



Involvement of monoaminergic system in the antidepressant effect of 3-substituted thietane-1,1-dioxide derivative

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Abstract

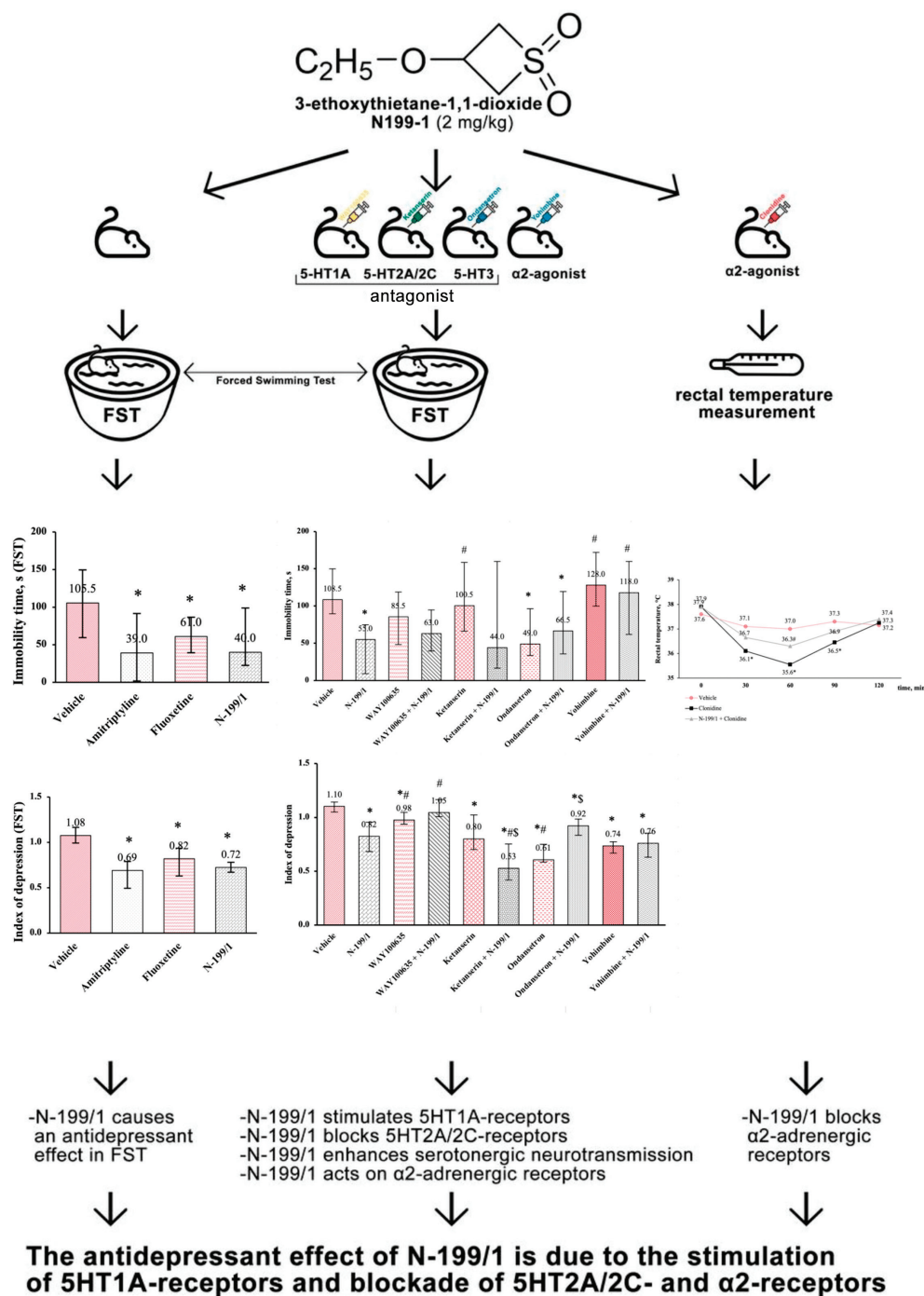
Introduction: The aim of the study was to assess the involvement of the monoaminergic system in the antidepressant effect of a new 3-substituted thietane-1,1-dioxide derivative (N-199/1) using tests with several pharmacological antagonists and agonists.

Materials and methods: We conducted 3 sets of experiments in white outbred male mice. In Experiment 1, we assessed the antidepressant effect of N-199/1 in the forced swimming test (FST) and tail suspension test (TST) when administered repeatedly for 2 weeks intraperitoneally (i.p.). In Experiment 2, we evaluated the antidepressant effect of N-199/1 in FST and TST when co-administered with 5HT1A- (WAY100635, 0.1 mg/kg), 5HT2A/2C- ([ketanserin](#), 5 mg/kg), 5HT3- ([ondansetron](#), 1 mg/kg) serotonergic and α 2-adrenergic ([yohimbine](#), 1 mg/kg) receptors antagonists. In Experiment 3, we assessed the effect of N-199/1 on the hypothermia induced by i.p. injection of α 2-adrenergic receptors agonist [clonidine](#) (0.3 mg/kg).

Results and discussion: N-199/1 reduced immobility time (IT) and index of depression (ID) in FST, and did not affect IT in TST, either when administered repeatedly in Experiment 1, or acutely in Experiment 2. In Experiment 2, [ketanserin](#) enhanced the effect of N-199/1, decreasing ID by 36%, while WAY100635 and [yohimbine](#) antagonized it, increasing ID by 27% and IT by 115%, respectively, in comparison with N-199/1. N-199/1 attenuated the effect of [ondansetron](#), increasing IT by 36%. In Experiment, 3 N-199/1 reduced clonidine-induced hypothermia 1 h after the injection of [clonidine](#). N-199/1 exhibited pronounced antidepressant properties in FST, an agonism to 5HT1A-receptors and an antagonism to 5HT2A/2C- and α 2-receptors in tests of neuropharmacological interaction, which indicates an atypical mechanism of its antidepressant action.

Conclusion: The antidepressant effect of N-199/1 is due to the stimulation of 5HT1A-receptors and blockade of 5HT2A/2C- and α 2-receptors.

Graphical abstract:



Keywords

animal outbred strain, antidepressants, clonidine, ketanserin, ondansetron, thietane, WAY100635, yohimbine.

Introduction

Depression is among the most common mental disorders, affecting about 6% of global population annually (Malhi and Mann 2018) and the second leading cause of disability worldwide (Bauer et al. 2019). The economic burden

of depression is rising steadily and is estimated at USD 210.5 billion per year, with about half of the economic costs attributed to the workplace and the remainder to direct medical costs (Maurer et al. 2018). It is important to note that during the COVID-19 pandemic the prevalence rate of depression has significantly increased: according

to the results of a systematic review, 53.2 million additional cases of depression are associated with the COVID-19 pandemic, which is a 27.6% increase (Santomauro et al. 2021). Therefore, there is an increasing need for the development of novel treatments for depression. Antidepressants are the main treatment option for depressive disorders. Antidepressants differ markedly in their side effect profile and potential for drug-drug interactions. The current antidepressants of the second (for example, [bupropion](#), [maprotiline](#), [mianserin](#), [trazodone](#)) and third generations (for example, selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors, [mirtazapine](#)) are generally better tolerated than tricyclic antidepressants (TCAs, first generation), which improves a treatment compliance (Bauer et al. 2013). Still there is no evidence of greater effectiveness or faster onset of action of any particular class of antidepressants, although certain advantages of classical TCAs over SSRIs for the treatment of severe depression have been shown (van den Broek et al. 2004). Therefore, when developing new antidepressants, their effect on the monoaminergic system of the brain is usually assessed.

Systematic studies carried out at the Department of Pharmacology with a course of Clinical Pharmacology of Bashkir State Medical University (BSMU, Ufa) have revealed a promising low-toxic compound – 3-ethoxythietane-1,1-dioxide (laboratory code N-199/1) which exhibits a pronounced antidepressant activity (Gaisina and Nikitina 2020; Khaliullin et al. 2020). The study of the mechanism of action of N-199/1 in tests of neuropharmacological interaction suggested that the antidepressant effect of the molecule may be due to its serotonin-positive properties, and probably the blockade of serotonin 5HT_{2A/2C} receptors and/or α_2 -adrenergic receptors (Nikitina and Gaisina 2021). Therefore, in the present study we evaluated the effect of N-199/1 on the monoaminergic system in tests with antagonists and agonists of serotonergic and adrenergic receptors.

Materials and methods

Experimental animals

The experiments were performed on white outbred male mice weighing 18–23 g in accordance with the requirements of *The European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* (ETS No.123, 1986) and *The Rules of Good Laboratory Practice of the Eurasian Economic Union in the Field of Drugs* (Decision No. 81 of the Council of the Eurasian Economic Commission dated November 3, 2016 "On Approval of Rules of Good Laboratory Practice of the Eurasian Economic Union in the Sphere of Circulation of Medicines"). The animals were kept in a 12-hour light regime (08:00–20:00) on a balanced diet (GOST R 50258-92, LLC "GROUP-SPETS-KOM", Moscow, Russia). The study was carried out in accordance with the BSMU research plan on the problem

of Drug Discovery and Development, and is approved by the Expert Council on biomedical ethics in theoretical disciplines of BSMU (Minutes No. 9, 2013).

Drugs and treatment

3-ethoxythietane-1,1-dioxide (N-199/1) was synthesized at the Department of Pharmaceutical Chemistry with courses of Analytical and Toxicological Chemistry of BSMU (Head of the Department – Elena E. Klen, Professor, Doctor of Pharmaceutical Sciences). N-199/1 (2 mg/kg) was suspended with Tween-80 (Panreac Quimica S.A.U., Spain), diluted in saline and injected intraperitoneally (i.p.) in accordance with the Experimental design at the rate of 0.2 ml/20 g of animal body weight. The reference drugs [fluoxetine](#) (Apo-Fluoxetine, capsules 20 mg, Apotex INC, Canada) and [amitriptyline](#) (Amitriptyline, solution for intravenous and intramuscular administration 10 mg/ml, Federal State Unitary Enterprise "Moscow Endocrine Plant", Russia) were diluted in saline with Tween-80 and injected i.p. at a dose of 10 mg/kg similarly to the compound. In tests of neuropharmacological interaction, we used 5HT_{1A}-antagonist WAY100635 (0.1 mg/kg, WAY100635, Toronto Research Chemicals, Canada), 5HT_{2A/2C}-antagonist [ketanserin](#) (5 mg/kg, Ketanserin tartrate, Thermo Fisher, Germany), 5HT₃-antagonist [ondansetron](#) (1 mg/kg, Latran, solution for intravenous and intramuscular administration 2 mg/ml, Federal State Unitary Enterprise SPC "Pharmzashchita" of FMBA of Russia), α_2 -antagonist [yohimbine](#) (1 mg/kg, [Yohimbine hydrochloride](#), Thermo Fisher, Germany) and α_2 -agonist [clonidine](#) (0.3 mg/kg, Clophelin, solution for intravenous administration 0.1 mg/ml, J.S.C. "Organica", Russia). All the antagonists and the agonists were also diluted in saline with 1–2 drops of Tween-80 and injected i.p. The control group received an equivalent volume of saline with Tween-80.

Behavioral tests

To assess the antidepressant activity of N-199/1, forced swimming test (FST) according to Porsolt (1979) in the modification by Shchetinin et al. (1989), tail suspension test (TST) according to Steru et al. (1985) and open field test (OFT) (Val'dman and Poshivalov 1984) were performed.

The behavior of the animals was recorded on camera (Panasonic V760), and the following parameters were assessed, using the BrainTest software (Gabidullin et al. 2008):

- TST: immobility time (IT), s;
- FST: IT and index of depression (ID) which was calculated as the ratio of short cycles (less than 6 s) of immobility to the number of active swimming cycles;
- OFT: the number of behavioral patterns "movement", "sniffing", "vertical rearing", "supported rearing", "hole peeking", "grooming", "movement in place", "sitting", and the calculated indicators "orientation-ex-

ploratory activity” (the sum of the patterns “movement”, “sniffing” and “hole peeking”) and “emotional anxiety” (the sum of the patterns “vertical rearing”, “supported rearing” and “movement in place”).

Experimental design

Experiment 1 (antidepressant activity assessment)

The antidepressant effect of N-199/1 was assessed using FST, TST and OFT when administered i.p. repeatedly. The animals (n=47) were divided into 4 groups: Group 1 (control) received saline, i.p.; Group 2 – amitriptyline (10 mg/kg), i.p.; Group 3 – fluoxetine (10 mg/kg), i.p.; and Group 4 – N-199/1 (2 mg/kg), i.p. N-199/1 and reference drugs were administered once a day i.p. for 14 days; on the Day 15, TST, FST and OFT were performed.

Experiment 2 (the effect of pharmacological antagonists on the activity of N-199/1)

The effect of 5HT1A- (WAY100635, 0.1 mg/kg), 5HT2A/2C- (ketanserin, 5 mg/kg), 5HT3- (ondansetron, 1 mg/kg) serotonergic and α 2-adrenergic (yohimbine, 1 mg/kg) receptors antagonists on the activity of N-199/1 in FST and TST was studied according to the methods described in Colla et al. (2012) and Karim et al. (2018). The animals (n=96) were divided into the following experimental groups:

- Group 1 – saline (control group);
- Group 2 – N-199/1 (2 mg/kg);
- Group 3 – WAY100635 (0.1 mg/kg);
- Group 4 – N-199/1 (2 mg/kg) + WAY100635 (0.1 mg/kg);
- Group 5 – ketanserin 5 mg/kg;
- Group 6 – ketanserin 5 mg/kg + N-199/1 (2 mg/kg);
- Group 7 – ondansetron (1 mg/kg);
- Group 8 – ondansetron (1 mg/kg) + N-199/1 (2 mg/kg);
- Group 9 – yohimbine 1 mg/kg;
- Group 10 – yohimbine 1 mg/kg + N-199/1 (2 mg/kg).

N-199/1 was administered once i.p. 30 min after a single i.p. injection of antagonists of 5HT2A/2C- (ketanserin)/5HT3- (ondansetron)/ α 2- (yohimbine) receptors or 30 min before the injection of 5HT1A-antagonist

(WAY100635). Thirty minutes after the administration of N-199/1 / WAY100635, FST and TST were performed according to the method described in the design of Experiment 1. The design of Experiment 2 is shown in Fig. 1.

Experiment 3 (clonidine-induced hypothermia)

N-199/1 was administered once i.p. 30 min before a single i.p. injection of clonidine, and the severity of the developed hypothermia was assessed every 30 min over 2 h (Fig. 2). The animals of Group 1 (n=8) received 2 injections of saline, i.p.; Group 2 (n=8) – saline and clonidine (0.3 mg/kg), i.p.; and Group 3 (n=8) – N-199/1 (2 mg/kg) and clonidine (0.3 mg/kg), i.p. Rectal temperature was measured 0, 30, 60, 90, 120, 150 min after the administration of N-199/1 using a TW2-193 electrothermometer (Braintree Scientific, USA).

Statistical analysis

The statistical analysis was performed using the STATISTICA 13.3 software (TIBCO Software Inc., USA). Descriptive statistics (the normality of distribution, median [Me], interquartile range [IQR]) and nonparametrics (Kruskall-Wallis, Mann-Whitney, Friedman, Wilcoxon tests) were calculated (White 2019). Graphical representation of the data obtained was carried out using the GraphPad Prism 8.0.1 program (GraphPad Software, USA). The results were considered statistically significant at a p-level<0.05.

Results

Experiment 1

N-199/1 caused a significant antidepressant effect in FST, reducing IT FST by 62% (p=0.035) and ID by 33% (p<0.001), compared with the control group (Fig. 3). The effect of N-199/1 in FST was similar to the effects of the reference drugs (p>0.05 compared to both amitriptyline and fluoxetine). N-199/1, as well as the reference drugs, caused a trend to decrease IT by 44% (p=0.150, Fig. 3) in TST and produced no effect in OFT.

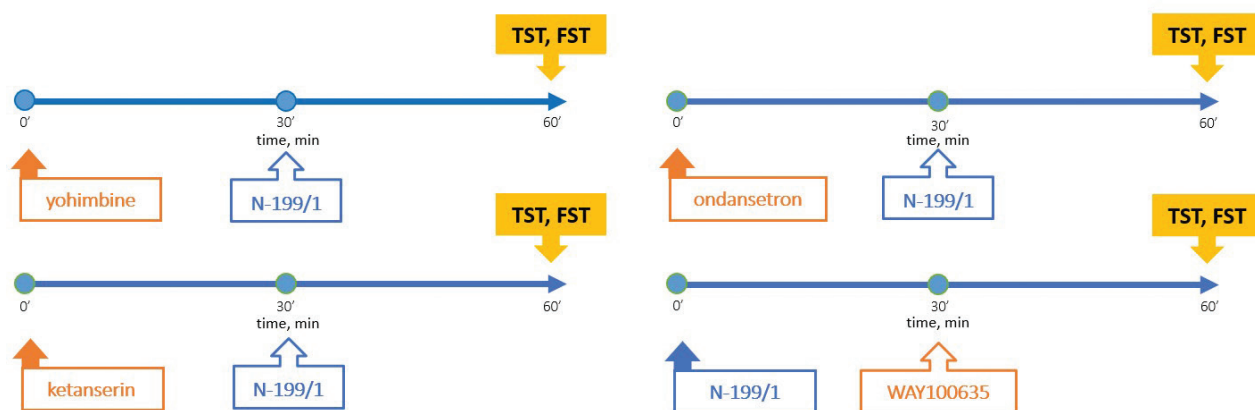


Figure 1. Design of the tests with pharmacological antagonists (Experiment 2). **Note:** TST – tail suspension test, FST – forced swimming test.

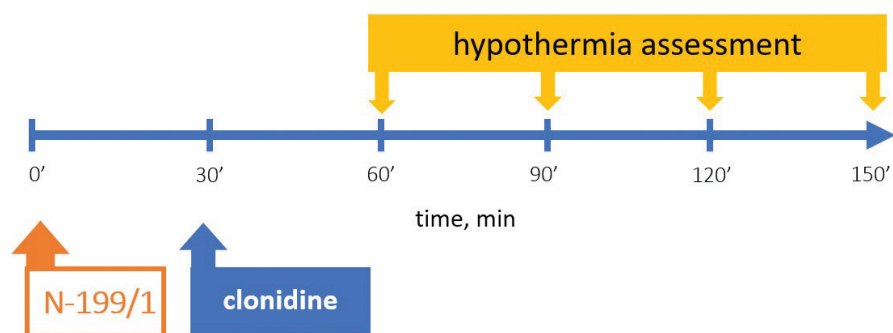


Figure 2. Design of the test of clonidine-induced hypothermia (Experiment 3).

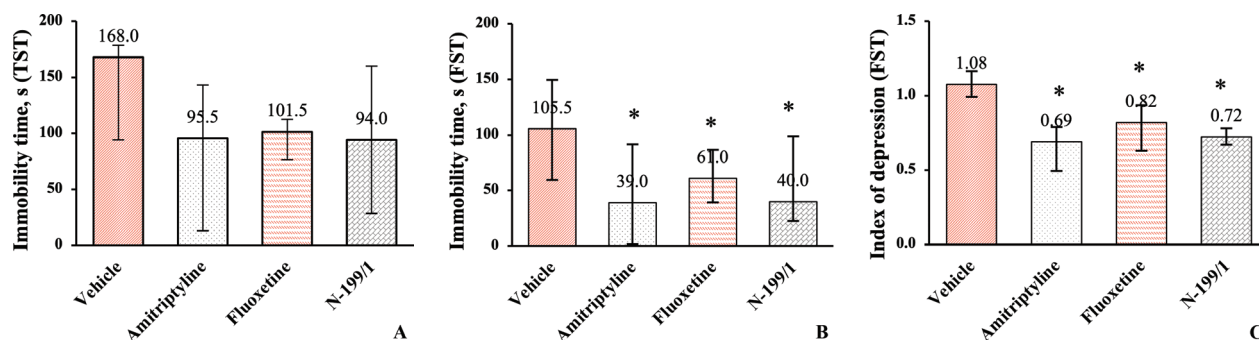


Figure 3. Effect of N-199/1 on immobility time in the tail suspension test (A), immobility time (B) and index of depression (C) in the forced swimming test, when administered repeatedly (for 2 weeks) intraperitoneally to male mice. **Note:** graphs show group medians and interquartile range; * – $p < 0.05$ for the Mann-Whitney test compared to the control group.

Experiment 2

N-199/1 did not affect IT in TST, which is consistent with the results obtained in single (Khaliullin et al. 2020) and repeated administrations (Experiment 1) and is typical for many antidepressants (Cryan et al. 2005b).

In FST, N-199/1 showed antidepressant properties, reducing IT by 49% ($p = 0.001$) and ID by 25% ($p < 0.001$) in comparison with the control group (Fig. 4).

All the antagonists significantly decreased ID FST: **ondansetron** – by 45%, **yohimbine** – by 33%, WAY100635 – by 11%, and **ketanserin** – by 27% ($p < 0.05$) compared to the control group (Fig. 4). **Ondansetron** decreased IT FST by 55% as well ($p = 0.008$).

WAY100635 (5HT_{1A}-antagonist) reversed the antidepressant effect of N-199/1: the effect of the combination of N-199/1 and the antagonist on the ID was comparable to the effect of the control group ($p = 0.284$), while the ID was 27% ($p = 0.001$) higher than in the only-N-199/1-treated group (Fig. 4).

The combined treatment with **ketanserin** (5HT_{2A/2C}-antagonist) and N-199/1 caused a more pronounced reduction of ID than in the N-199/1 group (by 36%, $p = 0.037$) or ketanserin group (by 34%, $p = 0.036$), and did not affect IT FST (Fig. 4).

The pre-treatment with **ondansetron** (5HT₃-antagonist) did not change the effect of N-199/1 in the FST: IT and ID in the group “**ondansetron** + N-199/1” were comparable to the N-199/1 group ($p > 0.05$). At the same time,

the ID of the combination was significantly higher than in the **ondansetron** group ($p = 0.002$, Fig. 4).

The combination of N-199/1 and yohimbine (α_2 -antagonist) increased IT FST twice compared to the N-199/1 group ($p = 0.014$, Fig. 4) and caused an effect, similar to that in the yohimbine group.

Experiment 3

Clonidine (0.3 mg/kg) reduced the rectal temperature of animals by 1.5–2.4 °C 30–90 min after its administration ($p < 0.05$ for the Mann-Whitney test compared with the control group, $p < 0.05$ for the Wilcoxon test compared with the base level of 0 min) (Fig. 5). N-199/1 counteracted clonidine-induced hypothermia: the body temperature of animals in the group N-199/1 + **clonidine** did not differ from the control group throughout the experiment, and, at the time point of 60 min, it was significantly higher than in the clonidine group (by 0.7 °C, $p = 0.042$, Fig. 5).

Discussion

We had previously shown that N-199/1 exhibits significant antidepressant properties after a single i.p. administration to male mice (Khaliullin et al. 2020), and the minimum dose that has a pronounced antidepressant effect in FST is a dose of 2 mg/kg (Gaisina and Nikitina 2020), which we used in this study.

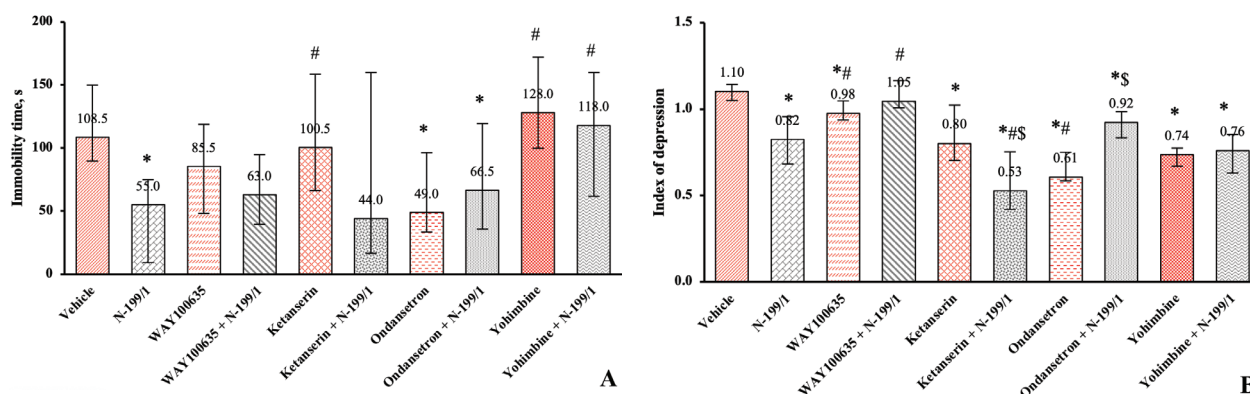


Figure 4. Effect of the combined treatment with N-199/1 and pharmacological antagonists on immobility time (A) and index of depression (B) in the forced swimming test when singly administered intraperitoneally to male mice. **Note:** graphs show group medians and interquartile range; * – $p < 0.05$ for the Mann-Whitney test compared to the control group; # – $p < 0.05$ for the Mann-Whitney test compared to N-199/1; \$ – $p < 0.05$ for the Mann-Whitney test compared to the corresponding antagonist.

It is known that most antidepressants have a delayed onset of action, and their clinical effect develops only in 2–4 weeks (Czeh et al. 2016). According to the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, response to antidepressant therapy should be assessed after 2 weeks of treatment, and achievement of symptoms reduction may require at least 8–10 weeks (Bauer et al. 2013). To assess how the activity of N-199/1 changes during chronic treatment, we evaluated the effect of the molecule in TST, FST and OFT, when administered repeatedly for 2 weeks (Experiment 1).

Similarly to our previous results obtained in a single administration, N-199/1 exhibited pronounced antidepressant properties in FST and did not cause any significant effect in TST, which is characteristic to atypical antidepressants (Cryan et al. 2005b) and suggests that N-199/1 has an atypical mechanism of action. In addition, we have found that an increase in the duration of the treatment course leads to a more pronounced antidepressant effect of N-199/1: in the FST, a significant decrease in both ID and IT was observed (by 33% и 62%, respectively compared to the control group, $p < 0.05$). It should also be noted that the effect of N-199/1 was similar to the effects of the reference drugs **amitriptyline** and **fluoxetine**.

The basic tests for studying the mechanism of action of molecules with antidepressant activity are tests of neuropharmacological interaction (Habrieu 2005). To study the mechanism of the antidepressant action of N-199/1 in FST (Experiment 2), we assessed its activity when co-administered with the antagonists of serotonergic 5HT1A- (WAY100635), 5HT2A/2C- (**ketanserin**), 5HT3-receptors (**ondansetron**), and α_2 -adrenergic receptors (**yohimbine**). The antagonists were selected based on the results of a reserpine test (Nikitina and Gaisina 2021), which showed that the mechanism of action of N-199/1 is associated with its serotonin-positive properties and, probably, blockade of 5HT2A/2C receptors and α_2 -adrenergic receptors.

In tests with antagonists, N-199/1 exhibited antidepressant properties in FST, reducing IT and ID, which is consistent with the results obtained when it was administered

repeatedly in Experiment 1, or singly in our previous studies (Khaliullin et al. 2020).

All the antagonists significantly reduced ID FST, and **ondansetron** (5HT3-antagonist) decreased IT FST as well, causing an antidepressant-like effect in FST in agreement with many *in vivo* studies. It has been shown that 5HT2A, 5HT2C and 5HT3-antagonists demonstrate antidepressant-like properties in behavioral tests and animal models of depression in rodents (Carr and Lucki 2011).

The agonists of 5HT1A-receptors have shown to produce antidepressant-like effect as well, while the antagonists have no activity in FST (Cryan et al. 2005a; Carr and Lucki 2011). However, in our experiment, 5HT1A-antagonist WAY100635 decreased ID FST, which may be associated with the blockade of not only postsynaptic receptors, but presynaptic 5HT1A receptors as well, which are negative feedback receptors (Cryan et al. 2005a). WAY100635 reversed the ID decrease caused by N-199/1, suggesting that the mechanism of antidepressant effect of N-199/1 is due to stimulation of 5HT1A-receptors.

The combination of the 5HT2A/2C antagonist **ketanserin** and N-199/1 potentiated the effects of both the antagonist and the molecule on the ID. This suggests that N-199/1 produces its antidepressant effect due to blockade of 5HT2A/2C receptors similar to **ketanserin** (which is consistent with the data obtained in the reserpine test), or, more likely, via other mechanisms, for example, by stimulating 5HT1A receptors.

The effect of the combination of the 5HT3-antagonist **ondansetron** and N-199/1 was similar to the effect of N-199/1 itself, so it can be concluded that the compound does not affect 5HT3 receptors. The significant difference between the **ondansetron** + N-199/1 combination and the **ondansetron** group by ID is probably related to the serotonin-positive properties of N-199/1.

Yohimbine (α_2 -antagonist) attenuated the antidepressant effect of N-199/1 on IT FST. An additional test with the α_2 -agonist **clonidine** (Experiment 3) allowed us to conclude that the observed findings are due to the blockade of α_2 -adrenergic receptors, which is consistent with the results of the test of neuropharmacological interaction with reserpine.

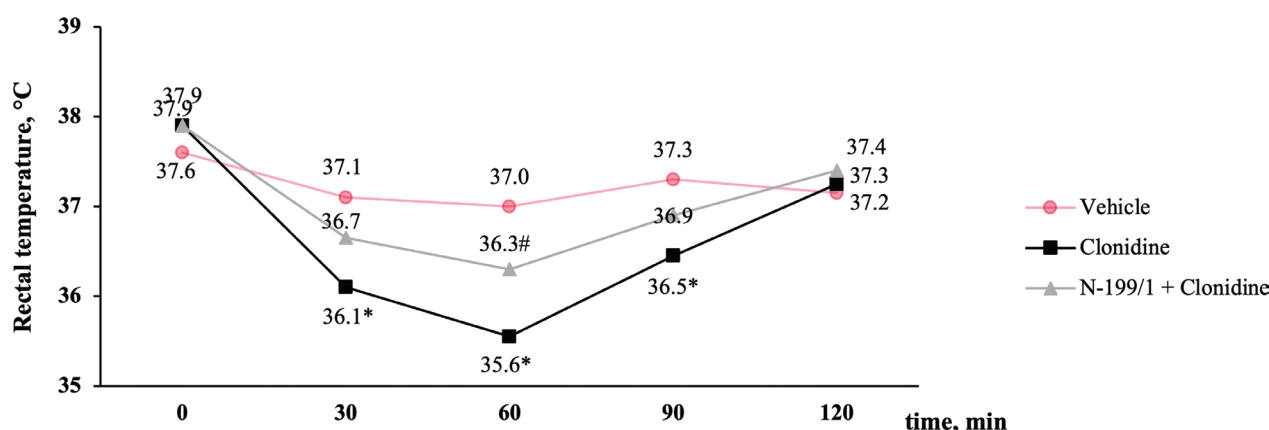


Figure 5. Effect of N-199/1 on clonidine-induced hypothermia. **Note:** clonidine was administered 30 min after N-199/1 at the time point of 0 min. The graph shows group medians; * – $p < 0.05$ for the Mann-Whitney test compared to the control group, # – $p < 0.05$ for the Mann-Whitney test compared to the clonidine group.

Conclusion

N-199/1 exhibits a pronounced antidepressant activity when administered i.p. to male mice singly or repeatedly. The mechanism of action of N-199/1 is probably associated with the stimulation of serotonergic 5HT_{1A}-receptors, blockade of 5HT_{2A/2C}-receptors and α ₂-adrenergic receptors, since the 5HT_{1A}-antagonist WAY100635 and

the α ₂-antagonist yohimbine counteracted the antidepressant effect of N-199/1 in FST, the 5HT_{2A/2C}-antagonist ketanserin enhanced it, and N-199/1 reversed the hypothermic effect of the α ₂ agonist clonidine.

Conflict of interest

The authors declare no conflict of interests.

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