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Blockade of GluA1 AMPA Receptors Reduces Impulsive Behavior in a Gambling Addiction Model by Modulating Extracellular Dopamine Levels

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ABSTRACT

BACKGROUND: The search for new agents for the pharmacological management of gambling addiction remains an urgent task in contemporary psychoneuropharmacology. A GluA1 AMPA receptor antagonist (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist), IEM-1460, has previously been proposed as a potential therapeutic option for addiction. Glutamatergic inputs are known to modulate the activity of the mesolimbic dopamine system. It can be hypothesized that the antiaddictive effect of IEM-1460 is mediated through the interaction between glutamatergic and dopaminergic systems.

AIM: The work aimed to investigate the effect of GluA1 AMPA receptor blockade on impulsive behavior in a gambling addiction model, its role in modulating extracellular dopamine levels in the nucleus accumbens, and its effects on ion currents in isolated neurons.

METHODS: Experiments were conducted *in vivo* in Wistar rats and *in vitro* in isolated *Danio rerio* neurons. The effect of IEM-1460 (1, 3, and 10 mg/kg, intraperitoneally) on impulsive behavior in a gambling addiction model using a three-arm maze, and on dopamine release in the nucleus accumbens in response to electrical stimulation of the ventral tegmental area, was assessed using intravital fast-scan cyclic voltammetry. In isolated *Danio rerio* neurons, the effect of IEM-1460 on ion currents induced by the AMPA receptor agonist kainic acid was evaluated using the patch-clamp technique.

RESULTS: IEM-1460 at 1 mg/kg administered intraperitoneally most effectively reduced impulsive behavior in the gambling addiction model and increased dopamine release in the nucleus accumbens in response to electrical stimulation of the ventral tegmental area. *In vitro*, IEM-1460 produced a pronounced blocking effect on AMPA glutamate receptors.

CONCLUSION: Selective blockade of GluA1-AMPA receptors with IEM-1460 reduced impulsive behavior in the gambling addiction model and increased extracellular dopamine levels in the nucleus accumbens, as measured by fast-scan cyclic voltammetry.

Keywords: IEM-1460; AMPA receptor; gambling disorder; voltammetry; extracellular dopamine; patch clamp.

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Блокада GluA1-AMPA-рецепторов снижает проявление импульсивного поведения в модели игровой зависимости, влияя на внеклеточный уровень дофамина

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АННОТАЦИЯ

Обоснование. Поиск новых соединений для фармакологической коррекции игровой зависимости — актуальная задача современной психонейрофармакологии. Ранее в качестве потенциальных лечебных средств против аддикции нами был предложен глутаматный GluA1-AMPA-антагонист (рецептор α-амино-3-гидрокси-5-метил-4-изоксазолпропионовой кислоты) ИЭМ-1460. Известно, что глутаматергические входы способны модулировать активность мезолимбической дофаминовой системы мозга. Можно предположить, что в основе антиаддиктивного действия ИЭМ-1460 лежит взаимодействие глутамат- и дофаминовой систем.

Цель — изучить влияние блокады GluA1-AMPA-рецепторов на проявление импульсивного поведения в модели игровой зависимости, на роль в модуляции внеклеточного уровня дофамина в прилежащем ядре, на ионные токи на изолированных нейронах.

Методы. Эксперименты проведены *in vivo* на крысах линии Вистар и *in vitro* — на изолированных нейронах *Danio rerio*. Исследовали действие ИЭМ-1460 (в дозах 1, 3, 10 мг/кг, внутрибрюшинно) на проявление импульсивного поведения на модели игровой зависимости в трехлучевом лабиринте и выброс дофамина в прилежащем ядре в ответ на электрическую стимуляцию вентральной области покрышки методом прижизненной циклической вольтамперометрии с быстрым сканированием. На изолированных нейронах рыб *Danio rerio* методом пэтч-кламп исследовали влияние ИЭМ-1460 на ионные токи, индуцированные аппликацией агониста AMPA-рецепторов — каиновой кислоты.

Результаты. ИЭМ-1460 в дозе 1 мг/кг внутрибрюшинно наиболее эффективно снижал проявление импульсивного поведения на модели игровой зависимости и увеличивал выброс дофамина в NAc в ответ на электрическую стимуляцию VTA. *In vitro* ИЭМ-1460 оказывал выраженное блокирующее действие на AMPA-глутаматные рецепторы.

Заключение. Селективная блокада GluA1-AMPA-рецепторов с помощью ИЭМ-1460 снижала проявление импульсивного поведения в модели игровой зависимости, увеличивала внеклеточный уровень дофамина в прилежащем ядре в методе циклической вольтамперометрии с быстрым сканированием.

Ключевые слова: ИЭМ-1460; AMPA-рецептор; игровое расстройство; вольтамперометрия; внеклеточный дофамин; пэтч-кламп.

Как цитировать

Лебедев А.А., Потапкин А.М., Пюрвеев С.С., Сизов В.В., Гмиро В.Е., Бычков Е.Р., Мухин В.Н., Нетеса М.А., Анисимов Д.Е., Дробленков А.В., Шабанов П.Д. Блокада GluA1-AMPA-рецепторов снижает проявление импульсивного поведения в модели игровой зависимости, влияя на внеклеточный уровень дофамина // Обзоры по клинической фармакологии и лекарственной терапии. 2025. Т. 23, № 2. С. 177–189. DOI: 10.17816/RCF646052 EDN: VNHXXW

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BACKGROUND

Given the current increase in the incidence of disorders due to addictive behaviors, research into problem gambling mechanisms is becoming increasingly relevant. According to ICD-11, disorders due to addictive behaviors are classified as follows: 6C50 Gambling disorder; 6C51 Gaming disorder. Gambling disorders are characterized by impulsivity and features typical of alcohol and drug addiction [1, 2]. The Iowa Gambling Task is used to assess impulsivity- and risk-associated behaviors in animal studies [3]. This approach is based on selecting the extent of reinforcement to increase the significance of reinforcement [4]. We previously used a modified Iowa Gambling Task in a Y-maze test in rats [5]. [D-Lys3]-GHRP-6, a ghrelin receptor antagonist, has been shown to reduce impulsivity in a maze-based problem gambling model by influencing dopamine metabolism [6]. Numerous research have addressed impulsivity [7–9].

The dopamine system of the brain plays a key role in the reward and reinforcement system in research into disorders due to addictive behaviors [6, 64]. Evidence suggests that glutamate plays the primary role in mechanisms of addiction associated with modified dopamine system activity [10–12]. Dopaminergic cells of the ventral tegmental area (VTA) and the nucleus accumbens (NAc), a terminal region of the mesolimbic system, receive substantial glutamatergic inputs primarily from the prefrontal cortex, amygdala, and hippocampus [13, 14]. These structures have a role in reward assessment in problem gambling [10, 15]. Glutamatergic inputs activate VTA cells and increase dopamine release in the NAc [16, 17]. The dopamine-releasing effect of glutamate in the NAc is primarily mediated by AMPA receptors, rather than NMDA receptors [18]. When an addiction develops, the AMPA/NMDA ratio shifts towards increased activity of AMPA receptors, facilitating plasticity of excitatory synapses of VTA dopaminergic neurons [20]. Increased activity of AMPA receptors in postsynaptic membranes of VTA dopaminergic neurons is associated with GluA2 subunit substitution in existing AMPA receptors or inclusion of new AMPA receptors with GluA1 subunits from the cytoplasmic pool. This is accompanied by increased AMPA receptor permeability to calcium ions [19]. Addictive behavior increases GluA1-AMPA receptors and decreases GluA2-AMPA receptors in the VTA and NAc [21]. Opiate withdrawal is also associated with a sharp increase in GluA1 receptors in the VTA [22].

AMPA receptor antagonists inhibit the glutamate-mediated activation of VTA and NAc neurons caused by drug addiction more effectively than NMDA receptor antagonists (memantine) [22]. There is direct evidence that AMPA receptor antagonists not only eliminate sensitization, tolerance, and withdrawal syndrome associated with cocaine, opiates, alcohol, and amphetamines, but also prevent reinstatement triggered by repeated administration of these substances [23]. AMPA receptor antagonists have a broader and more potent antiaddictive effect than NMDA and dopamine receptor antagonists [22]. AMPA receptor antagonists inhibit self-stimulation and self-administration responses in rats, whereas NMDA receptor antagonists activate them [24, 25].

Many allosteric AMPA receptor antagonists, such as talampanel* and perampanel, are non-selective to AMPA subunits, resulting in simultaneous inhibition of GluA2 and GluA1 receptors.

GluA2 inhibition impairs cognitive functions, locomotor activity, and exploratory behavior [24, 27, 28]. Topiramate, an AMPA receptor antagonist [29], and acamprosate, an NMDA receptor antagonist [30], have been proposed for the treatment of problem gambling in clinical practice; however, these drugs have low efficacy and severe side effects. The Neuropharmacology Department of the Institute of Experimental Medicine (Saint Petersburg, Russia) synthesized IEM-1460, a selective GluA1-AMPA receptor antagonist [31, 32] that is considerably superior to existing non-selective AMPA receptor antagonists. Experiments have demonstrated its potential antiaddictive effect [24].

This work assessed the effect of AMPA receptor antagonists on addictive behavior in rats using a modified Iowa Gambling Task in a Y-maze test and extracellular dopamine levels in the NAc in response to VTA stimulation. There are very few published research into the effect of AMPA receptor antagonists on problem gambling and dopamine release. There are anecdotal data on the inhibitory effect of AMPA receptor antagonists on problem gambling components and elevated extracellular dopamine levels in the NAc induced by the mGlu 2/3 receptor antagonist LY341495 [33].

This study aimed to investigate the antiaddictive effect of the GluA1-AMPA receptor antagonist IEM-1460 in a problem gambling model and its role in dopamine level modulation, as well as to demonstrate the antagonistic activity of IEM-1460 against glutamate AMPA receptors.

METHODS

The study used 42 adult male Wistar rats weighing 250–300 g and 15 isolated neurons from eight *Danio rerio* species. Animals were kept in standard cages (40×50×20 cm) with free access to water and pelleted feed in the vivarium of the Institute of Experimental Medicine. A lighting schedule with lights on between 8:00 and 20:00 was used, at 22 ± 2 °C. Wild-type *Danio rerio* species aged 6–8 months were provided by Aqua Peter

* The drug is not approved in Russia.

and reared at the Institute of Experimental Medicine. All experiments followed the ethical principles outlined in Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010, and were approved by the Bioethics Committee of the Institute of Experimental Medicine.

A modified Iowa Gambling Task was used to assess impulsivity in a problem gambling model [6, 34]. The test assesses reinforcements of different extents and likelihoods preferred by animals. The study used a modified Y-maze with a starting arena (33×50×35 cm) and three arms (50×15×35 cm each). Each arm ended with an automated feeder. Animals received food reinforcement (sunflower seeds) when they reached the feeder. When an animal exited the arm and entered the starting arena, the feeder was refilled. The number of visits to the feeder and returns to the starting arena were recorded for 10 min. Animals were trained once daily for 21 days. Animals were fed four times daily, with free access to water.

Experiments in the Y-maze included two stages. During the first stage, a training (simplified) food reinforcement mode was used to form a conditioned connection (arm–feeder). When choosing Arm-1, the animal received one sunflower seed every time. When choosing Arm-2 and Arm-3, the animal received two and three sunflower seeds, respectively. The training food reinforcement mode was used for five days. No tests were performed in the following two days. The second stage started on day 8 and used a food reinforcement mode with different extents and likelihoods of reinforcement. During each arm entry, a 100 lux light automatically turned on for 2 s. In Arm-1, animals received two sunflower seeds (reinforcement mode FR1-2). Animals received food reinforcement every time when they reached the feeder. In Arm-2, animals received three sunflower seeds in the FR2-3 mode; every second visit to the feeder was rewarded. In Arm-3, animals received four sunflower seeds in the FR3-4 mode; every third visit to the feeder was rewarded. Thus, one of two Arm-2 entries and two of three Arm-3 entries were not rewarded. Animals were trained in this mode for 2 weeks. During the first and second stages of training, different extents and likelihoods of reinforcement were used to model gambling-like behavior by the end of training [35]. Rats that did not enter the maze arms (no more than 15%) were excluded from the experiment.

Electrodes were implanted in animals that preferred Arm-3 of the Y-maze (n = 9). Electrodes were not implanted in animals that did not prefer Arm-3 of the maze and thus did not exhibit clear addictive behavior. Tiletamine + zolazepam 50 mg/kg was used for anesthesia. A stimulating electrode (0.2 mm insulated stainless steel bipolar electrode) was implanted into the VTA. The coordinates relative to bregma were: AP = –5.3 mm, L = 0.8 mm, H = 8.2 mm [36]. To record increased dopamine levels in the NAc, a glassy carbon electrode was implanted ipsilaterally (exposed fiber tip: 100 μm in length, 7 μm in diameter). A recording electrode was implanted as follows: AP = +2.0 mm (from bregma), L = 1.2 mm, H = 7.3 mm from the skull surface [36]. Moreover, a 3 mm high-pressure Ag/AgCl reference electrode was implanted: AP = +5.5 mm (from bregma), L = 0. The electrodes were secured to the skull surface with UV-acrylic adhesive. During the following week, animals were kept in individual cages to recover from surgery [37].

The experiment was carried out using the Cyclone telemetry-based hardware-software system, which includes several modules: a fast-scan cyclic voltammetry (FSCV) unit (potentiostat), an electrical stimulator (neural tissue stimulator), visual and auditory stimulators, an accelerometer to determine head position, and a video tracking module for monitoring the animal's position [38]. Dopamine release in response to electrical stimulation of the VTA was recorded [39]. Dopamine release was assessed by changes in its extracellular levels in the nucleus accumbens *in vivo* by FSCV in anesthetized animals following electrode implantation, in response to electrical stimulation of the VTA with a single pulse packet (240 μA, 100 Hz, 1 s) [66, 67]. The VTA is a source of dopaminergic (but not serotoninergic or noradrenergic) fibers entering the nucleus accumbens. Therefore, we assume that increased voltammetric signal intensity in the nucleus accumbens during VTA stimulation is associated with increased dopamine release [16, 17].

These values were considered as the baseline (control) dopamine release. Following that, 0.9% sodium chloride solution or the study substance (IEM-1460 1 mg/kg) was administered intraperitoneally. Dopamine release was assessed again after 20 minutes. To record increases in dopamine levels in response to VTA stimulation, a holding potential of –0.4 V and a scan duration of 9 ms were used. Scanning pulses were applied every 100 ms. The anodic limit was +1.3 V. For data analysis, the open-source web application Analysis Kid was used. Analysis Kid developed by Hashemi Lab (USA) enables visualization, calibration, and filtering of neurochemical signals [40].

Following the experiments, electrode positioning was morphologically verified. The rats were sacrificed by ethaminal sodium overdose, perfused with 0.9% sodium chloride solution, and fixed in formalin. The brain was then extracted, embedded in celloidin, sectioned coronally, and stained with cresyl violet using the Nissl method (Fig. 1). Electrode positioning was verified after the end of the experiments using histological brain sections and a stereotaxic atlas [36]. To confirm the position of the stimulating electrode in the VTA, a coronal section was made at the "Bregma –5.3 mm" level according to the

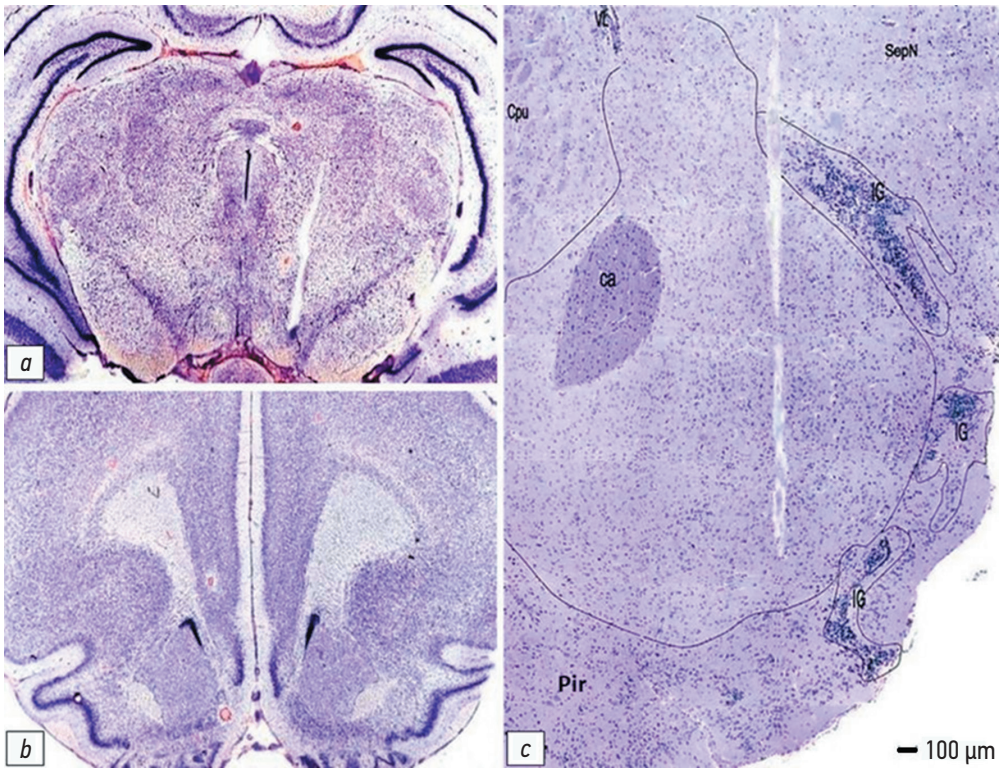

Fig. 1. Morphological verification of electrode tracts in the brain of rats: *a*, electrode tract for VTA stimulation at the "Bregma –5.3 mm" level: eyepiece lens ×4, objective lens ×10; *b*, search initiation area for a thin recording electrode tract at the "Bregma +2.7 mm" level: eyepiece lens ×4, objective lens ×10; *c*, anterior part of the nucleus accumbens with a defect in the thin recording electrode implantation area at the "Bregma +2.0 mm" level: eyepiece lens ×10, objective lens ×10. IG, olfactory nuclei; Cpu, striatopallidal complex; Pir, piriform cortex; SepN, septal nuclei; VL, lateral ventricle; ca, anterior commissure. Nissl staining.

stereotaxic atlas. In this brain region, the VTA tissue is at its most extensive and corresponds to the dopaminergic paranigral nucleus. To confirm the position of the electrode in the nucleus accumbens, a coronal section was made at the "Bregma +2.7 mm" level according to the atlas. Sectioning continued for 0.7–1 mm to the region of the forebrain where the nucleus accumbens occupies the largest area (Fig. 1). In this region of the brain, the anterior commissure was displaced toward the dorsomedial portion of the nucleus, whereas the recording electrode tract was located in its largest, central region (Fig. 1).

The effect of the AMPA receptor antagonist IEM-1460 was assessed using the patch clamp technique (SyncroPatch 384/768PE) in isolated *Danio rerio* brain neurons [41]. The test procedure is described elsewhere [65]. Transmembrane currents were recorded using the patch clamp technique. Whole-cell patch clamp technique (–80 mV) was used. AMPA responses were elicited using solution No. 1 [65] + kainic acid 100 µM (Sigma-Aldrich, USA) at 20 °C, pH 7.4 [42]. The study substance IEM-1460 at respective concentrations was dissolved in solution No. 1 [65] at 20 °C, pH 7.4.

Drug products. The study assessed the pharmacological activity of the AMPA receptor antagonist IEM-1460 [5-(1-adamentylmethylamino)pentyl trimetazolin bromide] (Fig. 2). IEM-1460 was dissolved in distilled water, and the pH was adjusted to 7.2 with 0.1 M NaOH. The substance was administered intraperitoneally 30 min before addictive behavior testing in the Y-maze. Following that, the substance was administered intraperitoneally during surgery after electrode implantation, and dopamine levels were measured every 5 min. The control was 0.9% sodium chloride solution (0.5 mL).

Statistical analysis. When processing the patch clamp analysis findings, concentration–response curves were built using a non-linear approximation of a regression curve, representing the relationship between logarithm of AMPA receptor antagonist concentration and steady-state current attenuation (%). The curve was used to determine the IC50 of the AMPA receptor antagonist. Graph Pad Prism 9 for Windows, version 9.5.1 (GraphPad Software, USA), was used for statistical analysis and graph plotting. When processing data on behavior and dopamine levels, the D'Agostino–Pearson test was used for normality testing of random variables. Data were analyzed using nonparametric statistics with the Mann–Whitney *U* test for small samples. The data in figures are presented as medians and quartiles [Q_1, *Me*, Q_3]. Differences were considered significant at $p < 0.05$.

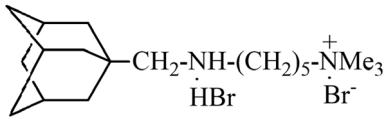

Fig. 2. Structural formula of IEM-1460.

RESULTS

When assessing addictive behavior, the extents and likelihoods of reinforcement (modified Iowa Gambling Task) determined the number of entries for each arm of the Y-maze. Seven rats did not enter the maze arms during the first stage of training and were excluded from the experiment. Thirty-five rats were trained for 21 days and tested on days 22 and 23. Intraperitoneal (IP) IEM1460 1 mg/kg reduced the proportion of Arm-3 entries relative to 0.9% sodium chloride solution (from 46.55% ± 1.86% to 39.63% ± 2.80%, $p < 0.01$) and increased the proportion of Arm-1 entries relative to 0.9% sodium chloride solution (from 31.5% ± 3.1% to 38.5% ± 4.1%, $p < 0.05$), indicating an antiaddictive effect of the substance (Table 1).

IEM-1460 3 mg/kg reduced the proportion of Arm-3 entries relative to 0.9% sodium chloride solution (from 46.55% ± 1.86% to 41.98% ± 3.70%, $p < 0.05$), which also indicates an antiaddictive effect of the substance (Fig. 3). There were no significant changes with IEM-1460 10 mg/kg, with a lower proportion of Arm-3 entries relative to 0.9% sodium chloride solution. There were no significant changes in the total number of arm entries.

Therefore, the AMPA receptor antagonist IEM-1460 reduces impulsivity in a problem gambling model by decreasing the number of arm entries with a more significant but less likely food reinforcement.

IEM-1460 at an active dose of 1 mg/kg IP, determined during addictive behavior testing in the Y-maze, increased stimulation-induced dopamine responses. The induced phasic response 5 min after IEM-1460 did not differ significantly from dopamine release in the control group that received 0.9% sodium chloride solution. However, phasic dopamine release 30 min after IEM-1460 injection was significantly higher than in the control group, where the phasic release was measured 30 min after injection of 0.9% sodium chloride solution ($p \leqslant 0.01$) (Fig. 4).

Therefore, VTA stimulation increases phasic dopamine release with IEM-1460 (Fig. 5).

We assessed the inhibition of AMPA receptors by IEM-1460 3 μM. Fig. 6 shows the patch clamp analysis protocol.

Therefore, our study confirmed that IEM-1460 inhibits AMPA receptors. The degree of AMPA receptor inhibition by IEM-1460 at a single dose of 3 μM was 86.7% ± 8%, which is consistent with previous research [32].

DISCUSSION

This study found that the selective GluA1-AMPA receptor antagonist IEM-1460 reduces impulsivity in a problem gambling model by decreasing the number of Y-maze arm entries, which is associated with a more significant but less likely food reinforcement. This is consistent with existing data that AMPA receptor inhibition reduces chemical addiction [22]. AMPA receptor antagonists are known to reduce alcohol, psychostimulant, and opiate addiction. Moreover, they prevent reinstatement triggered by these substances [22]. Our previous studies showed that the GluA1-AMPA receptor antagonist IEM-1460 inhibits the rewarding effect of electrical stimulation of the hypothalamus [24]. There is evidence that the AMPA receptor antagonist topiramate inhibits problem gambling components [29].

Therefore, it is reasonable to use selective GluA1-AMPA receptor antagonists to assess and treat such problem gambling components as impulsivity. Our study confirmed that IEM-1460 inhibits AMPA receptors, which is consistent with the effect on GluA1R. The degree of AMPA receptor inhibition by IEM-1460 3 μM was 86.7% ± 8%, which is consistent with previous research [32]. Spermine could also be used for this purpose. Spermine, a natural polyamine NMDA receptor antagonist with AMPA receptor antagonist properties, inhibits interneuronal GluA1 receptors. Spermine enhances memory, learning, locomotor activity, and exploratory behavior; however, it does not completely reduce the toxic effects of kainate and promotes the toxic effects of glutamate on NMDA receptors

Table 1. Proportions of Y-maze arm entries for the control and the GluA1-AMPA receptor antagonist IEM-1460

Parameter	Proportion of arm entries			Total number of arm entries
	Arm-1	Arm-2	Arm-3	
0.9% sodium chloride solution	31.5 ± 3.12	21.4 ± 3.4	46.55 ± 1.86	39.3 ± 1.9
IEM 1460 1 mg/kg IP	38.5 ± 4.1*	23.1 ± 5.5	39.63 ± 2.8**	42.8 ± 4.5
IEM 1460 3 mg/kg IP	34.7 ± 4.1	24.6 ± 3.7	41.98 ± 3.7*	36.8 ± 4.5
IEM 1460 10 mg/kg IP	34.6 ± 3.8	22.4 ± 3.3	43.5 ± 1.3	31.4 ± 6.5

Note. *$p \leqslant 0.05$; **$p \leqslant 0.01$ vs control (0.9% sodium chloride solution). IP, intraperitoneally.

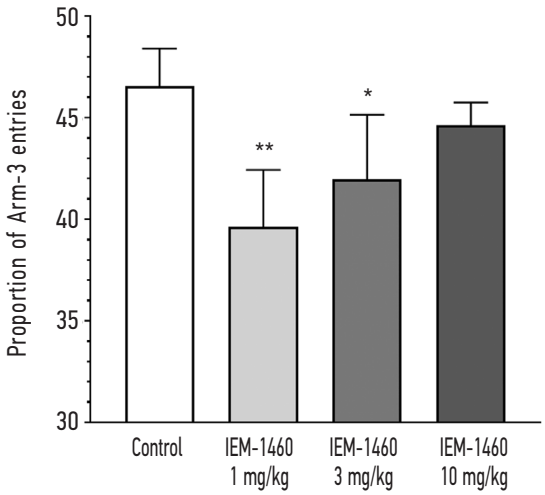

Fig. 3. Proportion (%) of Y-maze Arm-3 entries in rats that received intraperitoneal IEM-1460 at various doses versus control (0.9% sodium chloride solution). *$p \leqslant 0.05$; **$p \leqslant 0.01$ vs control.

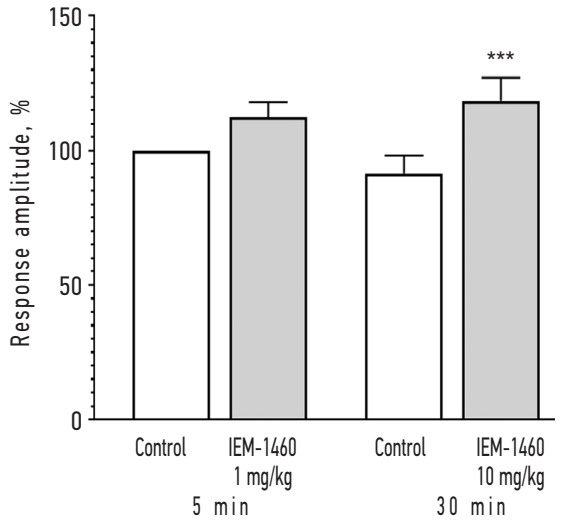

Fig. 4. Changes in phasic dopamine release in the nucleus accumbens in response to electrical stimulation of the ventral tegmental area following intraperitoneal administration of IEM-1460 1 mg/kg. ***$p \leqslant 0.01$.

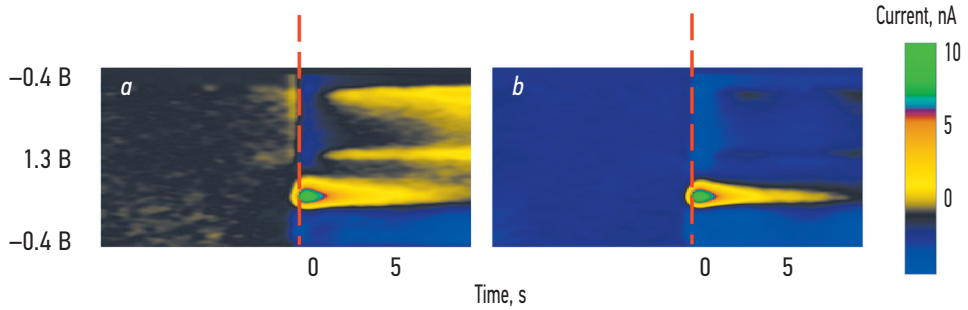

Fig. 5. Kinetics of changes in extracellular dopamine levels in the nucleus accumbens in response to electrical stimulation of the ventral tegmental area. Voltammogram following stimulation of the ventral tegmental area in animals receiving 0.9% sodium chloride solution (*a*) and IEM-1460 (*b*). The color scale represents electric current variations relative to its baseline level at time point 0.

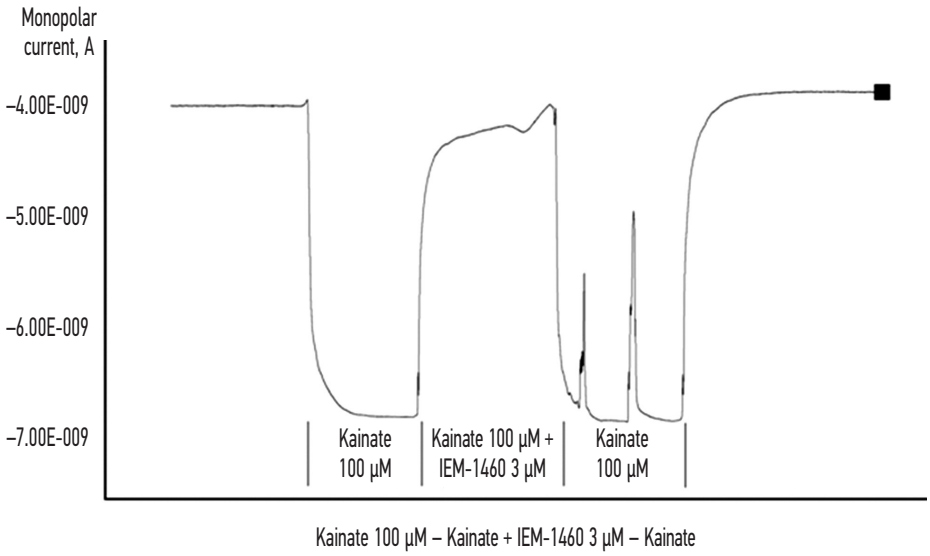

Fig. 6. Testing of IEM-1460 antagonist at a dose of 3 μM. Ala VC3/4 perfusion system is used for sequential administration of agonist (kainate 100 μM), agonist (kainate 100 μM) + antagonist (IEM-1460 3 μM), and agonist (kainate 100 μM)

in the cortex, VTA and NAc [26]. IEM-1460 activity is twice as high as that of spermine [44]. Unlike spermine, IEM-1460 completely inhibited GluA1-AMPA receptors and showed high neuroprotective activity [45, 46].

IEM-1460 is a selective GluA1-AMPA receptor antagonist that also inhibits alpha-3 beta-4 nicotinic receptors and acts as a direct GluA2-AMPA receptor agonist [26]. Alpha-3 beta-4 nicotinic receptor antagonists inhibit self-stimulation and self-administration of cocaine, amphetamine, morphine, nicotine, and other addictive substances, reduce behavioral sensitization and tolerance to these substances, and eliminate withdrawal syndrome [47]. Alpha-3 beta-4 nicotinic receptors are located in interneuronal presynapses, and their activation promotes a massive release of endogenous glutamate, resulting in seizures caused by GluA1-AMPA receptor activation in the cortex. Alpha-3 beta-4 nicotinic receptors are primarily found in interneuronal presynapses of pyramidal cells of the brain [48]. This likely explains glutamate release caused by this type of stimulation [49]. IEM-1460 is a selective blocker of parasympathetic ganglia [50], including alpha-3 beta-4 nicotinic receptors [51]. IEM-1460 eliminates nicotine-induced seizures and analgesia [52]. Therefore, the inhibitory effect of IEM-1460 on parasympathetic alpha-3 beta-4 nicotinic receptors in glutamatergic nerve terminals in the NAc is a significant component of its potential antiaddictive effect. Furthermore, unlike memantine, IEM-1460 lacks phencyclidine-like activity and can eliminate this activity of memantine and MK-801 [23], indicating its high antiaddictive potential [24]. IEM-1460 is a direct agonist of GluA2-AMPA receptors on pyramidal cells of the cortex [53].

IEM-1460 has a unique combination of three antiaddictive effects (GluA1-AMPA receptor inhibition, nicotinic acetylcholine receptor inhibition, and GluA2 activation), indicating a significant antiaddictive potential. No other products for the treatment of problem gambling have the same set of properties. This combination of properties in a single drug must ensure its high efficacy in other tests, as confirmed in our experiments using a modified Iowa Gambling Task to assess impulsivity in a Y-maze-based problem gambling model in rats.

The key indicator of antiaddictive properties is the drug's efficacy in modulating extracellular dopamine levels in the NAc, a brain structure that determines the resultant component of a motive state and transforms it into approach or avoidance behavior [54]. Changes in phasic dopamine release in the NAc in response to electrical stimulation of the VTA indicated an increase in phasic dopamine release following IEM-1460 injection at an active dose of 1 mg/kg IP. This dose was most effective when assessing impulsivity in a Y-maze-based problem gambling model using a modified Iowa Gambling Task. These findings are consistent with published research. The mGlu 2/3 receptor antagonist LY341495 increases extracellular dopamine levels in the NAc [33]. Antiaddictive properties have been reported for drugs that effectively modulate extracellular dopamine levels, increasing or reducing its release in the NAc [55]. Dopamine receptor antagonists have also been shown to increase dopamine release in the NAc. According to *in vivo* microdialysis, levo-tetrahydropalmatine (L-THP), a dopamine D_1 and D_2 receptor antagonist, increases extracellular dopamine levels in the NAc, with a dose-dependent increase in cocaine-induced dopamine release. L-THP inhibits cocaine-induced conditioned place preference and prevents cocaine- or methamphetamine-triggered reinstatement [56]. Moreover, L-THP attenuates cocaine-enhanced brain stimulation reward and provides a dose-dependent decrease in cocaine self-administration under progressive-ratio reinforcement [57]. This self-administration mode is similar to problem gambling patterns that we attempted to model in this work, where impulsivity was assessed in a Y-maze-based problem gambling model.

The question is how increased extracellular dopamine levels can produce a potential therapeutic effect of AMPA receptor antagonists in addictive behavior. Reinforcement-induced phasic dopamine release in the NAc (triggered by gambling or addictive substances) can also activate neural adaptation processes. Signals from the NAc activate striatopallidal and pallidal-thalamocortical circuits, including the dorsal striatum, resulting in adaptive changes and stereotyped behavior, which underlies impulsive and compulsive reward-seeking behaviors [58]. The key synaptic changes in this case are associated with NMDA and AMPA receptor-mediated glutamatergic transmission from the prefrontal cortex and amygdala to the VTA and NAc [59]. Long-term use of addictive substances is likely associated with impaired dopamine function, as indicated by reduced dopamine release and the number of D_2 receptors. Furthermore, reduced striatal D_2 receptors are associated with decreased activity of the orbitofrontal cortex (implicated in salience attribution, motivation, and compulsive behavior) and the anterior cingulate cortex (implicated in inhibitory control regulation and impulsivity). This results in impaired prefrontal self-regulation, loss of control, and compulsive drug taking, indicating addiction [60]. Reinforcing effects of addictive substances and stimuli are primarily determined by the extent and rate of dopamine release in the NAc, and chronic exposure activates glutamate-mediated neural adaptation in dopamine terminals of the mesolimbic system, reducing dopamine release and the number of D_2 receptors [61]. Increased risk of relapse in the treatment of disorders due to addictive behaviors, depression, and dysphoria are frequently associated with impaired dopamine function [61, 62]. Therefore, antiaddictive therapies that increase extracellular dopamine levels are superior to substitution therapy [63].

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CONCLUSION

Inhibition of GluA1-AMPA receptors with IEM-1460 reduces impulsivity in a problem gambling model by modulating extracellular dopamine levels. IEM-1460 reduces the number of visits to the Y-maze arm with a more significant but less likely food reinforcement, decreasing impulsivity in a problem gambling model using a modified Iowa Gambling Task. Changes in phasic dopamine release in the NAc in response to electrical stimulation of the VTA indicated an increase in phasic dopamine release following IEM-1460 injection at an active dose of 1 mg/kg IP. This dose was most effective when assessing impulsivity in a Y-maze-based model. Our work confirmed that IEM-1460 is a potent AMPA receptor antagonist, which is consistent with published research.

ADDITIONAL INFO

Author contributions: A.A. Lebedev: project administration, data curation, writing—original draft; A.M. Potapkin: conceptualization, formal analysis, investigation, writing—review & editing; S.S. Pyurveev, V.V. Sizov, V.N. Mukhin, M.A. Netesa: investigation; V.E. Gmiro: resources, writing—review & editing; P.D. Shabanov— conceptualization, supervision. All the authors approved the version of the draft to be published and agreed to be accountable for all aspects of the work, ensuring that issues related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. А.А. Лебедев — организация проведения экспериментов, обзор литературы, сбор и анализ литературных источников, написание текста; А.М. Потапкин — продвижение идеи, биоинформатический анализ данных, экспериментальные процедуры, редактирование статьи; С.С. Пюрвеев, В.В. Сизов, В.Н. Мухин, М.А. Нетеса — экспериментальные процедуры; В.Е. Гмиро — синтез соединения, редактирование статьи; П.Д. Шабанов — общая идея и руководство работой. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

Этическая экспертиза. Исследование одобрено локальным этическим комитетом ФГБНУ «Институт экспериментальной медицины», протокол № 2/23 от 15.06.2023.

Источники 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».

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

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

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

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

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

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