



The mechanism of antidepressant action of a new 3-substituted thiethane-1,1-dioxide derivative in tests of neuropharmacological interaction

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Abstract

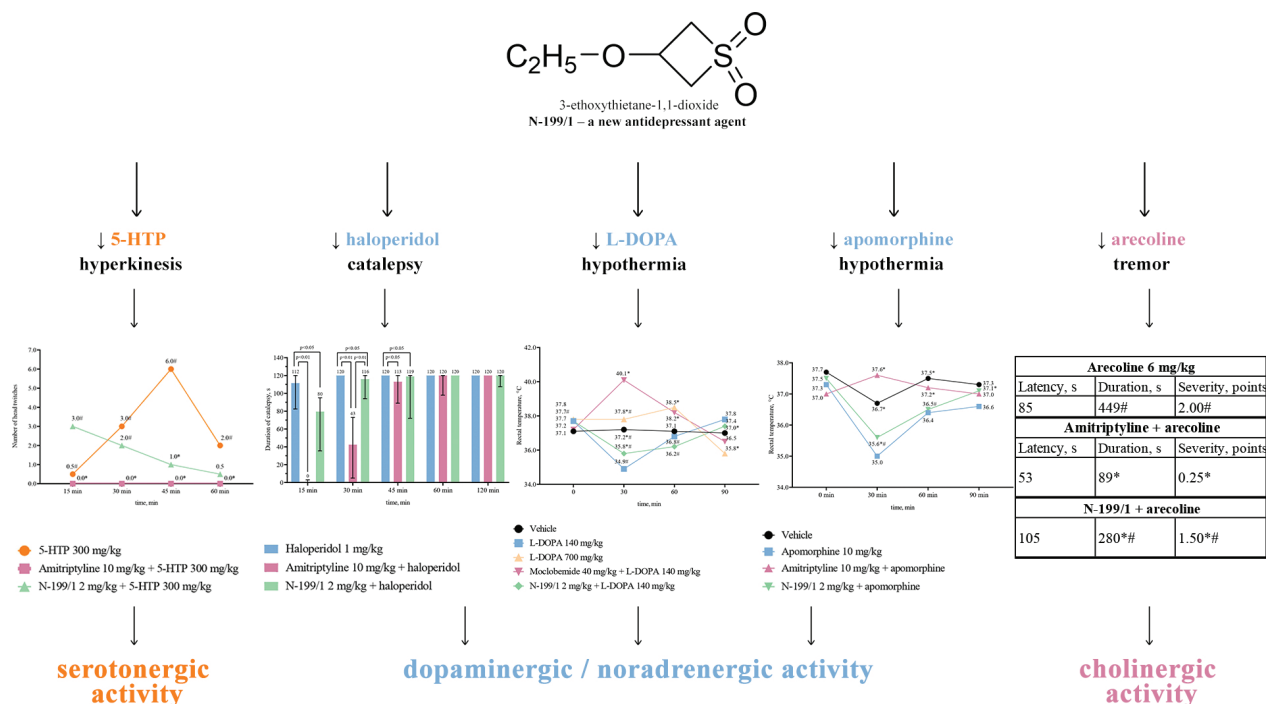
Introduction: The present study is aimed at investigation of the mechanism of action of a new 3-substituted thiethane-1,1-dioxide derivative (N-199/1) exhibiting antidepressant properties, in several tests of neuropharmacological interaction.

Materials and methods: To study the mechanism of action of N-199/1, its effect on 5-hydroxytryptophan (5-HTP)-induced head-twitch response (50 mg/kg and 300 mg/kg), haloperidol-induced catalepsy (1 mg/kg), arecoline-induced tremor (6 mg/kg), picrotoxin-induced seizures (6 mg/kg) and hypothermia, induced by apomorphine (10 mg/kg) or L-3,4-dihydroxyphenylalanine (L-DOPA, 140 mg/kg), was assessed when administered singly to white outbred male mice at a dose of 2 mg/kg.

Results and discussion: N-199/1 reduced the number of head twitches, induced by 5-HTP (300 mg/kg), by 83% 45 min after 5-HTP injection; decreased the duration of haloperidol catalepsy by 1–32 s 15–45 min after haloperidol injection; attenuated L-DOPA-induced hypothermia by 0.7 °C and apomorphine-induced hypothermia by 0.6 °C at the timepoint of 30 min; reduced the duration and severity of arecoline tremor and did not affect the convulsive effect of picrotoxin.

Conclusion: N-199/1 acts on serotonergic, noradrenergic, dopaminergic and cholinergic neurotransmission and does not affect neuronal reuptake of monoamines or monoamine oxidase. The mechanism of action of N-199/1 is probably due to stimulation of serotonergic 5HT1A-receptors and/or blockade of 5HT2A/2C-receptors and/or α 2-adrenergic receptors; dopaminergic and cholinergic receptors may also be involved.

Graphical abstract



Keywords

5-hydroxytryptophan, animal outbred strain, antidepressants, apomorphine, arecoline, haloperidol, L-DOPA, thietane.

Introduction

In the context of the COVID-19 pandemic, the problem of effective treatment of mental (including depressive) disorders has become particularly relevant. The incidence of depression has increased significantly: during the period from 2005 to 2015, the number of people suffering from depression increased by 18.4% (Malhi and Mann 2018), but during the pandemic – by 27.6% due to 53.2 million additional cases of major depressive disorder associated with COVID-19 (Santomauro et al. 2021). In addition, the association between COVID-19 and psychiatric disorders is bilateral, and the presence of mental disorders is an independent risk factor for severe and poor outcome of COVID-19 (Morozov et al. 2021).

According to the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, the first-line medications for the acute and continuation treatment of a major depressive disorder are antidepressants (Bauer et al. 2013), and for the maintenance treatment – antidepressants and lithium (Bauer et al. 2015).

At the same time, none of the classes of antidepressants has proven advantages in terms of effectiveness and timing of onset of therapeutic effect compared to

other classes (Akhapkin et al. 2021). Therefore, when determining the adequate treatment strategy, a personalized approach is used (Kostyukova and Mosolov 2013), which implies choosing the most appropriate antidepressant based on the characteristics of its pharmacodynamic spectrum and mechanism of action. Thus, the need to develop new drugs for the treatment of depressive disorders is still relevant.

The studies conducted at the Department of Pharmacology with a course of Clinical Pharmacology and the Department of Pharmaceutical Chemistry with courses of Analytical and Toxicological Chemistry of Bashkir State Medical University (BSMU) led to the discovery of a new promising class of 3-substituted thietane-1,1-dioxides, characterized by low toxicity and pronounced psychotropic (antidepressant) properties (Ivanova et al. 2011a, b, 2012; Klen et al. 2017; Nikitina et al. 2021). Further studies within the class revealed 3-ethoxythietane-1,1-dioxide (laboratory code N-199/1), which also exhibits significant antidepressant activity in a wide range of doses (Gaisina and Nikitina 2020; Khaliullin et al. 2020) and is of interest in terms of developing a drug candidate.

Commonly, to evaluate the mechanism of action of new molecules possessing antidepressant activity, tests of neuropharmacological interaction are used (Habriev 2005).

Based on our previous results obtained in tests of reserpine-induced hypothermia, ptosis and akinesia, clonidine-induced hypothermia and tests with antagonists of serotonergic and adrenergic receptors, we suggested that the antidepressant effect of N-199/1 is due to the stimulation of 5HT_{1A}-receptors and blockade of 5HT_{2A/2C}- and α ₂-receptors (Nikitina and Gaisina 2021). In order to determine other possible mechanisms of action of the molecule, the effect of N-199/1 on serotonergic, dopaminergic, cholinergic and γ -aminobutyric acid mediated (GABAergic) neurotransmission was studied using several tests of neuropharmacological interaction.

Materials and methods

Experimental animals

The experiments were performed on outbred male mice (18–25 g) kept under standard vivarium conditions with a 12-hour light regime (light on/off at 08:00/20:00) on a balanced diet GOST R 50258-92 (pellets for laboratory animals, LLC “GROUP-SPETSKOM”, Moscow, Russia).

The studies were approved by the Expert Council on Biomedical Ethics in Theoretical Disciplines of BSMU (minutes No. 9, 2013) and comply with the requirements of the International Recommendations 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 Medicine Circulation”).

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 under the supervision of Elena E. Klen, Professor, Doctor of Pharmaceutical Sciences. N-199/1 was diluted in saline with 1–2 drops of Tween-80 (Panreac Quimica SAU, Spain) and administered intraperitoneally (i.p.) at a dose of 2 mg/kg (0.2 ml/20 g of animal body weight) in accordance with the Design of the experiment (see “Experimental design”).

The reference drugs included amitriptyline (Amitriptyline, solution for intravenous (i.v.) and intramuscular (i.m.) administration 10 mg/ml, Federal State Unitary Enterprise “Moscow Endocrine Plant”, Russia) at a dose of 10 mg/kg (i.p.), moclobemide (Aurorix, tablets 150 mg, F.Hoffmann-La Roche, Switzerland) at a dose of 40 mg/kg (i.p.) and diazepam (Relanium, solution for intravenous and intramuscular administration 5 mg/ml, Polfa S.A., Poland) at a dose of 1 mg/kg (i.p.). For neuropharmacological interaction tests, 5-hydroxytryptophan (5-HTP, 50 and 300 mg/kg i.p.,

substance, Acros Organics, Belgium), haloperidol (1 mg/kg subcutaneously (s.c.), Haloperidol-ratiopharm, oral drops 2 mg/ml, Ratiopharm GmbH, Germany), L-3,4-dihydroxyphenylalanine (L-DOPA, 140 and 700 mg/kg i.p., substance, Acros Organics, Belgium), apomorphine (10 mg/kg i.p., substance, Acros Organics, Belgium), arecoline (6 mg/kg s.c., substance, Sigma Aldrich, USA) and picrotoxin (6 mg/kg s.c., substance, Acros Organics, Belgium) were used (see “Experimental design”). The animals of the control group received an equivalent volume of saline i.p.

Experimental design

To study the mechanism of action of N-199/1, tests of neuropharmacological interaction with 5-HTP, haloperidol, L-DOPA, apomorphine, arecoline and picrotoxin were performed (Habriev 2005; Mironov 2012).

Effect of N-199/1 on 5-HTP-induced hyperkinesia

The effect of N-199/1 (2 mg/kg, i.p.) on the severity of hyperkinesia induced by the administration of 5-HTP at doses of 50 and 300 mg/kg was studied. For the two experiments conducted, we used 4 experimental groups of 8 animals each:

- Group 1 – saline (control group);
- Group 2 – 5-HTP;
- Group 3 – amitriptyline (10 mg/kg) + 5-HTP;
- Group 4 – N-199/1 (2 mg/kg) + 5-HTP.

In Experiment 1, 5-HTP was administered at a low dose (50 mg/kg) that did not cause hyperkinesia in animals; in Experiment 2, a high dose of 5-HTP (300 mg/kg) was used to induce head-twitch response. N-199/1 and the reference drug (amitriptyline, 10 mg/kg) were injected singly i.p. 30 min prior to 5-HTP. The severity of the developed head-twitch response (the number of head twitches per minute) was assessed 15, 30, 45, and 60 minutes after the 5-HTP injection (Fig. 1).

Effect of N-199/1 on haloperidol-induced catalepsy

The effect of N-199/1 on the duration of haloperidol-induced catalepsy was evaluated. The animals were divided into 4 experimental groups (8 in each group):

- Group 1 – saline (control group);
- Group 2 – haloperidol (1 mg/kg);
- Group 3 – amitriptyline (10 mg/kg) + haloperidol (1 mg/kg);
- Group 4 – N-199/1 (2 mg/kg) + haloperidol (1 mg/kg).

Haloperidol was administered singly s.c. 30 minutes after the administration of N-199/1 or amitriptyline (i.p.). The duration of catalepsy was assessed 15, 30, 45, 60 and 120 min after the administration of haloperidol (Fig. 2), with the time of an animal remaining with its forepaws on a horizontal bar (for 2 min).

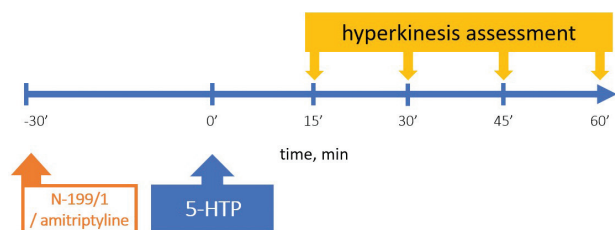


Figure 1. Design of the test with 5-HTP. **Note:** 5-HTP – 5-hydroxytryptophan.

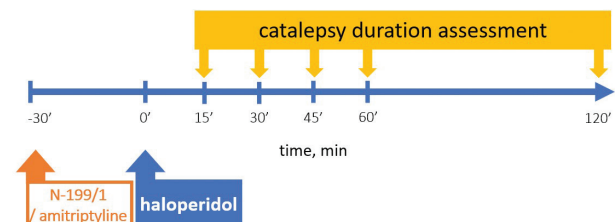


Figure 2. Design of the test with haloperidol.

Effect of N-199/1 on apomorphine-induced hypothermia

In the test with apomorphine, the ability of N-199/1 to counteract the development of hypothermia was evaluated. There were 4 experimental groups of 6 animals each:

- Group 1 – saline (control group);
- Group 2 – apomorphine (10 mg/kg);
- Group 3 – amitriptyline (10 mg/kg) + apomorphine (10 mg/kg);
- Group 4 – N-199/1 (2 mg/kg) + apomorphine (10 mg/kg).

Apomorphine was injected i.p. 30 minutes after N-199/1 or amitriptyline (i.p.), and then the rectal temperature of the animals was measured using a TW2-193 electrothermometer (Braintree Scientific, USA) 30, 60, and 90 minutes after the injection of apomorphine (Fig. 3).

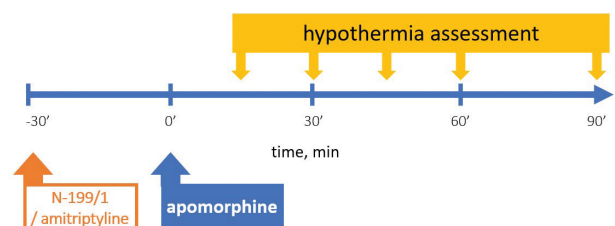


Figure 3. Design of the test with apomorphine.

Effect of N-199/1 on L-DOPA-induced hypothermia

The L-DOPA test evaluated the ability of N-199/1 to influence the effect of a low dose of L-DOPA (140 mg/kg, i.p.). The animals (n=40) were divided into 5 groups of 8 mice each:

- Group 1 – saline (control group);
- Group 2 – L-DOPA (140 mg/kg);
- Group 3 – L-DOPA (700 mg/kg) – positive control;
- Group 4 – moclobemide (40 mg/kg) + L-DOPA (140 mg/kg);
- Group 4 – N-199/1 (2 mg/kg) + L-DOPA (140 mg/kg).

L-DOPA was injected i.p. 30 min after the i.p. administration of N-199/1 or moclobemide, and after 30, 60 and 90 min the body temperature of the animals was measured (Fig. 4) using a TW2-193 electrothermometer (Braintree Scientific, USA).

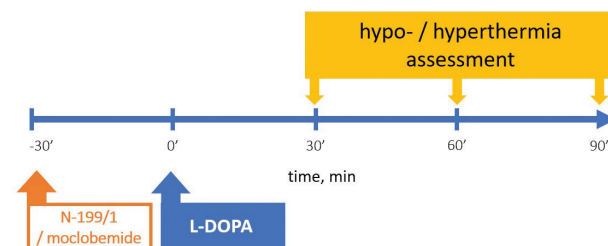


Figure 4. Design of the test with L-3,4-dihydroxyphenylalanine. **Note:** L-DOPA – L-3,4-dihydroxyphenylalanine.

Effect of N-199/1 on arecoline-induced tremor

In the test with arecoline (6 mg/kg, s.c.), the effect of N-199/1 (2 mg/kg) on the timing of onset, duration, and severity of tremor induced in animals was evaluated. The experimental groups (n=8 in each group) received:

- Group 1 – saline (control group);
- Group 2 – arecoline (6 mg/kg);
- Group 3 – amitriptyline (10 mg/kg) + arecoline (6 mg/kg);
- Group 4 – N-199/1 (2 mg/kg) + arecoline (6 mg/kg).

Arecoline was administered singly s.c. 30 min after N-199/1 or amitriptyline (i.p.) and the timing of tremor onset (s), its duration (s), and severity (points) were assessed (Fig. 5A):

- 0 no tremor
- 0.5 slight twitching of the head muscles
- 1 intermittent slight tremor of all muscle groups
- 2 persistent tremor
- 3 constant tremor with high-amplitude movements, resembling convulsions

Effect of N-199/1 on picrotoxin-induced seizures

The picrotoxin (2.5 mg/kg) test was used to evaluate the ability of N-199/1 to prevent seizures and death in mice. Diazepam was used as the reference drug (1 mg/kg). The experimental groups (n=8 in each group) received:

- Group 1 – picrotoxin (2.5 mg/kg);
- Group 2 – diazepam (1 mg/kg) + picrotoxin (2.5 mg/kg);
- Group 3 – N-199/1 (2 mg/kg) + picrotoxin (2.5 mg/kg).

Picrotoxin was administered singly s.c. 30 min after the i.p. administration of N-199/1 or diazepam (i.p.), and the latency of seizures (s), the number of animals with seizures in the group, and the number of animals that died within 60 min were measured (Fig. 5B).

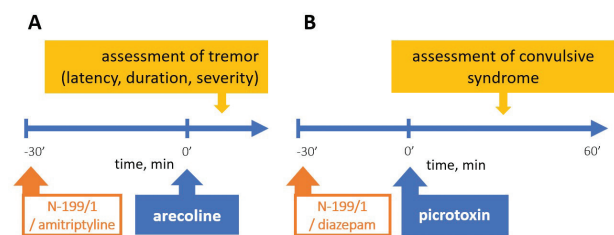


Figure 5. Design of the tests with arecoline (A) and picrotoxin (B).

Statistical analysis

For statistical analysis, the following indicators were calculated using the Statistica 13.3 software package (TIBCO Software Inc., USA): the pattern of distribution, median, interquartile range, Kruskal-Wallis, Mann-Whitney, Friedman, and Wilcoxon tests (White 2019). The results were considered statistically significant at a p-level < 0.05. Graphs were plotted using GraphPad Prism 8.0.1 software (GraphPad Software, USA).

Results

Effect of N-199/1 on 5-HTP-induced hyperkinesia

The administration of a high dose of 5-HTP (300 mg/kg) led to the development of a head-twitch response in animals, which persisted throughout the experiment (p < 0.05 compared with the control group), and the maximum number of head twitches was observed 45 min after the administration of 5-HTP. N-199/1 reduced the severity of hyperkinesia induced by 5-HTP (300 mg/kg) at the timepoint of 45 min by 83% (p = 0.040 compared with the 5-HTP group). The effect of N-199/1 was less pronounced than the effect of amitriptyline (p = 0.010), which completely reversed hyperkinesia throughout the experiment (p < 0.05) (Fig. 6). Neither N-199/1 nor amitriptyline potentiated the effect of a low dose of 5-HTP (50 mg/kg): the median was equal zero in all the groups.

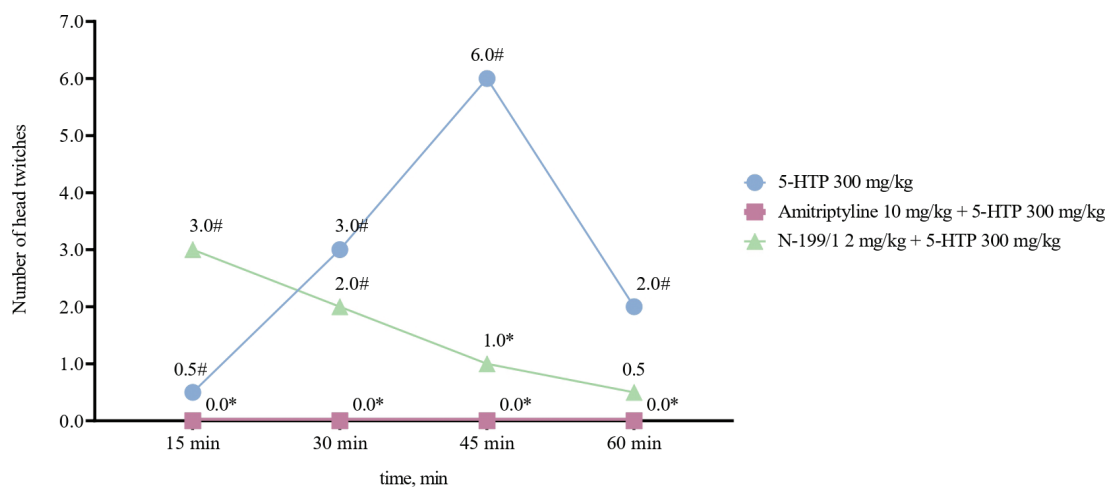


Figure 6. Effect of N-199/1 on 5-HTP-induced hyperkinesia (5-HTP 300 mg/kg). **Note:** graphs show group medians; * p < 0.05 for the Mann-Whitney test compared with the 5-HTP group; # p < 0.05 for the Mann-Whitney test compared with the amitriptyline group.

Effect of N-199/1 on haloperidol-induced catalepsy

Haloperidol (1 mg/kg) caused the development of catalepsy in animals that maintained an externally imposed posture with the forepaws on a horizontal bar throughout the experiment (from 30 to 120 min of the experiment). N-199/1 significantly reduced the duration of the catalepsy 15–45 min after the administration of haloperidol by 1–32 seconds (p < 0.05). The effect of N-199/1 was inferior to the effect of amitriptyline (p = 0.009 at the timepoint of 30 min), which shortened catalepsy by 7–120 s at the timepoints of 15–45 min (p < 0.05) (Fig. 7).

Effect of N-199/1 on apomorphine-induced hypothermia

Apomorphine (10 mg/kg) caused the development of hypothermia in the animals 30–60 minutes after its administration: the body temperature decreased by 1.1–1.7 °C (p < 0.05 for the Mann-Whitney test compared with the control group, p < 0.05 for the Wilcoxon test compared with the timepoint of 0 min) (Fig. 8). N-199/1 reduced the severity of apomorphine hypothermia: the body temperature of the animals was higher than in the apomorphine group at the timepoints of 30 min (by 0.6 °C, p = 0.013) and 90 min (by 0.5 °C, p = 0.013). Amitriptyline increased the rectal temperature compared with the apomorphine group 30 and 60 min after apomorphine administration by 0.8 °C (p = 0.008) and 2.6 °C (p = 0.017), respectively. The effect of amitriptyline was more pronounced than the effect of N-199/1 (p < 0.05 compared to N-199/1) (Fig. 8).

Effect of N-199/1 on L-DOPA-induced hypothermia

L-DOPA (140 mg/kg) reduced the rectal temperature in the animals with a maximum decrease by 2.4 °C (p = 0.001 vs. control) 30 min after L-DOPA administration. N-199/1 attenuated L-DOPA-induced hypothermia by 0.9 °C (p = 0.046) at the timepoint of 30 min. The reference drug moclobemide counteracted the development of hypothermia by increasing the rectal temperature of the animals by

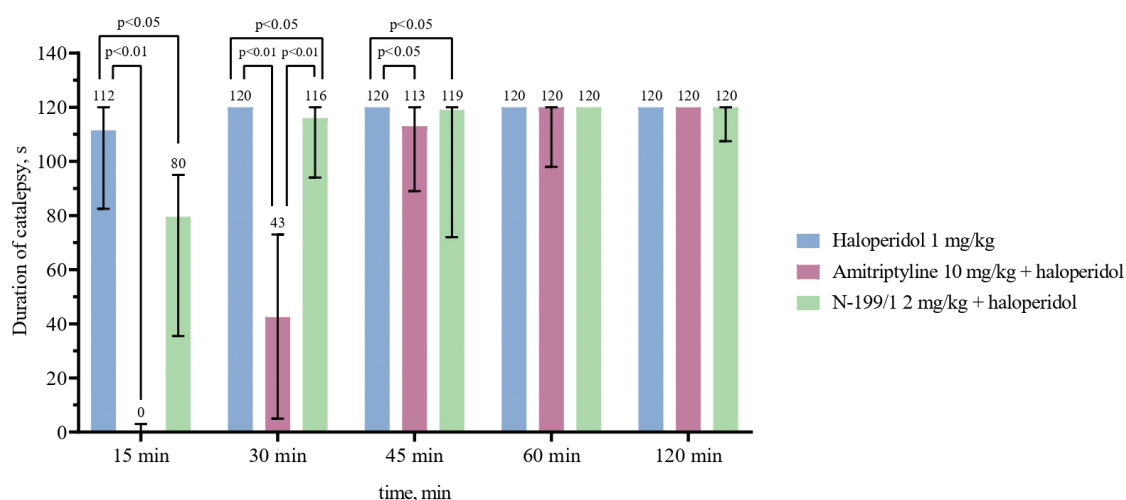


Figure 7. Effect of N-199/1 on haloperidol-induced catalepsy. **Note:** graphs show group medians and interquartile range.

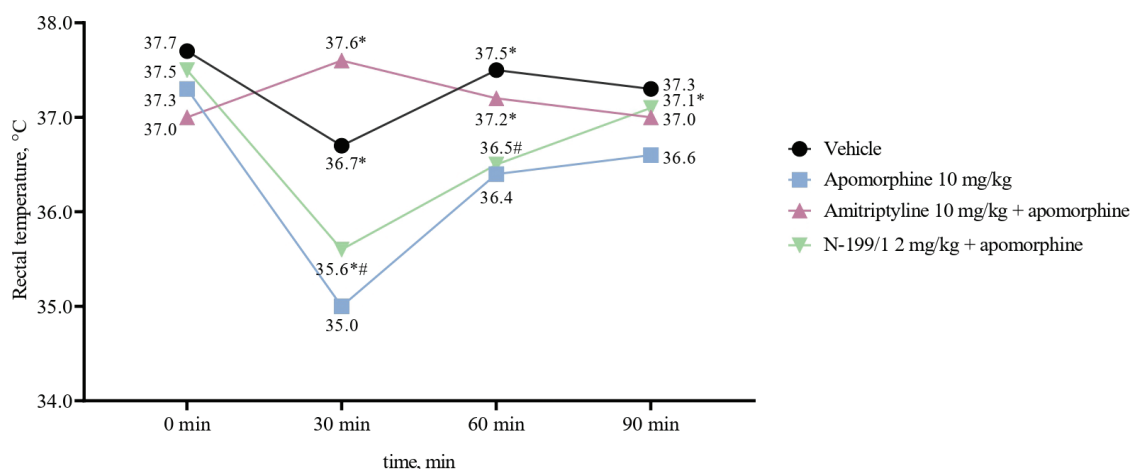


Figure 8. Effect of N-199/1 on apomorphine-induced hypothermia. **Note:** graphs show group medians; * $p < 0.05$ for the Mann-Whitney test compared with the apomorphine group; # $p < 0.05$ for the Mann-Whitney test compared with the amitriptyline group.

1.4–5.2 °C 30 and 60 min after L-DOPA administration (140 mg/kg, $p < 0.05$ compared with L-DOPA) to the level of the L-DOPA group (700 mg/kg) (Fig. 9).

Effect of N-199/1 on arecoline-induced tremor

After the injection of arecoline, the animals developed a tremor with a latency of 85 s, a severity level of 2 points, and a duration of 449 s (Fig. 9). N-199/1 reduced tremor duration (by 169 s, $p = 0.021$) and its severity (by 0.5 points, $p = 0.041$) compared to the arecoline group, but the effect of N-199/1 was inferior to that of amitriptyline ($p < 0.05$) (Table 1).

Effect of N-199/1 on picrotoxin-induced seizures

Picrotoxin caused seizures in 100% of the animals in the group (latency 446 s), and within the first hour after its administration, all the animals in the group died. N-199/1 had no effect on the convulsive effect of picrotoxin, while the reference drug diazepam significantly increased the latency of seizures (by 341 s, $p = 0.002$) (Fig. 10) and prevented the death of animals (2 out of 8 animals died).

Table 1. Effect of N-199/1 on the latency, duration and severity of arecoline tremor

Group	Latency, s	Duration, s	Severity, points
Arecoline 6 mg/kg	85 (55-97) n=8	449 [#] (395-532) n=8	2.00 [#] (2.00-3.00) n=8
Amitriptyline + arecoline	53 (0-164) n=8	89* (0-209) n=8	0.25* (0.00-0.75) n=8
N-199/1 + arecoline	105 (80-137) n=8	280* [#] (228-356) n=8	1.50* [#] (1.00-2.00) n=8

Note: the table shows group medians, interquartile range and the number of animals (n) in the group; * – $p < 0.05$ for the Mann-Whitney test compared with the arecoline group, # – $p < 0.05$ for the Mann-Whitney test compared to the amitriptyline group.

Discussion

Over the past decades, tests of neuropharmacological interaction have remained the basic method for preclinical assessment of the mechanism of action of antidepressants (Habriev 2005) and have allowed studying the effect of substances with antidepressant activity on the main neurotransmitter systems of the brain.

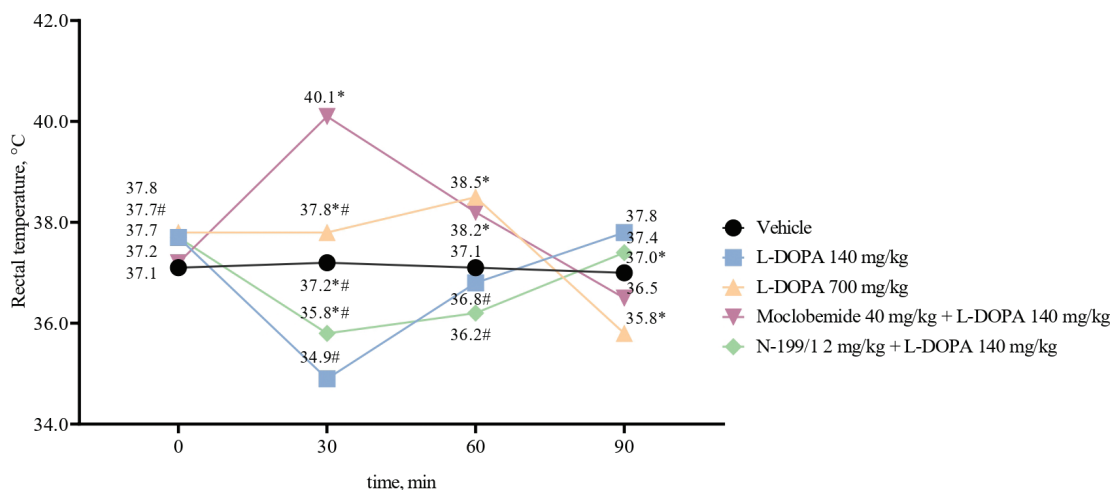


Figure 9. Effect of N-199/1 on L-DOPA-induced hypothermia (L-DOPA 140 mg/kg). **Note:** graphs show group medians; * $p < 0.05$ for the Mann-Whitney test compared with the group of L-DOPA (140 mg/kg); # $p < 0.05$ for the Mann-Whitney test compared with the moclobemide group.

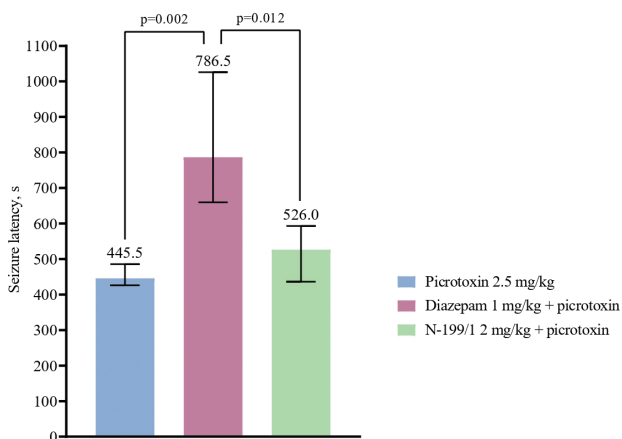


Figure 10. Effect of N-199/1 on latency of picrotoxin-induced seizures. **Note:** graphs show group medians and inter-quartile range.

Our previous studies of the mechanism of antidepressant action of N-199/1, which included tests of reserpine-induced hypothermia, ptosis and akinesia, clonidine-induced hypothermia and tests with antagonists of serotonergic 5HT1A- (WAY100635), 5HT2A/2C- (ketanserin) and 5HT3- (ondansetron) receptors and $\alpha 2$ -adrenergic receptors (yohimbine), showed the ability of N-199/1 to enhance serotonergic neurotransmission due to stimulation of serotonergic 5HT1A-receptors and blockade of 5HT2A/2C-receptors and $\alpha 2$ -adrenergic receptors (Nikitina and Gaisina 2021). The present study is a continuation of our previous research on the mechanism of antidepressant action of N-199/1 and is aimed at evaluating the effect of N-199/1 on the main neurotransmitter systems of the brain, such as serotonergic, dopaminergic, cholinergic and GABAergic systems.

The test with the precursor of serotonin 5-HTP is used to assess the effect of substances on the central serotonergic structures. 5-HTP is known to cause hyperkinesia (head-twitch response) in mice when administered at high doses (300 mg/kg), with almost no effect at low doses (50 mg/kg).

Different classes of antidepressants act differently in this test: for example, monoamine oxidase (MAO) inhibitors potentiate the effect of low doses of 5-HTP, leading to the development of a head-twitch response, while reuptake inhibitors and atypical antidepressants reduce the severity of hyperkinesia, exhibiting a serotonin-negative effect (Mashkovsky et al. 1983). In our experiment, N-199/1 did not cause hyperkinesia when co-administered with a low dose of 5-HTP (50 mg/kg) similar to the reference drug amitriptyline, and reduced the number of head twitches, induced by a high dose of 5-HTP (300 mg/kg). The effect of N-199/1 was significantly inferior to the effect of amitriptyline ($p < 0.05$), which prevented the development of hyperkinesia. These findings, combined with our previous results from the reserpine test and tests with antagonists (Nikitina and Gaisina 2021), suggest that N-199/1 has an antiserotonergic action, probably due to stimulation of presynaptic 5HT1-receptors and/or blockade of postsynaptic 5HT2-receptors and/or $\alpha 2$ -adrenergic receptors.

The effect of N-199/1 on dopaminergic neurotransmission was studied in tests with haloperidol, L-DOPA, and apomorphine.

It is known that antidepressants are able to counteract the cataleptogenic action of typical neuroleptics (Mashkovsky et al. 1983). The development of catalepsy under the influence of haloperidol is associated with blockade of dopamine D2-receptors; at the same time, there is evidence of the serotonergic mechanisms involvement, associated mainly with 5HT1A-receptors. For example, 5HT1A- and 5HT2A/2C- receptor agonists are able to eliminate catalepsy, while 5HT2A/2C- receptor antagonists have no effect (Wadenberg 1996). N-199/1 reduced the duration of haloperidol catalepsy, although to a lesser extent than amitriptyline ($p < 0.05$), which may be associated with stimulation of 5HT1A-, but not 5HT2A/2C-receptors; a direct action on dopaminergic neurotransmission is also not excluded. Therefore, the next step was to study the activity of N-199/1 in the test with the precursor of dopamine L-DOPA.

L-DOPA at low doses (100–200 mg/kg) leads to the development of hypothermia in mice, while at high doses (more than 500 mg/kg), on the contrary, it causes hyperthermia (Mashkovsky et al. 1983). Typically, the L-DOPA test is used to identify MAO inhibitors that are able to potentiate the effect of low doses of L-DOPA and cause hyperthermia in mice (Habriev 2005). The described effect in our experiment was caused by the reference drug **moclobemide** (MAO A inhibitor), while N-199/1 only slightly reduced hypothermia caused by a low dose of L-DOPA, which may be associated with a dopaminergic effect, but not with MAO inhibition.

It is believed that the hyperthermic effect of **apomorphine** (an agonist of dopamine D1- and D2-receptors) at high doses (10–25 mg/kg) is associated with noradrenergic mechanisms rather than dopaminergic ones, and is eliminated by antidepressants that do not inhibit MAO (Mashkovsky et al. 1983). N-199/1 reduced the severity of **apomorphine** hypothermia, while **amitriptyline** eliminated it. Since serotonergic agents, as a rule, do not demonstrate activity in this test (Mashkovsky et al. 1983), the effect of N-199/1 is probably due to its noradrenergic and/or dopaminergic action and is not associated with MAO inhibition.

Thus, the results obtained in tests with L-DOPA and **apomorphine** make it possible to exclude the effect of N-199/1 on MAO, as well as to suggest the presence of a dopaminergic component in its mechanism of action.

The central cholinergic agonist **arecoline** causes tremor in mice; therefore, antidepressants with anticholinergic

properties are able to prevent its development (Mashkovsky et al. 1983). N-199/1 reduced the duration and intensity of tremor, but to a lesser extent than **amitriptyline**. This suggests that the effect of N-199/1 may be associated not only with the blockade of cholinergic receptors, but also with serotonergic mechanisms (Martin et al. 1985).

The effect on GABAergic neurotransmission was assessed in the test of **picROTOXIN**-induced seizures. The reference drug **diazepam** increased the latency of seizures and decreased the incidence of death of animals in the group, while N-199/1 did not affect these parameters, which indicates that N-199/1 does not act on GABAergic neurotransmission.

Conclusion

The ability of N-199/1 to influence serotonergic, noradrenergic, dopaminergic and cholinergic neurotransmission using tests of neuropharmacological interaction was shown. The mechanism of the antidepressant action of N-199/1 is probably due to stimulation of 5HT1A-receptors and/or blockade of serotonin 5HT2A/2C-receptors and/or α 2-adrenergic receptors; the involvement of dopaminergic receptors and/or cholinergic receptors is also possible. The results obtained allow us to conclude that N-199/1 belongs to atypical antidepressants, but not neuronal reuptake inhibitors or MAO inhibitors.

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