formula of a compound IEM-1460.

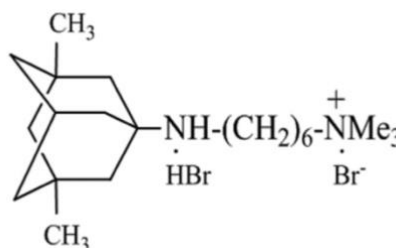


Figure 2. Structural formula of a compound IEM-2131 (zampaxidol).

Experimental design

Animals were separated into 3 groups: the first group was administered saline (0.5 mL of 0.9% NaCl, i.p.), the second group – IEM-1460 (3 mg/kg), and the third group – zampaxidol (1 mg/kg). All rats were exposed to stress and fed with chocolate treat. FS was conducted no more frequently than once a week 1 hour before, while drugs were administered 30 minutes after stress and, as a consequence, 30 minutes before binge eating experiment.

Patch-clamp technique

The AMPAR antagonist IEM-1460 and zampaxidol actions were examined using patch-clamp (SyncroPatch 384/768PE) technique on isolated neurons of *Danio rerio* (Zoodsma et al. 2020). The methodology of the experiment is presented in (Potapkin et al. 2023). The study utilized a point potential clamp of -80 mV in the whole-cell configuration. To obtain AMPA responses, solution No. 1 (Brusina et al. 2024) + 100 μ M kainic acid (Sigma-Aldrich, USA) was used at a temperature of 20°C and a pH of 7.4 (Kim et al. 2007). The test substance IEM-1460 was dissolved in the appropriate concentrations in solution No. 1 (Brusina et al. 2024), at a temperature of 20°C and a pH of 7.4.

Statistics and graphical visualisation

The statistical analysis and graphical visualization of experimental data were made in the Python language (<https://www.anaconda.com/>). For the patch-clamp results analysis and visualization, a Graph Pad Prism 9 for windows, version 9.5.1. (GraphPad Software, USA) was employed. To assess a stress exposure on rats, a Student's T test was performed. For evaluation of value significance for drug's effects, an ANOVA analysis of variance with a subsequent Dunnett's post hock test was calculated. The differences were considered reliable at $p < 0.05$. To illustrate the patch-clamp values with the concentration-effect curves, we used a nonlinear approximation of the regression curve representing the dependence of the logarithm of the AMPA antagonist concentration on the degree of inhibition (in percent) of the steady-state current. The IC_{50} of the studied antagonist was calculated by fitting a nonlinear logistic curve using OriginPro 2019b (64-bit) implementing the formula:

$$y = A_2 + \frac{A_1 - A_2}{1 + \left(\frac{x}{x_0}\right)^p}$$

The fitting error was used as the error term, where y – the degree of inhibition of the steady-state current (%); A_1 – the initial value (bottom plateau, %); A_2 – the final value (top plateau, %); x – the concentration of the antagonist (μ M); x_0 – the half-maximal inhibitory concentration, IC_{50} (μ M); p – the hill slope.

Results and Discussion

It was observed that 50% of rats formed food addiction. A criterion for food addiction was the quantity of eaten chocolate treats of over 10 grams. Addicted rats ate on average 15.9 ± 0.5 grams of chocolate treat in the absence of any influences. FS exposure led to an increase in mean treat consumption to 18.6 ± 0.9 grams ($p = 0.024$), while the saline administration after FS caused no effect on this parameter (18.2 ± 0.8 , $p = 0.994$).

Administration of AMPAR antagonist IEM-1460 reduced the average quantity of eaten treat to 10.0 ± 0.9 g. ($p = 0.002$) (Table 1), which was reliably lower compared to results with no impact and with FS stress. Administration of AMPAR antagonist zampaxidol lessened the mean chocolate treat consumption up to 11.5 ± 1.6 g. ($p = 0.0003$) (Table 1), which likewise was significantly lower than both in no impact and FS stress groups (Fig. 3).

Table 1. Effects of AMPA glutamate receptor antagonists IEM-1460 and IEM-2131 on stress-induced activation of binge eating

No	Impact	Mean consumed chocolate treat, gramm	Compared to intact control, p	Compared to FS, p
1	Intact Control	15.9±0.5		
2	Foot-shock (FS)	18.6±0.9	$p = 0.024$	
3	FS + saline	18.2±0.8	$p = 0.027$	$p = 0.994$
4	FS + IEM-1460	10.0±2.0	$p = 0.007$	$p = 0.0003$
5	FS + zampaxidol	11.5±1.6	$p = 0.021$	$p = 0.002$

Note: p – statistical significance.

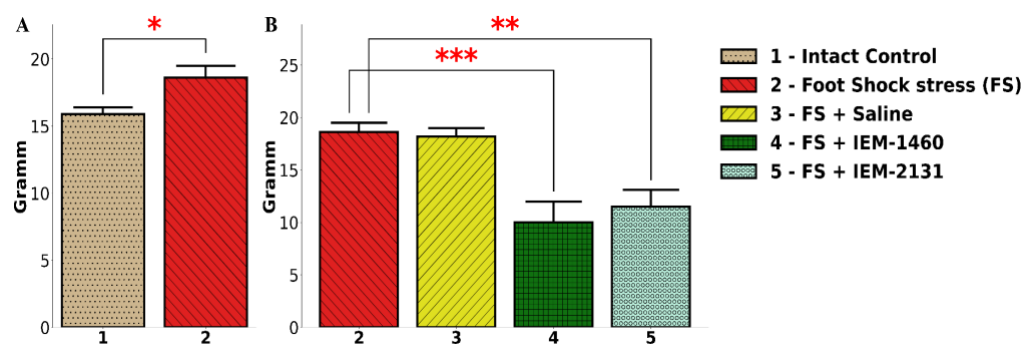


Figure 3. (A) Impact on foot shock stress on rat's treat consumption. (B) Effects of the AMPA glutamate receptor antagonists IEM-1460 and zampaxidol (IEM-2131) on stress-induced binge eating. **Note:** group 1 - animals receiving chocolate treat without any impacts; group 2 - animals receiving chocolate treat after foot-shock (FS) stress; group 3 - animals receiving chocolate treat after FS and saline administration; group 4 - animals receiving chocolate treat after FS and IEM-1460 3 mg/kg administration; group 5 - animals receiving chocolate treat after FS and zampaxidol (IEM-2131) 1 mg/kg administration; * – $p < 0.05$; ** – $p < 0.005$; *** – $p < 0.0005$.

We explored the AMPAR blocking effects of the AMPA antagonists IEM-1460 and IEM-2131 in the dosage 3 μM . The protocols for patch-clamp studies are presented in Figures 4 and 5.

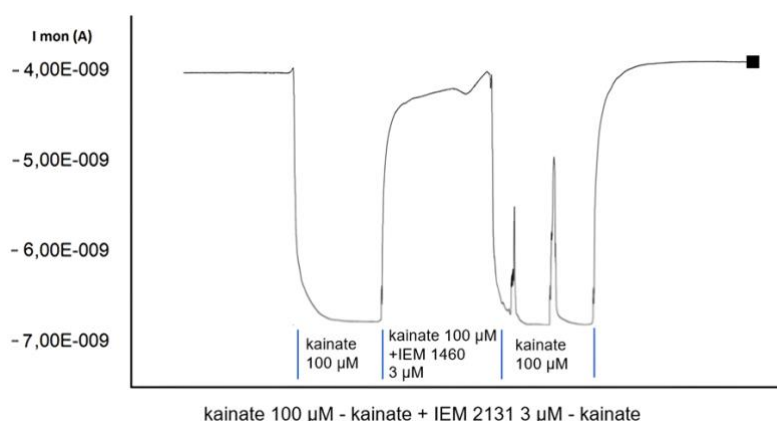


Figure 4. Result of the IEM-1460 antagonist activity at a dose of 3 μM analysis using patch clamp technique. **Note:** The Ala VC3/4 perfusion system was used, feeds in series: agonist (100 μM kainate) — followed by agonist (100 μM kainate) + antagonist (IEM-1460 3 μM) — followed by agonist (100 μM kainate).

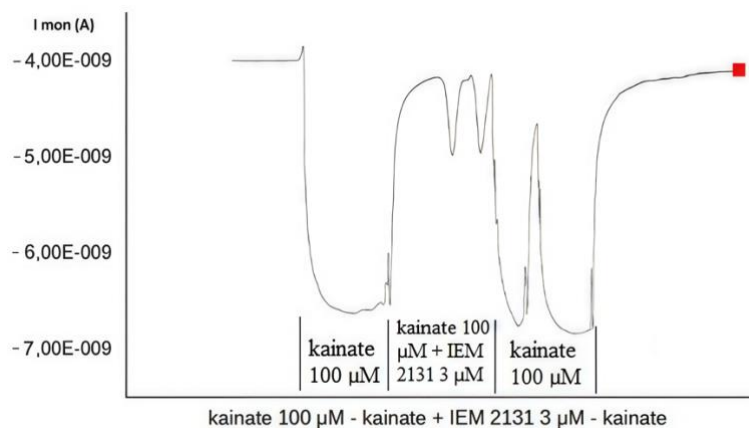


Figure 5. Result of the zampaxidol (IEM-2131) antagonist activity at a dose of 1 μM analysis using patch clamp technique. **Note:** The Ala VC3/4 perfusion system was used, feeds in series: agonist (100 μM kainate) — followed by agonist (100 μM kainate) + antagonist zampaxidol (IEM-2131) 3 μM — followed by agonist (100 μM kainate).

Thus, in our investigation, we demonstrated that IEM-1460 and zampaxidol have blocking impacts on AMPA receptors. The degree of AMPAR inhibition in the doses of 3 μ M for IEM-1460 was $86.7 \pm 8\%$, which was higher than such for zampaxidol (IEM-2131) – $81 \pm 8\%$. According to our data, IC₅₀ for zampaxidol was $0.65 \pm 0.15 \mu$ M (Fig. 6), which correlates with results from another study (Gmiro and Zhigulin 2022).

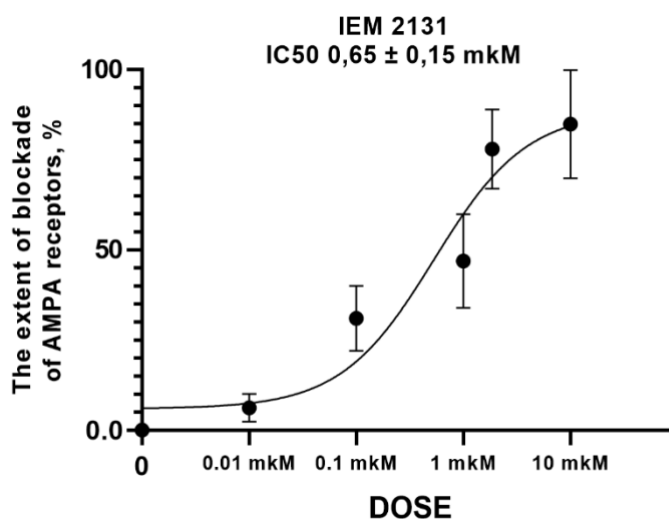


Figure 6. Dose-effect AMPAR response blocking curve for compound zampaxidol (IEM-2131) (patch clamp, whole cell, *D. Rerio*).

The dopamine system of the brain plays a key role in the reward system and, therefore, is of particular interest in the issue of addictive behavioral disorders (Lebedev et al. 2022). There is convincing evidence highlighting the leading role of glutamate in the mechanisms of addiction associated with the modulation of the dopamine system activity (Weidacker et al. 2020). Glutamatergic input activates VTA cells and increases dopamine release in the NAc (Blaha et al. 1997). Dopamine-releasing effect in the NAc is predominantly mediated by AMPA (rather than NMDA) receptors (Youngren et al. 1993). NMDA and AMPA receptors are engaged in glutamatergic projections from the prefrontal cortex and amygdala to the VTA and NAc (Wolf and Ferrario 2010). Long-term drug abuse appears to be associated with decrease in dopamine function, as a result of lowered dopamine release and narrowing in D2 receptor quantity. Moreover, decreased D2 receptor numbers in the striatum are associated with declined activity in the orbitofrontal cortex (an area associated with valuation and motivation, as well as compulsive behavior) and the cingulate gyrus (an area related to lessened control and impulsivity), leading to prefrontal cortex dysregulation, loss of control, and compulsive drug use, which characterizes the state of addiction (Wolf and Ferrario 2010). The reinforcing effects of addictive drugs and stimuli depend primarily on the strength and rate of dopamine release in the NAc, and chronic exposure triggers glutamatergic-mediated neuroadaptation in the dopamine terminal regions of the mesolimbic system, reducing dopamine release and the number of D2 receptors (Grunze et al. 2021). An increased risk of relapse, depressive symptoms, and dysphoria in terms of addictive behaviors could be associated with low dopamine functioning (Grunze et al. 2021).

The main indicator of a substance's anti-addictive properties is its effectiveness in modulating extracellular dopamine levels in the NAc, a brain structure that determines the motivational state and its transformation into activity (Lingford-Hughes et al. 2010; Scofield et al. 2016). In the phasic dopamine waves analysis in the NAc in response to electrical stimulation of the VTA, we showed an increase in the dopamine level after the administration of IEM-1460 at a dose of 1 mg/kg i.p. (which was the most effective in the studies of impulsive behavior applying the Iowa Gambling Task). This is consistent with the example from the literature, where the mGlu 2/3 receptor antagonist LY341495 raised the extracellular level of dopamine in the NAc, as well (Karasawa et al. 2010). It is known that dopamine receptor antagonists can also increase the release of dopamine in the NAc. In vivo microdialysis has shown that levo-tetrahydropalmatine (l-THP), a dopamine D1 and D2 receptor antagonist, elevates extracellular DA levels in the NAc and dose-dependently enhances dopamine release followed by cocaine pre-administration. l-

THP has been shown to reduce the acquisition of a conditioned preference response for cocaine administration and its reinstatement induced by cocaine or methamphetamine (Becker et al. 2010). 1-THP also attenuated the reinforcing properties of hypothalamic self-stimulation after cocaine exposure and, moreover, dose-dependently reduced cocaine self-administration under a progressive reinforcement schedule (Xi et al. 2007). The self-administration schedule has much in common with the excitement and risk of gambling, which could be modeled employing the Iowa Gambling Task.

The AMPAR antagonist IEM-1460 was synthesized in the Department of Neuropharmacology at the Institute of Experimental Medicine (Russia) before its analogue zampaxidol (IEM-2131) and is possessed as a GluA1 AMPA and $\alpha 3\beta 4$ n-cholinergic receptor selective blocker (Magazanik et al. 1997). IEM-1460 has been repeatedly studied in experimental models using patch-clamp technique, so in this study, IEM-1460 was used as a reference substance. For IEM-1460, the IC-50 values were $2.6 \mu\text{M}$, $3.1 \pm 0.4 \mu\text{M}$, and $3.0 \pm 1.3 \mu\text{M}$ and for zampaxidol the IC-50 was $0.29 \pm 0.07 \mu\text{M}$ in evaluations with AMPAR that do not contain GluA2 (Magazanik et al. 1997; Gmiro and Zhigulin 2022). Thus, IEM-2131 demonstrated high AMPA-blocking activity, reliably greater than that of IEM-1460 (IC50 - $0.27 \mu\text{M}$ and $3 \mu\text{M}$, respectively), besides for zampaxidol there was observed high AMPA selectivity. IEM-1460 was selected as a comparison substance (it exerts GluA1 AMPA blocking and $\alpha 3\beta 4$ n-cholinergic receptor blocking activity), and zampaxidol as a compound that was found to have an order of magnitude greater AMPA-blocking activity (Gmiro and Zhigulin 2022).

Based on characteristic behavioral patterns and impacts of high palatable foods (containing a large amount of sugars and fats) on some biological processes, a concept of “food addiction” was formed. In the literature, there is evidence indicating that binge eating is a manifestation of food addiction (Leigh and Morris 2018). In the current study, a binge eating model according to a Monday-Wednesday-Friday schedule with the preliminary 15 minutes of the only visual and olfactory stimulation with a chocolate treat was employed. Interestingly, in rats who were given the chocolate treat every day, the food addiction did not form (Lebedev et al. 2023). Data from several studies supports that stress exposure raises the vulnerability to addiction. Some authors suppose that stress could enhance the reward of the addictive drugs through the process common to sensitization (Goeders 2003). Our experiments demonstrated that foot shock stress significantly raises the mean quantity of eaten chocolate treat for rats with formed food addiction.

In the current study, it was shown that AMPAR antagonist zampaxidol (likewise the reference substance IEM-1460) reliably lessens binge eating under stress conditions in rats. Accordingly, AMPAR receptor antagonists seem to be promising in the therapy of disordered eating stimulated by psychogenic stress. In the experiment, AMPAR antagonists demonstrated a significant anorexigenic effect in the rat binge eating model, both in comparison with the intact control group and with the group exposed to FS ($p < 0.05$). Obtained data is largely consistent with the literature. AMPAR antagonists have been shown not only to reduce the manifestations of pathological addiction to alcohol, psychostimulants, and opiates, but to prevent the relapse caused by the administration of psychoactive drugs (Rasmussen 1995). In our earlier works, it was shown that the GluA1 AMPAR antagonist IEM-1460 suppresses the reinforcing properties of the hypothalamus electrical stimulation (Potapkin et al. 2017). The AMPAR antagonist topiramate was shown to have a suppressive effect on the elements of gambling addiction (Dannon et al. 2005) and binge eating disorder (Nourredine et al. 2021). Topiramate's efficacy in the treatment of disordered eating has been demonstrated using a meta-analysis of clinical trials involving 528 patients with binge eating disorder. Topiramate was significantly more effective than placebo in reducing the number of binge eating episodes per week. Nevertheless, patients in the topiramate group often refused to continue treatment due to side effects of the drug (Nourredine et al. 2021).

In conclusion, the data obtained in the present study emphasize the important role of AMPARs in the development and maintenance of food addiction. It should be noted that the new GluA1 AMPA receptor antagonist zampaxidol, developed by the staff of the S.V. Anichkov Neuropharmacology Department, Institute of Experimental Medicine (Russia), demonstrated high efficacy in a rats binge eating model after a foot-shock stress exposure, which suggests new ways of synthesizing and usage of the pharmacological agents based on AMPA receptor antagonists in the treatment of binge eating accompanied by psychogenic stress.

Conclusion

The findings demonstrate that the selective GluA1-containing AMPA receptor antagonist zampaxidol (IEM-2131) significantly reduces high-palatable food intake in rats under a binge eating model potentiated by foot-shock stress. Its efficacy is comparable to that of the reference compound IEM-1460, yet zampaxidol exhibits higher AMPA-blocking activity

(IC₅₀ = 0.65 μ M). These results confirm the critical role of AMPA receptors in the mechanisms of food addiction and stress-induced hyperphagic behavior. Hence, pharmacological agents selectively targeting the GluA1 subunit of AMPA receptors may represent a promising therapeutic strategy for psychogenic binge eating disorder.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

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Ethics statement

All experiments were performed in accordance with the ethical principles set out in Directive 2010/63/EC of the European Parliament and of the Council of 22 September 2010, approved by the Bioethics Committee of the Institute of Experimental Medicine.

Data availability

All relevant data generated and analyzed during this study are included in this article.

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