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 μM), piracetam (100 μM), 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 depressive 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 μM) 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 μM), like ketamine at a concentration of 5 μM stimulated synaptic transmission, but to a lesser degree. Ketamine at a concentration 5 μM under combined effect with piracetam induced the same effect as that at a concentration of 20 μM 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 ketamine, 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 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 post synaptic 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 Mg²⁺ 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[sub]A[/sub] 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):

\[
P = \frac{\text{weight of consumed sucrose solution}}{\text{weight of consumed liquid}} \times 100 \tag{1}
\]

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±4.9 % (p<0.05) against control under the influence of Krebs solution with 5 μM of ketamine, and 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.

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. 2011).
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 postsynapsis (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 Mg2+, whereas spontaneous Ca2+-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 Ca2.3 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 psychodelic 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 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 AMPAkine, 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 AMPAKines (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
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±5.3 % against 159.7±4.9 % of 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.

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 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

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

<table>
<thead>
<tr>
<th>Administered drugs</th>
<th>Time of immobilization (s)</th>
<th>% preference for consumption of sucrose solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (vehicle)</td>
<td>59.4±3.4</td>
<td>79.4±2.4</td>
</tr>
<tr>
<td>Ketamine 5 mg/kg after 60 min</td>
<td>46.4±3.2’</td>
<td>72.1±2.5</td>
</tr>
<tr>
<td>Ketamine 20 mg/kg after 60 min</td>
<td>38.7±3.6’</td>
<td>83.6±3.1</td>
</tr>
<tr>
<td>Piracetam 100 mg/kg after 60 min</td>
<td>62.2±3.6</td>
<td>75.8±4.24</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Administered drugs</th>
<th>Time of immobilization (s)</th>
<th>% preference for consumption of sucrose solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (vehicle)</td>
<td>59.4±3.4</td>
<td>79.4±2.4</td>
</tr>
<tr>
<td>1st day after termination of swimming stress (vehicle)</td>
<td>114.0±5.1’</td>
<td>54.0±1.8’</td>
</tr>
<tr>
<td>Ketamine 5 mg/kg after 60 min</td>
<td>79.8±3.9’</td>
<td>66.1±2.1’</td>
</tr>
<tr>
<td>Ketamine 20 mg/kg after 60 min</td>
<td>68.4±3.7’</td>
<td>71.2±2.3’</td>
</tr>
<tr>
<td>Piracetam 100 mg/kg after 30 min</td>
<td>99.4±5.4</td>
<td>59.6±2.4</td>
</tr>
<tr>
<td>Piracetam 100 mg/kg after 30 min + ketamine 5 mg/kg after 60 min</td>
<td>54.7±3.1’’</td>
<td>85.5±3.2’’</td>
</tr>
<tr>
<td>Piracetam 100 mg/kg after 30 min + ketamine 20 mg/kg after 60 min</td>
<td>47.4±4.1’’</td>
<td>88.3±4.2’’</td>
</tr>
</tbody>
</table>

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.
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 it 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 glycogensynthase (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

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