



Piracetam potentiates neuronal and behavioral effects of ketamine

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Abstract

Introduction: Ketamine has a fast, but short-term antidepressant effect. To support the therapeutic effect, repeated administrations of the drug are needed, which causes cognitive disorders. The drugs with cerebroprotective action can potentially intensify the main and weaken the side effects of drugs.

Materials and methods: The impact of ketamine (5 and 20 μ M), piracetam (100 μ M), and their combinations on the synaptic transmission was studied on hippocampal slices in the CA1 area of rat hippocampus by means of electrophysiological methods. In behavioral experiments were aimed at studying an impact of the used drugs on the predictors which mark depressant behavior of rats: the duration of immobilization in a forced swimming test and preference for the consumption of sucrose solution (comparably with water). The behavioral experiments were performed on intact rats and rats with behavioral depression induced by chronic swimming stress.

Results and discussion: Ketamine (5 and 20 μ M) potentiates synaptic transmission in the radial layer of the CA1 hippocampal area. At a smaller concentration, ketamine potentiates synaptic transmission only due to the postsynaptic action, and at a greater concentration – with help of post- and presynaptic action. Piracetam (100 μ M), like ketamine at a concentration of 5 μ M stimulated synaptic transmission, but to a lesser degree. Ketamine at a concentration 5 μ M under combined effect with piracetam induced the same effect as that at a concentration of 20 μ M without piracetam, only due to a postsynaptic action. Ketamine at doses of 5 and 20 mg/kg one hour after a single systemic administration resulted in the reduced immobilization duration, but not predictors of preference for consuming a sweet solution; piracetam at a dose of 100 mg/kg under these conditions had no impact on the parameters of the rats' behavior. The studied behavior parameters in cases of behavioral depression also changed after a single administration of ketamine at the doses of 5 and 20 mg/kg. Piracetam significantly stimulated an antidepressant action of ketamine under these circumstances.

Conclusion: Piracetam potentiates a ketamine-induced enhancement of the synaptic transmission at the radial layer of the CA1 hippocampal area when investigating at the brain slices. Piracetam stimulates an antidepressant action of a single dose of ketamine in cases of behavioral depression, though it has no antidepressant effect when administered at a single dose.

Keywords

Piracetam, ketamine, hippocampus, synaptic transmission, behavioral depression.

Introduction

Major depressive disorder (MDD), prevailing in 7–12% of men and 20–25% of women, is a leading cause of disability and a serious public health problem. The current estimates by the WHO caution that MDD will become the second leading cause of disability after 2020. In addition to the increasing prevalence and the behavioral sequelae with it, MDD is an enormous economic burden on society. The existing treatments of MDD usually last from weeks to months to achieve their antidepressant effects, and many patients do not experience any sufficient improvement even after months of treatment. There is a danger of patients committing suicides during treatment. The fact is that twice as many people die from committing suicide each year than by homicide, and every fourth suicide victim had been treated by antidepressants until death (Greenberg et al. 2015, Karch 2012).

Early 2000 showed that a single sub-anesthetic dose (0.5 mg/kg) of **ketamine**, a non-selective non-competitive antagonist of ionotropic N-methyl-D-aspartate (NMDA) glutamatergic receptors, produced a rapid and long-lasting antidepressant effects in patients suffering from MDD (Berman et al. 2000). But together with a pronounced antidepressant effect, **ketamine** also has a psychosis-producing properties, thus there is a threat of development of drug abuse (Browne and Lucki 2013). Adverse side effects of **ketamine** require correction, but the ways of doing so are poorly apprehended.

In pre-clinical trial, it was discovered that drugs with brain protective activity, e.g. **piracetam** (nootropil), reinforce an impact of tricyclic antidepressant imipramine on manifestations of behavioral depression in rats caused by a swimming stress (Zayka et al. 2018). Against the background of **piracetam**, a partial dose of imipramine produces the same effect as a full dose of an antidepressant. This fact is of interest because, if there is a chance of adverse side effects of using some drug when increasing its dose, by potentiating the effect of this drug it is possible to achieve the main effect at lesser drug doses, thus decrease the chance of adverse side effects.

The paper presents the results of studying the influence of nootropic drug **piracetam** on changes of glutamatergic synaptic transmission in the CA1 hippocampal area caused by sub-anesthetic doses of **ketamine**. At the same time, the paper looks at the changes of influence of **ketamine** on a duration of immobility in the forced swimming test and the preference for consuming sweet solution in cases of behavioral depression induced by chronic swimming stress at the background of **piracetam** action.

Materials and methods

The research was performed on white inbred rats. The impact of **ketamine** and **piracetam** on glutamatergic transmission in the synapses formed by axons of pyramidal neurons of the CA3 area (Schaffer's collaterals) and by

dendrites of pyramidal neurons of the CA1 area was studied on the slices of the hippocampus, using a conventional electrophysiological method. The electrophysiological studies were performed on the slices of the rat dorsal hippocampus. The details of the method were given in (Abramets et al. 2011). The dorsal hippocampus was isolated from the posterior pole of the brain. The 400 μm thick slices were prepared using a Vibratome. The field (f) excitatory postsynaptic potentials (EPSP) of pyramidal neurons of the CA1 region, which had been caused by electrical stimulation of Schaffer's collaterals, were recorded extracellularly in the hippocampus slices, using glass microelectrodes filled with 2 M of NaCl solution with tip resistance of 2–5 megohms. The stimulation of synaptic inputs was carried out by a bipolar nickel-chromium electrode by rectangular current pulses of 0.1 ms duration. The N-methyl-D-aspartate (NMDA) component of the fEPSP of pyramidal hippocampal neurons was isolated pharmacologically. To do this, the brain slices were superfused with Krebs solution with a concentration of Mg^{2+} reduced to 0.2 mM (in favour 1 mM) and the addition of 10 μM of an α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor blocker – 6,7-dinitroquinoxalin-2,3-dione (DNQX), 50 μM of a non-competitive GABA_A receptors blocker picrotoxin and 1 μM of a co-agonist of NMDA receptors, glycine. Paired pulse ratio (PPR) was determined as a ratio of the second/first amplitudes of fEPSP caused at an interpulse interval of 50 ms.

The level of depressiveness in rats was assessed by recording the parameters of the forced swimming test (FST) (Porsolt et al. 1978). The rats were placed in a plexiglass cylinder of 46 cm in diameter and 45 cm in height, filled with water (temperature 23–25 °C) to a level of 30 cm from the bottom. On the first day, the duration of the swimming was 15 minutes (pre-test); 24 hours later, the rats were placed in water for 6 minutes, and, using videorecording, the basic parameters of their behavior were recorded and stored in a separate file. The immobilization behavior was characterized by positioning the rats vertically, motionless, with their forelegs pressed to the chest, hind legs extended, and the head above the water. The longer immobilization lasted, the higher level of depression the animals had.

The test of sucrose preference characterizing a hedonic behavior of rats was carried out by the method from (Benelli et al. 1999). For this, on the first day, the rats were placed in individual cages with two drinking bowls filled with 1% sucrose solution. The next day, there was water in one drinking bowl, and the solution of sucrose – in the other. For 23 hours on the third day, the animals were deprived of food and water, and then 2 pre-weighed drinking bowls filled with water and a solution of sucrose were returned to the cages for 60 minutes. One hour later, the drinking bowls were weighed. In the next 2 hours of the fourth day, the animals received food and water, after which they were deprived of food and water for 21 hours. Then again, the drinking bowls were returned for 1 hour,

and the percentage of preference for the consumption of sucrose solution (P) was determined by the formula (1):

$$P = \frac{\text{The weight of consumed sucrose solution}}{\text{The weight of consumed liquid}} \times 100 \quad (1)$$

First, an impact of intraperitoneally (i/p) administrated **ketamine** (5 and 20 mg/kg) and **piracetam** (100 mg/kg) on rats' immobilization duration in FST was studied, as well as the percentage of preference for consumption of sucrose solution (PCSS) in the intact rats. Then, a depression syndrome was simulated according to the method from (Sun et al. 2011). For that, after determination of the initial behavioral indicators on the first day, for the next five days the rats were subjected to a swimming stress by placing the animals in water for 10 min. On the sixth day, after terminating the stress procedure, the rats were divided into 6 groups. The rats of Group 1 were administrated **piracetam** (100 mg/kg) i/p and 30 min later – **ketamine** (5 mg/kg). The rats of Group 2 also received **piracetam** and **ketamine** (20 mg/kg). The rats of Groups 3 and 4 were administrated a some volume vehicle as it with **piracetam** i/p and 30 min later – **ketamine** at doses of 5 and 20 mg/kg, respectively. The rats of Group 5 received **piracetam** (100 mg/kg) and 30 min later – a dosing vehicle. The rats of Group 6 were administrated the vehicle twice, at 30 min interval. One hour after the last injection, the immobilization duration in FST was determined in the rats of the first halves of each group, and in the second halves – percentage of PCSS. Each group had 6–8 rats.

The research results were analyzed using the conventional methods of variation statistics and licensed Medstat software. For each series, the mean and standard error of the mean were determined. The significance of the differences in the compared values was assessed using a paired Student t-test.

Results and discussion

The study looked at the impact of (R,S)-ketamine at concentration of 5 and 20 μM , which approximately corresponded to the doses of 5 and 20 mg/kg systemically administrated to rats, on glutamatergic excitatory synaptic transmission in the CA1 area of hippocampus. Amplitudes of fEPSPs of pyramidal neurons of the CA1 area significantly increased to $122.1 \pm 4.9\%$ ($p < 0.05$) against control under the influence of Krebs solution with 5 μM of **ketamine** on the slices for 60 min. With **ketamine** at a dose of 20 μM influencing the slices, the amplitude of fEPSPs increased ($p < 0.01$) to a greater extent to $166.8 \pm 6.6\%$ (Fig. 1). The complex postsynaptic EPSP of pyramidal neurons have two components, due to the action of glutamate on postsynaptic AMPA and NMDA glutamate receptors (Hestrin et al. 1990). Under the action of **ketamine** (5 μM) on slices, the amplitude of an NMDA component of fEPSP hardly changed; but it significantly ($p < 0.05$) increased to $119.4 \pm 4.2\%$ under the influence of **ketamine** at a dose of 20 μM (Fig. 1). To identify the localization of **ketamine**

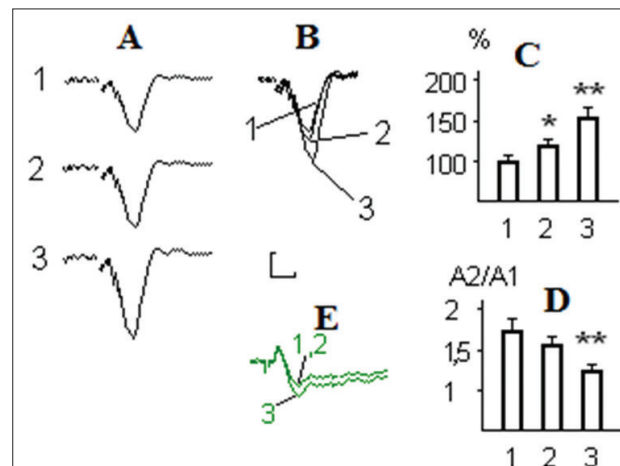


Figure 1. Impact of **ketamine** on parameters of synaptic transmission in pyramidal neurons of CA1 hippocampal area. *Note:* A – oscillograms of complex fEPSPs of pyramidal neurons, obtained in a separate experiment; 1 – control, 2 – one hour later with 5 μM of **ketamine**, 3 – one hour later with 20 μM of **ketamine**; B – three overlapping oscillograms; C – dependence of changes in amplitudes of complex fEPSPs on acting concentrations of **ketamine**; 1 – control, 2 and 3 – **ketamine** action at concentrations of 5 and 20 μM , respectively; D – changes of PPR of fEPSPs with **ketamine** impact on slices; 1–3 – as in C; E – **ketamine** impact on amplitudes of NMDA components of fEPSPs of pyramidal neurons; 1 – control, 2 and 3 – with **ketamine** at concentrations of 5 and 20 μM , respectively. Calibrations – 0.2 mV; 5 ms. * and ** – differences are significant at $p < 0.05$ and $p < 0.01$, respectively.

action (pre- or postsynaptic) on the pyramidal neuron synapses, the ranges of correlation between the amplitudes of the second responses to the amplitudes of the first responses were measured at 50 ms interpulse interval (PPR). Thus, with **ketamine** (5 μM) impact on slices, PPR did not change – 1.64 ± 0.09 against 1.75 ± 0.09 in control; with an increased concentration of **ketamine** to 20 μM , PPR significantly ($p < 0.05$) decreased to 1.37 ± 0.07 (Fig. 1).

When affecting hippocampal slices, **ketamine**, though it noncompetitively blocks all types of NMDA glutamate receptors, caused increased amplitudes in fEPSP of pyramidal neurons (Fig. 1). This effect may be due to increasing of efficacy of postsynaptic AMPA glutamate receptors or enhancement of presynaptic release of a mediator from the Schaffer's collaterals. Apparently, **ketamine** (5 μM) operates postsynaptically, which is proved by increased amplitudes of complex fEPSPs without shifts in amplitudes of their NMDA components and PPR (Fig. 1). On the other hand, **ketamine** (20 μM) enhances synaptic transmission predominantly in a presynaptic way. Indeed, along with increased amplitudes of complex fEPSPs, there was an increased in amplitudes of their NMDA components and a decrease in PPR (Fig. 1), meaning enhancement of presynaptic release of the mediator (Foster and McNaughton 1991).

Ketamine-induced enhancement of glutamatergic synaptic transmission in hippocampus was also observed by other researchers (Autry et al. 2011, Nosyreva et al.

2013). But the nature of this phenomenon is still not clear. It may be due to enhanced phosphorylation of Ser845 in the structure of GluA1 subunit [site of protein kinase A (PKA)] and intensification of the subunit transport to the surface of a neuron. Ketamine-induced enhancement of synaptic transmission was prevented by PKA inhibitor H89; a blocker of tyrosine kinase receptors K225a and an inhibitor of protein translation anisomycin inhibited GluA1 subunit transport to the surface of a neuron and in postsynaptic (Zhang et al. 2017). These changes can be due to blockade by ketamine of postsynaptic NMDA glutamate receptors. It was determined that ketamine used at certain range of doses blocks miniature EPSPs at physiological concentrations of Mg^{2+} , whereas spontaneous Ca^{2+} -independent release of glutamate from Schaffer's collaterals regulates the number of postsynaptic AMPA glutamate receptors and synaptic plasticity (Autry et al. 2011). An inhibition of spontaneous release of glutamate or miniature EPSPs in synapses causes an increased activity of elongation factor of eEF2 kinase and enhances the local dendritic translation of proteins, primarily, neurotrophin BDNF and GluA1 subunit of AMPA receptors.

Enhancement of glutamate presynaptic release, caused by 20 μM ketamine, is associated with blockade of more ketamine-sensitive NMDA glutamate receptors, containing GluN2C and GluN2D subunits, in Schaffer's collaterals (Zhang et al. 2017). Along with this, ketamine blocks an HCN1 subunit of cationic channels activated by hyperpolarization and cyclic nucleotide-gated (HCN). In turn, the blocking of HCN channels increases the activity of voltage gated $Ca_v2.3$ channels and enhances presynaptic release of glutamate (Noam et al. 2010, Huang et al. 2011). S-ketamine is twice as powerful as RS-ketamine when blocking HCN1 cationic channels and EC50 of RS-ketamine when blocking NMDA glutamate receptors ~ four times as weaker as its EC50 by its ability to inhibit HCN cationic channels (Chen et al. 2009). Therefore, to inhibit HCN1 channels and enhance presynaptic release of glutamate, higher doses of ketamine are needed. Ketamine at doses of 3–10 mg/kg, which approximately correspond to brain concentration of 3–10 μM , produces a pronounced antidepressant effect (Autry et al. 2011) and enhances the synaptic transmission in hippocampus due to postsynaptic mechanisms (Fig. 1). At greater doses (20–30 mg/kg), ketamine also produces an antidepressant effect and enhances presynaptic release of glutamate in the hippocampal synapses (Zhang et al. 2017; Fig. 1). It remains unclear whether presynaptic mechanism of ketamine has anything to do only with an antidepressant, or with both antidepressant, and psychedelic effects of the drug.

The nootropic drug piracetam influenced the synaptic transmission at synapses formed by Schaffer's collaterals and dendrites of pyramidal neurons of the CA1 area of hippocampus. When piracetam (100 μM) affects slices, the amplitudes of complex fEPSPs of pyramidal neurons significantly ($p < 0.05$) increased to 122.4 ± 5.1 % in relation to control (Fig. 2). The increase in amplitudes of complex fEPSPs was not followed by changes in amplitudes

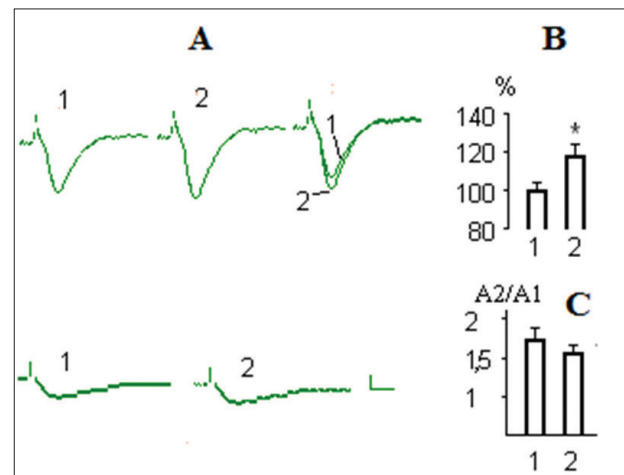


Figure 2. Piracetam enhances synaptic transmission in pyramidal neurons of the CA1 hippocampal area. *Note:* **A top** – overlapping oscillograms of complex fEPSPs of pyramidal neurons before (1), 30 min after piracetam's (100 μM) action on slices (2); **A bottom** – overlapping oscillograms of NMDA components of fEPSPs of pyramidal neurons before (1) and after (2) piracetam's action. The oscillograms were obtained in a separate experiment. **B and C** – impact of 100 μM of piracetam on amplitudes of complex fEPSPs of pyramidal neurons and PPR, respectively. Calibrations – 0.2 mV; 5 ms. * – differences are significant at $p < 0.05$.

of their NMDA components (Fig. 2). Piracetam did not affect PPR: 1.64 ± 0.11 against 1.76 ± 0.12 in control (Fig. 2). These facts mean that piracetam stimulates the synaptic transmission in hippocampus through a postsynaptic mechanism. In fact, piracetam exhibits the properties of an AMPA kinase, i.e. increases the amplitude of synaptic responses by potentiating the AMPA component of fEPSPs. The potentiating action of piracetam on fEPSPs was conditioned by reduced desensitization of AMPA glutamate receptors caused by glutamate, which is characteristic of AMPA kinases (Ahmed and Oswald 2010).

Piracetam enhanced an impact of ketamine on synaptic transmission in the CA1 area of hippocampus. In fact, preliminary action of 100 μM piracetam for 30 min on the slices caused an increase in amplitudes of complex fEPSPs of pyramidal neurons to 121.3 ± 4.7 % in relation to control. The influence of 5 μM ketamine on slices in the presence of piracetam 60 min later induced a further increase in amplitudes of complex fEPSPs to 167.6 ± 5.8 % in relation to control (Fig. 3). But ketamine (5 μM) had no impact on PPR – 1.68 ± 0.13 in control and 1.71 ± 0.11 after the influence of ketamine (Fig. 3). It means that a significant increase in amplitudes of complex fEPSPs of pyramidal neurons of the CA1 hippocampal area induced by a joint action of ketamine and piracetam was conditioned by the postsynaptic mechanism. An increased reactivity of postsynaptic AMPA glutamate receptors, underlying this mechanism, may be a consequence of enhanced phosphorylation of Ser845 in GluA1 receptor subunit and reduced desensitization of AMPA receptors (Zhang et al. 2017, Ahmed and Oswald 2010). It is important that a combined action of piracetam and 5 μM ketamine on

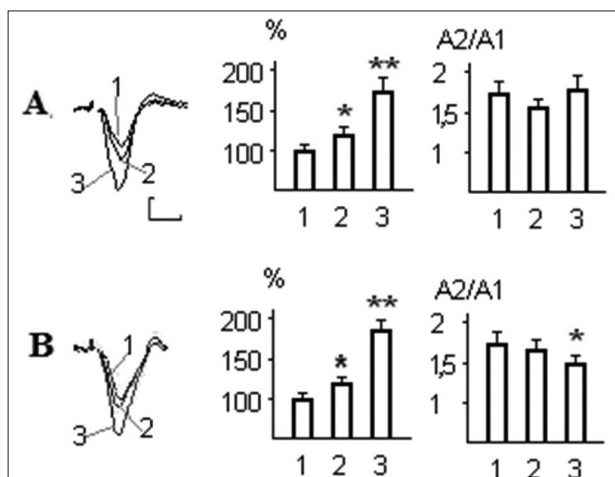


Figure 3. Piracetam potentiates an impact of ketamine on synaptic transmission in pyramidal neurons of the CA1 hippocampal area. *Note:* **A left** – overlapping oscillograms of complex fEPSPs of pyramidal neurons before (1) and 30 min after applying 100 μM of piracetam onto slices (2) and 60 min after applying ketamine (5 μM) in the presence of piracetam (3). **A at center** – changes in amplitudes of complex fEPSPs. **A right** – changes in PPRs in control (1), under the influence of piracetam (2) and of ketamine and piracetam (3). **B** – the same under the influence of piracetam (100 μM) and ketamine (20 μM) on slices. Calibrations – 0.2 mV; 5 ms. * and ** – differences are significant at $p < 0.05$ and $p < 0.01$, respectively.

slices results in the same effect as only 20 μM ketamine is applied on slices (Fig. 1, 3). However, in the latter case, an increase in amplitudes of complex fEPSPs was caused by both post- and presynaptic mechanisms. In the presence of piracetam, when ketamine at concentration of 20 μM was applied on slices, there was an increase in amplitudes of complex fEPSPs to $178.8 \pm 5.3\%$ against $159.7 \pm 4.9\%$ without piracetam in relation to control (Figs 1, 3). It is of interest that under the joint influence of piracetam and 20 μM ketamine on slices, an unreliable trend was found towards the weakening of a presynaptic action of ketamine: PPR under the influence of ketamine only was 1.37 ± 0.07 , whereas under the influence of both drugs it was 1.49 ± 0.08 (Figs 1, 3). Consequently, piracetam enforces the action of ketamine on synaptic transmission in hippocampus predominantly through postsynaptic mechanisms.

Further, the study examined an impact of ketamine and piracetam on behavioral parameters of the intact rats relating to behavioral depression. One hour after i/p administration of 5 mg/kg ketamine, the time of immobilization of the rats in forced swimming test (FST) significantly reduced; after administration of a greater (20 mg/kg) dose, the time of immobilization reduced to a greater extent (Table 1). The differences of the effects of the two doses of ketamine, however, are unreliable ($P = 0.141$), therefore the assumption about dose-dependent ketamine effects is wrong. At both doses used, ketamine has no effect (Table 1) on the percentage of preference for consumption of sucrose solution (PCSS). Other researchers (Li et al. 2011) also observed no ketamine impact on this predictor in the

Table 1. An impact of tested drugs on behavioral responses in control rats.

Administered drugs	Time of immobilization (s)	% preference for consumption of sucrose solution
Control (vehicle)	59.4 ± 3.4	79.4 ± 2.4
Ketamine 5 mg/kg after 60 min	$46.4 \pm 3.2^*$	72.1 ± 2.5
Ketamine 20 mg/kg after 60 min	$38.7 \pm 3.6^*$	83.6 ± 3.1
Piracetam 100 mg/kg after 60 min	62.2 ± 3.6	75.8 ± 4.24

Note: * – differences are significant at $p < 0.05$.

Table 2. Impact of tested drugs on behavioral responses of rats in behavioral depression caused by swimming stress.

Administered drugs	Time of immobilization (s)	% preference for consumption of sucrose solution
Control (vehicle)	59.4 ± 3.4	79.4 ± 2.4
1 st day after termination of swimming stress (vehicle)	$114.0 \pm 5.1^*$	$54.0 \pm 1.8^*$
Ketamine 5 mg/kg after 60 min	$79.8 \pm 3.9^\#$	$66.1 \pm 2.1^\#$
Ketamine 20 mg/kg after 60 min	$68.4 \pm 3.7^\#$	$71.2 \pm 2.3^\#$
Piracetam 100 mg/kg after 30 min	99.4 ± 5.4	59.6 ± 2.4
Piracetam 100 mg/kg after 30 min + ketamine 5 mg/kg after 60 min	$54.7 \pm 3.1^{\#\wedge}$	$85.5 \pm 3.2^{\#\wedge}$
Piracetam 100 mg/kg after 30 min + ketamine 20 mg/kg after 60 min	$47.4 \pm 4.1^{\#\wedge}$	$88.3 \pm 4.2^{\#\wedge}$

Note: * – differences from control, # – from indicators after stress impact, ^ – from indicators against the action of ketamine only at doses of 5 and 20 mg/kg are significant at $p < 0.05$.

intact animals. Piracetam at a dose of 100 mg/kg had no influence on either behavioral parameters (Table 1).

One day after the termination of the swimming stress impact, behavioral depression was observed, which was marked by an increased immobilization duration in FST and by anhedonia – a decreased PCSS (Table 2). One hour after a single administration of ketamine at both doses to rats, under these circumstances the manifestations of behavioral depression were observed weakening: a decrease in immobilization duration and an increase in PCSS (Table 2). A single administration of piracetam had no influence on animal’s behavior (Table 2). The effects of ketamine administrated on the background of the action of piracetam significantly increased; the effect of ketamine on behavior at a dose of 5 mg/kg under these circumstances exceeded its effects at a dose of 20 mg/kg without piracetam (Table 2). Therefore, piracetam intensifies the impact of single-administered ketamine on the animals’ behavior in stress-induced behavioral depression. It still remains unclear why both tested drugs stimulate synaptic transmission in hippocampus through the postsynaptic action, but single-administered ketamine exhibits an antidepressant effect, whereas piracetam has no

such effect. So **piracetam** increases the functional activity of the existing postsynaptic AMPA glutamate receptors, whereas **ketamine**, by activating a signal pathway mTOR, intensifies translation and expression of presynaptic proteins Arc and synapsin I, postsynaptic protein PSD95 and GluA1 subunit of AMPA receptors, which are involved in formation, maturation and functioning of new spine synapses (Li et al. 2010). However, only after chronic administration, **piracetam** exhibits an antidepressant-like effect (Zayka et al. 2018).

The main advantage of **ketamine** is its fast antidepressant effect, but it lasts a week at most, therefore requiring the repeated administration of the drug. This is accompanied by adverse side effects – cognitive disturbances, disorders of memory, psychotic symptoms, increasing of oxidative stress in brain and developing drug addiction (Zuo et al. 2007, Krystal et al. 2005). To reduce adverse side effects and to enhance an antidepressant effect of **ketamine**, it is recommended that **ketamine** be combined with a mood stabilizer **lithium** (Chiu et al. 2014). **Lithium** is known to directly inhibit both isoforms of kinase-3 glycogen synthase (GSK-3) and to enhance expression of neurotrophin BDNF, which provides for a pronounced cerebroprotective effect of the drug (Liu et al. 2013). **Piracetam** also has a pronounced cerebroprotective effect (Vostrikov 2017) and enhances neuronal and behavioral effects of **ketamine**. In fact in the presence of **piracetam**,

ketamine at a concentration of 5 μM causes the same neuronal effect as at its concentration of 20 μM without **piracetam**; however, **ketamine** (5 μM) does not stimulate presynaptic release of glutamate (Fig. 3). On the other hand, **ketamine** in the systemic administration at a dose of 5 mg/kg, which approximately corresponds to the concentration of 5 μM affecting the slices, causes an antidepressant effect (Table 2). Therefore, the postsynaptic effect of low concentrations of **ketamine** on the brain limbic structures is sufficient for developing of antidepressant effect. An addition of a presynaptic component – influence of **ketamine** at greater doses/concentrations – stimulates the antidepressant effect of the drugs, but it can be a source of psychotic side effect. One of the advantages of **piracetam** as a potentiator of **ketamine** action is better patients' tolerance towards it, when compared with **lithium**.

Conclusion

Piracetam potentiates enhancement of the ketamine-induced synaptic transmission in the radial layer of the CA1 hippocampal area in studies of the brain slices. When administered systemically, **piracetam** enhances an antidepressant effect of single-administered **ketamine** in behavioral depression, though **piracetam** has no antidepressant effect on its own in single administration.

References

- Abramets II, Evdokimov DV, Talalayenko AN (2011) Early anoxic damages of hippocampus and their changes caused by antidepressants. *Neurophysiology [Neyrofiziologiya]* 43(2): 123–133. <https://doi.org/10.1007/s11062-011-9193-5>
- Ahmed AH, Oswald RE (2010) Piracetam defines a new binding site for allosteric modulators of α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. *Journal of Medicinal Chemistry* 53(5): 2197–2203. <https://doi.org/10.1021/jm901905j> [PubMed] [PMC]
- Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavali ET, Monteggia LM (2011) NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* 475(7354): 91–95. <https://doi.org/10.1038/nature10130> [PubMed] [PMC]
- Benelli A, Filafarro M, Bertolini A, Genedani S (1999) Influence of S-adenosyl-L-methionine on chronic mild stress-induced anhedonia in castrated rats. *British Journal of Pharmacology* 127(3): 645–654. <https://doi.org/10.1038/sj.bjp.0702589> [PubMed] [PMC]
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry* 47(4): 351–354. [https://doi.org/10.1016/S0006-3223\(99\)00230-9](https://doi.org/10.1016/S0006-3223(99)00230-9) [PubMed]
- Browne CA, Lucki I (2013) Antidepressant effects of ketamine: Mechanisms underlying fast-acting novel antidepressants. *Frontiers in Pharmacology* 4: 161. <https://doi.org/10.3389/fphar.2013.00161> [PubMed] [PMC]
- Chen X, Shu S, Bayliss DA (2009) HCN1 channel subunits are molecular substrate for hypnotic action of ketamine. *Journal of Neuroscience* 29(3): 600–609. <https://doi.org/10.1523/JNEUROSCI.3481-08.2009> [PubMed] [PMC]
- Chiu CT, Scheuing L, Liu G, Liao HM, Linares GR, Lin D, Chuang DM (2014) The mood stabilizer lithium potentiates the antidepressant-like effects and ameliorates oxidative stress induced by acute ketamine in a mouse model of stress. *International Journal of Neuropsychopharmacology* 18(6): pyu102. <https://doi.org/10.1093/ijnp/pyu102> [PubMed] [PMC]
- Foster TC, McNaughton BL (1991) Long-term enhancement of CA1 synaptic transmission due to increased quantal size, not quantal content. *Hippocampus* 1(1): 79–91. <https://doi.org/10.1002/hipo.450010108> [PubMed]
- Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC (2015) The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *Journal of Clinical Psychiatry* 76(2): 155–162. <https://doi.org/10.4088/JCP.14m09298> [PubMed]
- Hestrin S, Nicoll RA, Perkel DJ, Sah P (1990) Analysis of excitatory synaptic action in pyramidal cells using whole-cell recording from rat hippocampal slices. *Journal of Physiology (Lond)* 422: 203–225. <https://doi.org/10.1113/jphysiol.1990.sp017980> [PubMed] [PMC]
- Huang Z, Lujan R, Kadurin I, Uebele VN, Renger JJ, Dolphin AC, Shah MM (2011) Presynaptic HCN1 channels regulate Cav3.2 activity and neurotransmission at select cortical synapses. *Nature Neuroscience* 14(4): 478–486. <https://doi.org/10.1038/nn.2757> [PubMed] [PMC]
- Karch DL (2012) Surveillance for violent deaths – National Violent Death Reporting System, 16 states, 2009. *MMWR Surveillance Summaries* 61(6): 1–43. [PubMed]

- Krystal JH, Perry EBJr, Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, Macdougall L, Abi-Saab W, D'Souza DC (2005) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. *Archives of General Psychiatry* 62(9): 985–994. <https://doi.org/10.1001/archpsyc.62.9.985> [PubMed]
- Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 329(5994): 959–964. <https://doi.org/10.1126/science.1190287> [PubMed] [PMC]
- Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, Duman RS (2011) Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biological Psychiatry* 69(8): 754–761. <https://doi.org/10.1016/j.biopsych.2010.12.015> [PubMed] [PMC]
- Liu RJ, Fuchikami M, Dwyer JM, et al. (2013) GSK-3 inhibition potentiates the synaptogenic and antidepressant-like effects of sub-threshold doses of ketamine. *Neuropsychopharmacology* 38(11): 2268–2277. <https://doi.org/10.1038/npp.2013.128> [PubMed] [PMC]
- Noam Y, Zha Q, Phan L, Wu RL, Chetkovich DM, Wadman WJ, Baram TZ (2010) Trafficking and surface expression of hyperpolarization-activated cyclic nucleotide-gated channels in hippocampal neurons. *Journal of Biological Chemistry* 285(19): 14724–14736. <https://doi.org/10.1074/jbc.M109.070391> [PubMed] [PMC]
- Nosyreva E, Szabla K, Autry AE, Ryazanov AG, Monteggia LM, Kavalali ET (2013) Acute suppression of spontaneous neurotransmission drives synaptic potentiation. *Journal of Neuroscience* 33(16): 6990–7002. <https://doi.org/10.1523/JNEUROSCI.4998-12.2013> [PubMed] [PMC]
- Porsolt RD, Bertin A, Jalfre M (1978) “Behavioural despair” in rats and mice: strain differences and the effects of imipramine. *European Journal of Pharmacology* 51(3): 291–294. [https://doi.org/10.1016/0014-2999\(78\)90414-4](https://doi.org/10.1016/0014-2999(78)90414-4) [PubMed]
- Sun P, Wang F, Wang L, Zhang Y, Yamamoto R, Sugai T, Zhang Q, Wang Z, Kato N (2011) Increase in cortical pyramidal cell excitability accompanies depression-like behavior in mice: a transcranial magnetic stimulation study. *Journal of Neuroscience* 31(45): 16464–16472. <https://doi.org/10.1523/JNEUROSCI.1542-11.2011> [PubMed]
- Vostrikov VV (2017) Role of piracetam in the modern practice of medicine. *Reviews on Clinical Pharmacology and Drug Therapy [Obzory po Klinicheskoy Farmakologii i Lekarstvennoy Terapii]* 15(1):14–25. <https://doi.org/10.17816/RCF15114-25> [in Russian]
- Zayka TO, Evdokimov DV, Abramets II (2018) Experimental studies of interaction of substances with cerebroprotective activity with imipramine. *Journal of Fundamental Medicine and Biology [Zhurnal Fundamental'noy Meditsiny i Biologii]* 7(3): 18–23. [in Russian]
- Zhang K, Xu T, Yuan Z, Wei Z, Yamaki VN, Huang M, Haganir RL, Cai X (2017) Essential roles of AMPA receptor GluA1 phosphorylation and presynaptic HCN channels in fast-acting antidepressant responses of ketamine. *Science Signal* 9(458): ra123. <https://doi.org/10.1126/scisignal.aai7884> [PubMed] [PMC]
- Zuo DY, Wu YL, Yao WX, Cao Y, Wu CF, Tanaka M (2007) Effect of MK-801 and ketamine on hydroxyl radical generation in the posterior cingulate and retrosplenial cortex of free-moving mice, as determined by *in vivo* microdialysis. *Pharmacological Biochemistry and Behavior* 86(1): 1–7. <https://doi.org/10.1016/j.pbb.2006.05.010> [PubMed]

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