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Short communication

Agomelatine and tianeptine antidepressant activity in mice behavioral despair tests is enhanced by DMPX, a selective adenosine A_{2A} receptor antagonist, but not DPCPX, a selective adenosine A_1 receptor antagonist

Aleksandra Szopa[a,*], Karolina Bogatko[a], Anna Serefko[a], Elżbieta Wyska[b], Sylwia Wośko[a], Katarzyna Świąder[a], Urszula Doboszewska[c], Aleksandra Wlaź[d], Andrzej Wróbel[e], Piotr Wlaź[c], Jarosław Dudka[f], Ewa Poleszak[a]

[a] Department of Applied Pharmacy, Medical University of Lublin, Lublin, Poland
[b] Department of Pharmacokinetics and Physical Pharmacy, Collegium Medicum, Jagiellonian University, Kraków, Poland
[c] Department of Animal Physiology, Institute of Biology and Biochemistry, Faculty of Biology and Biotechnology, Maria Curie-Skłodowska University, Lublin, Poland
[d] Department of Pathophysiology, Medical University of Lublin, Lublin, Poland
[e] Second Department of Gynecology, Medical University of Lublin, Lublin, Poland
[f] Chair and Department of Toxicology, Medical University of Lublin, Lublin, Poland

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ABSTRACT

Background: Adenosine, an endogenous nucleoside, modulates the release of monoamines, *e.g.*, noradrenaline, serotonin, and dopamine in the brain. Both nonselective and selective stimulation of adenosine receptors produce symptoms of depression in some animal models. Therefore, the main objective of our study was to assess the influence of a selective adenosine A_1 receptor antagonist (DPCPX) and a selective adenosine A_{2A} receptor antagonist (DMPX) on the activity of agomelatine and tianeptine.
Methods: The forced swim test (FST) and tail suspension test (TST) were performed to assess the effects of DPCPX and DMPX on the antidepressant-like activity of agomelatine and tianeptine. Drug serum and brain levels were analyzed using HPLC.
Results: Co-administration of agomelatine (20 mg/kg) or tianeptine (15 mg/kg) with DMPX (3 mg/kg), but not with DPCPX (1 mg/kg), significantly reduced the immobility time both in the FST and TST in mice. These effects were not associated with an enhancement in animals' spontaneous locomotor activity. The observed changes in the mouse behavior after concomitant injection of DMPX and the tested antidepressant agents were associated with elevated brain concentration of agomelatine and tianeptine.
Conclusion: Our study shows a synergistic action of the selective A_{2A} receptor antagonist and the studied antidepressant drugs, and a lack of such interaction in the case of the selective A_1 receptor antagonist. The interaction between DMPX and agomelatine/tianeptine at least partly occurs in the pharmacokinetic phase. A combination of a selective A_{2A} receptor antagonist and an antidepressant may be a new strategy for treating depression.

Introduction

Depression, a severe and often recurrent affective disorder, affects millions of people. According to the World Health Organization (WHO), depression is in the 4th place on the list of serious diseases, and it is projected to be in the 2nd place in 2020. Because the number of patients suffering from depression is growing and the effectiveness of currently used drugs is unsatisfactory [1–4], intensive search for new treatment options for depression is underway. Recently, attention has been paid to the adenosine neurotransmission and the participation of the adenosine system in the action of antidepressants [5–9]. Adenosine, an extracellular neuromodulator, can activate four subtypes of adenosine receptors: A_1, A_{2A}, A_{2B}, and A_3 [10]. In the central nervous system (CNS), especially in the cortex and striatum, A_1 and A_{2A} adenosine receptors are more abundant. Adenosine A_1 receptors are located mainly in the hippocampus, cerebellum

* Corresponding authors.
E-mail addresses: aleksandra.szopa@umlub.pl (A. Szopa), ewa.poleszak@umlub.pl (E. Poleszak).

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and brain cortex, whereas A_{2A} adenosine receptors are more abundant in the striatopallidal neurons and olfactory bulb. These receptors mediate the release of all known neurotransmitters and the action of neuromodulators, such as neurotrophic factors or neuropeptides [11].

So far, we have shown that caffeine, which non-selectively inhibits the adenosine A_1 and A_{2A} receptors, exerts antidepressant-like effects, as well as that it potentiates the action of atypical antidepressants in the FST and TST in mice [12]. Here we decided to examine whether selective A_1 receptor antagonist (DPCPX) or selective A_{2A} receptor antagonist (DMPX) is able to potentiate the antidepressant-like activity of agomelatine and tianeptine, with the aim of verifying whether such combinations represent a potential strategy for the treatment of depressive disorders. Both antidepressant drugs that have been chosen by us belong to the group of atypical antidepressants. Agomelatine acts either as a melatonin MT_1 and MT_2 receptors agonist, or as a serotonin 5-HT_{2A} and 5-HT_{2C} receptors antagonist, indirectly enhancing the release of noradrenaline (NA) and dopamine (DA) in the CNS [13]. Tianeptine selectively augments serotonin (5-HT) uptake in the brain, increases the extracellular level of DA in mesolimbic structures, and increases α_1-adrenergic system responsiveness [14]. Both of these agents do not inhibit biogenic amine transporters responsible for the re-uptake of 5-HT, NA or DA [13,15], which are the main targets of classic antidepressants. Moreover, agomelatine does not possess affinity for most receptors, *e.g.*, adrenergic, benzodiazepine, dopaminergic, GABA-ergic, histamine, glutamatergic, muscarinic, nicotinic, sigma and adenosine receptors [13].

In addition, by determining concentrations of the tested antidepressant agents in mouse serum and brain tissue, we examined the nature of the interaction between each of them and A_1 and A_{2A} receptor antagonists. To our knowledge, this is the first study which demonstrates the antidepressant-like activity of these combinations and thus the potential clinical utility of such combinations.

Materials and methods

Animals

The experiments were conducted on adult Albino Swiss male mice (25–30 g) obtained from the licensed breeder (Kołacz, Warsaw, Poland). Rooms, where the animals lived, were lit up on a 12 h darkness/light cycle (light on at 6:00 a.m. light off at 6:00 p.m.), and the temperature and humidity therein were 20–23 °C and 45–55%, respectively. The experimental groups consisted of 8–10 mice, randomly assigned prior to the drug administration. Behavioural tests were video recorded and then analysed by two blind experimenters. All procedures were carried out between 8.00 a.m. and 3.00 p.m. to minimize circadian influences. Housing and experimental procedures were conducted in accordance with the European Union Directive of 22 September 2010 (2010/63/EU) and Polish legislation acts concerning animal experimentation. The procedures and protocols were approved by the Local Ethics Committee in Lublin. All efforts were made to minimize animal suffering as well as the number of animals used in the study.

Drug administration

DPCPX (8-cyclopentyl-1,3-dipropylxanthine, Sigma–Aldrich, Poznań, Poland), DMPX (3,7-dimethyl-1-propargylxanthine, Sigma–Aldrich, Poznań, Poland), and agomelatine (Sigma–Aldrich, Poznań, Poland) were suspended in a 0.9% saline with Tween 80 (1%) (POCH, Gliwice, Poland), whereas tianeptine sodium (Sigma–Aldrich, Poznań, Poland) was dissolved in 0.9% saline. All the used solutions/suspensions were administered intraperitoneally (*ip*) at a constant volume of 10 ml per kg body weight. DPCPX (1 mg/kg) and DMPX (3 mg/kg) were administrated 30 min prior to the experiment, whereas agomelatine (20 mg/kg) and tianeptine (15 mg/kg) were administered 60 min prior to the experiment. The treatment regimen and the doses of the tested agents were chosen based on our previous studies and literature data.

Forced swim test (FST)

The FST was performed according to the method that was described in detail earlier [16]. The total immobility time was counted for the last 4 min of the 6-min test. The animal was considered motionless when it made only the movements needed to keep the head just above the water.

Tail suspension test (TST)

The TST was performed according to the method that was described in detail earlier [17]. The total immobility time was counted for the last 4 min of the 6-min test. The animal was considered motionless when it made only the movements needed to breathe.

Locomotor activity test

Opto-Varimex-4 Auto-Track (Columbus Instruments, Columbus, OH, USA) was used to assess the distance travelled by an animal between 2nd and 6th min of the locomotor activity test [12].

HPLC measurement of antidepressants concentration

Blood and brains were collected immediately after the decapitation, which was carried out 60 min after injection of an antidepressant with or without an adenosine receptor antagonist. Blood, after collection into Eppendorf tubes, was left until clotted, then centrifuged for 10 min at 1000 rpm. The obtained supernatant (serum) was transferred to new tubes and frozen (−25 °C). Brains were removed from the skulls, washed in 0.9% saline, and also frozen. Serum and brain levels of the studied antidepressant drugs were measured by HPLC as described in detail earlier [12,18].

The extraction yields of agomelatine, tianeptine and internal standards were 66–97%. Levels of tested agents in serum were presented in ng/ml, whereas in brain in ng/g wet tissue.

Statistical analysis

A two-way ANOVA followed by a Bonferroni's *post hoc* test was used to analyze the results of the behavioral tests, whereas Student's *t*-test was used to evaluate the results of HPLC analysis. The differences were considered statistically significant when $p < 0.05$.

Results

FST and TST

Lack of statistical significance was observed in the FST and TST ($p > 0.05$) in the groups receiving only 1 mg/kg DPCPX, 3 mg/kg DMPX, 20 mg/kg agomelatine, or 15 mg/kg tianeptine (Figs. 1 and 2).

Agomelatine co-administered with DPCPX (20 and 1 mg/kg, respectively) did not influence the mice immobility time in both the FST and TST ($p > 0.05$) (Figs. 1A and 2 A). Joint administration of agomelatine with DMPX (20 and 3 mg/kg, respectively) produced a

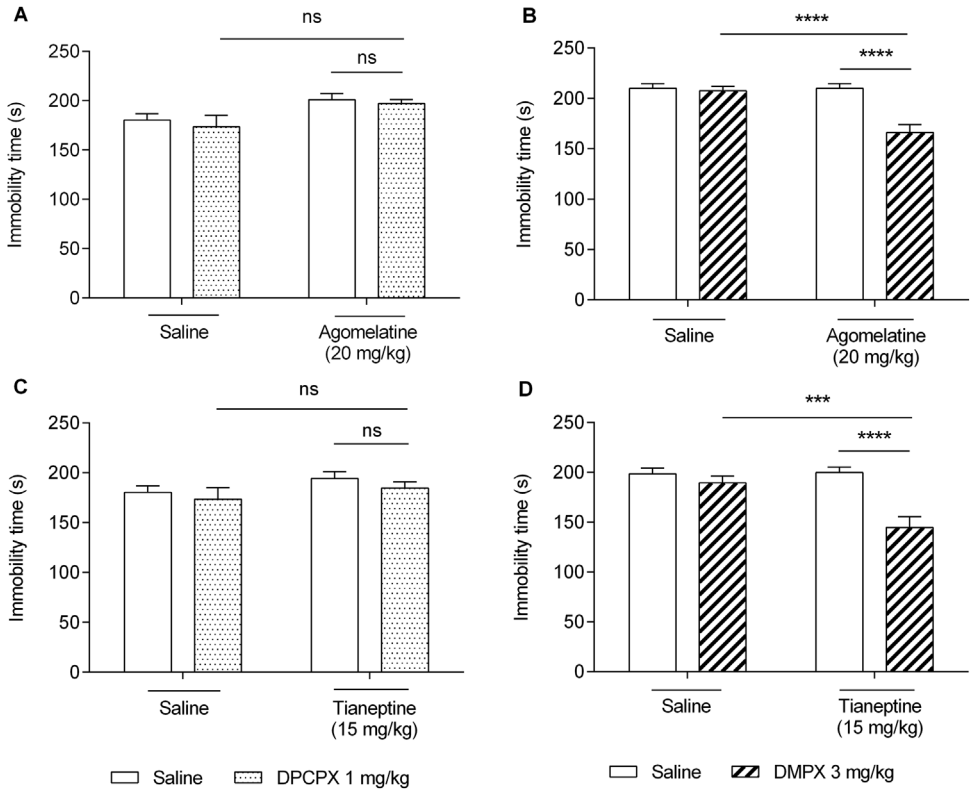

Fig. 1. The effects of combined administration of DPCPX (A, C) and DMPX (B, D) with agomelatine (A, B) and tianeptine (C, D) in the FST in mice. Antidepressants and saline were administered *ip* 60 min, whereas DPCPX and DMPX were administered *ip* 30 min before the test. Each experimental group consisted of 10 animals. The data are presented as the means + SEM. (A) ns $p > 0.05$ *vs.* DPCPX-treated group and agomelatine-treated group (two-way ANOVA followed by Bonferroni's *post-hoc* test). (B) ****$p < 0.0001$ *vs.* DMPX-treated group and agomelatine-treated group (two-way ANOVA followed by Bonferroni's *post-hoc* test). (C) ns $p > 0.05$ *vs.* DPCPX-treated group and tianeptine-treated group (two-way ANOVA followed by Bonferroni's *post-hoc* test). (D) ***$p < 0.001$*vs.* DMPX-treated group, ****$p < 0.0001$ *vs.* tianeptine-treated group (two-way ANOVA followed by Bonferroni's *post-hoc* test).

statistically significant reduction in mouse immobility in these tests (FST: $p < 0.0001$ *vs.* DMPX-treated group and agomelatine-treated group; TST: $p < 0.01$ *vs.* DMPX-treated group and $p < 0.0001$ *vs.* agomelatine-treated group) (Figs. 1B and 2 B).

Tianeptine co-administered with DPCPX (15 and 1 mg/kg, respectively) did not influence the mice immobility time in both the FST and TST ($p > 0.05$) (Figs. 1C and 2 C). Joint administration of tianeptine with DMPX (15 and 3 mg/kg, respectively) contributed to a statistically significant reduction in mouse immobility in these tests (FST: $p < 0.001$ *vs.* DMPX-treated group and $p < 0.0001$ *vs.* tianeptine-treated group; TST: $p < 0.0001$ *vs.* tianeptine-treated group) (Figs. 1D and 2 D).

In the FST the two-way ANOVA demonstrated

(A) a significant effect of agomelatine [$F(1,36) = 8.219$, p=0.0069], no effect of DPCPX [$F(1,36) = 0.4907$, p = 0.4881], and no interaction between agomelatine and DPCPX [$F(1,36) = 0.03786$, p = 0.8468].

(B) a significant effect of agomelatine [$F(1,35) = 14.01$, $p = 0.0007$], a significant effect of DMPX [$F(1,35) = 17.44$, $p = 0.0002$], and a significant interaction between agomelatine and DMPX [$F(1,35) = 14.01$, $p = 0.0007$].

(C) no effect of tianeptine [$F(1,36) = 2.380$, $p = 0.1316$], no effect of DPCPX [$F(1,36) = 1.029$, $p = 0.3173$], and no interaction between tianeptine and DPCPX [$F(1,36) = 0.02754$, $p = 0.8691$].

(D) a significant effect of tianeptine [$F(1,36) = 8.338$, $p = 0.0065$], a significant effect of DMPX [$F(1,36) = 18.27$, p = 0.0001], and a significant interaction between tianeptine and DMPX [$F(1,36) = 9.533$, p = 0.0039].

In the TST two-way ANOVA demonstrated

(A) a significant effect of agomelatine [$F(1,36) = 4.189$, $p = 0.0480$], no effect of DPCPX [$F(1,36) = 1.485$, p = 0.2309], and no interaction between agomelatine and DPCPX [$F(1,36) = 0.03267$, p = 0.8576].

(B) a significant effect of agomelatine [$F(1,36) = 8.116$, p = 0.0072], a significant effect of DMPX [$F(1,36) = 31.81$, $p < 0.0001$], and a significant interaction between agomelatine and DMPX [$F(1,36) = 6.528$, p = 0.0150].

(C) no effect of tianeptine [$F(1,34) = 0.2420$, $p = 0.6259$], no effect of DPCPX [$F(1,34) = 1.859$, p = 0.1817], and no interaction between tianeptine and DPCPX [$F(1,34) = 1.210$, p = 0.2790].

(D) no effect of tianeptine [$F(1,34) = 1.842$, $p = 0.1836$], a significant effect of DMPX [$F(1,34) = 22.00$, $p < 0.0001$], and no interaction between tianeptine and DMPX [$F(1,34) = 3.377$, p = 0.0749].

Locomotor activity test

No significant differences were observed in the locomotor activity test ($p > 0.05$) between all tested groups (Table 1).

In locomotor activity test two-way ANOVA demonstrated

(A): no effect of agomelatine [$F(1,28) = 0.2647$, $p = 0.6110$], no effect of DPCPX [$F(1,28) = 0.4716$, $p = 0.4979$], and no interaction [$F(1,28) = 0.4048$, $p = 0.5298$].

(B): no effect of agomelatine [$F(1,28) = 0.2647$, $p = 0.6110$], no effect of DMPX [$F(1,28) = 0.4716$, $p = 0.4979$], and no interaction [$F(1,28) = 0.4048$, $p = 0.5298$].

(C): no effect of tianeptine [$F(1,28) = 0.4140$, $p = 0.5252$], no effect of DPCPX [$F(1,28) = 0.2241$, $p = 0.6396$], and no interaction [$F(1,28) = 0.2108$, $p = 0.6497$].

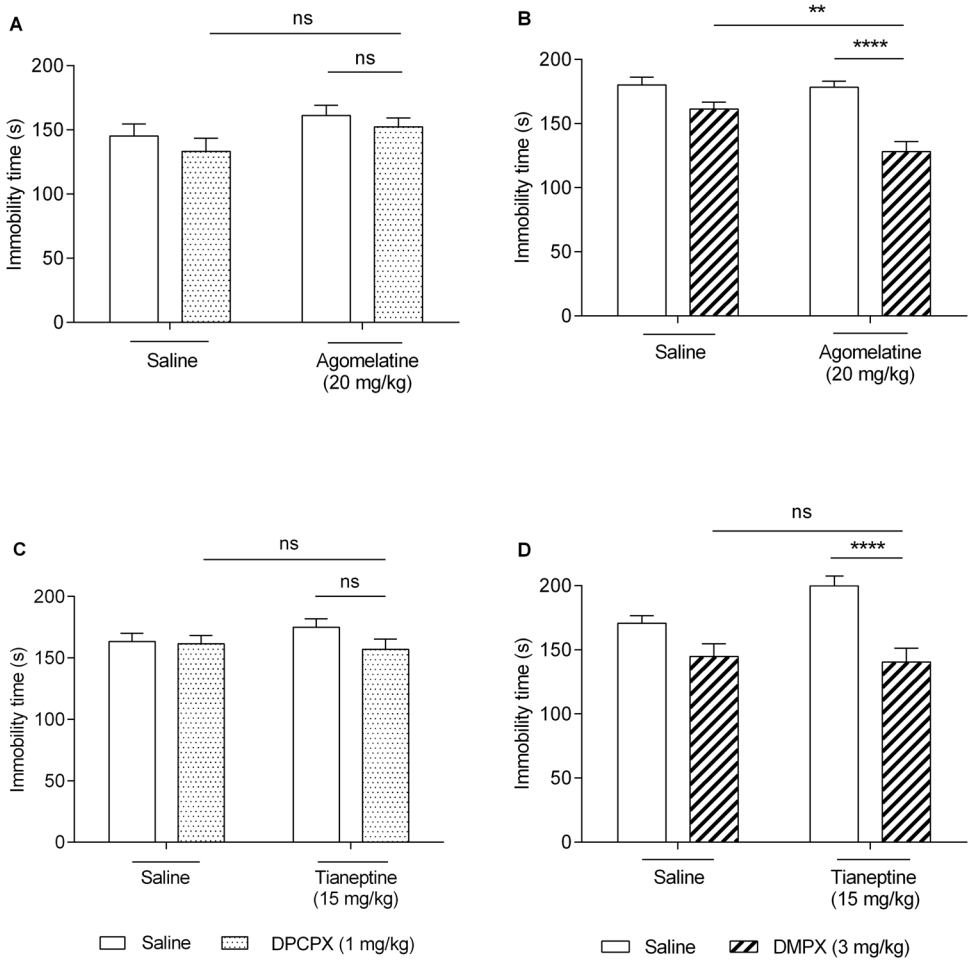

Fig. 2. The effects of combined administration of DPCPX and DMPX with agomelatine and tianeptine in the TST in mice. Antidepressants and saline were administered *ip* 60 min, whereas DPCPX and DMPX were administered *ip* 30 min before the test. Each experimental group consisted of 10 animals. The data are presented as the means + SEM. (A) ns $p > 0.05$ *vs.* DPCPX-treated group and agomelatine-treated group (two-way ANOVA followed by Bonferroni's *post-hoc* test). (B) $^{**}p < 0.01$ *vs.* DMPX-treated group, $^{****}p < 0.0001$ *vs.* agomelatine-treated group (two-way ANOVA followed by Bonferroni's *post-hoc* test). (C) ns $p > 0.05$ *vs.* DPCPX-treated group and tianeptine-treated group (two-way ANOVA followed by Bonferroni's *post-hoc* test). (D) ns $p > 0.05$ *vs.* DMPX-treated group, $^{****}p < 0.0001$ *vs.* tianeptine-treated group (two-way ANOVA followed by Bonferroni's *post-hoc* test).

(D): no effect of tianeptine [$F(1,28) = 0.4140$, $p = 0.5252$], no effect of DMPX [$F(1,28) = 0.2241$, $p = 0.6396$], and no interaction [$F(1,28) = 0.2108$, $p = 0.6497$].

HPLC measurement of antidepressants concentration

The results of the pharmacokinetic studies are presented in Table 2. Concomitant injection of DPCPX and agomelatine or tianeptine caused a significant decrease in the level of antidepressants in serum (*t*-test: $p < 0.05$ and $p < 0.001$ respectively) without a significant increase/decrease in the concentrations of these drugs in brain tissue (*t*-test: $p > 0.05$). In contrast, concomitant injection of DMPX with agomelatine caused a significant increase in agomelatine level in both serum and brain tissue (*t*-test: $p < 0.01$ and $p < 0.0001$ respectively). Nonetheless, joint administration of DMPX with tianeptine elevated the concentration of tianeptine in brain tissue (*t*-test: $p < 0.05$) with a decrease in blood level (*t*-test: $p < 0.01$).

Discussion

Here we show for the first time the effects of selective A_1 and A_{2A} receptor antagonists on the antidepressant-like activity of agomelatine and tianeptine. Thus far, no attempt has been made to specify the type of the interaction between these substances. We observed a meaningful decrease in the immobility time in groups of mice treated with DMPX and agomelatine or tianeptine at ineffective doses in both the FST and TST, and no such changes in the DPCPX-agomelatine or DPCPX-tianeptine treated groups. Moreover, none of the substances injected alone or in combination induced hyperactivity of mice. These results point to a synergistic interaction between the selective A_{2A} receptor inhibitor and the tested antidepressants and to the lack of such interaction in case of the selective A_1 receptor blocker and the studied drugs. The pharmacokinetic analysis indicated that the effects observed in behavioral tests, at least in part, may result from the pharmacokinetic interaction. In the case of co-administration of agomelatine with DPCPX or tianeptine with DPCPX, the concentration of antidepressants in murine serum was decreased, however, there were no significant changes in the concentration of these agents in brain tissue. The injection of DMPX with the studied antidepressants contributed to an increase in both agomelatine and tianeptine levels in brain tissue with a simultaneous increase in agomelatine and a decrease in tianeptine concentrations in serum.

Preclinical and clinical studies have shown that the adenosine system is involved in the regulation of behavior, mood and emotions [19]. There is evidence that adenosine and adenosine receptor agonists induce depressive-like behavior in laboratory

Table 1
The **e**ffect of treatments on the spontaneous locomotor activity of mice.

	Treatment (mg/kg)	Distance traveled between 2nd and 6th min (cm)
(A)	saline + saline (control group)	490.6 ± 50.75
	DPCPX 1 + saline	487.9 ± 72.85
	agomelatine 20 + saline	553.2 ± 30.86
	DPCPX 1 + agomelatine 20	481.2 ± 54.85
	tianeptine 15 + saline	703.7 ± 297.4
	DPCPX 1 + tianeptine 15	523.5 ± 230.4
(B)	saline + saline (control group)	640.7 ± 74.67
	DMPX 3 + saline	955.8 ± 121.8
	agomelatine 20 + saline	573.1 ± 161.9
	DMPX 3 + agomelatine 20	643.2 ± 68.10
	tianeptine 15 + saline	485.8 ± 100.3
	DMPX 3 + tianeptine 15	822.1 ± 131.1

Antidepressants and saline were administered *ip* 60 min, whereas DPCPX and DMPX were administered *ip* 30 min before the test. n = 8 animals. Data are presented as the means ± SEM (two-way ANOVA followed by Bonferroni's *post-hoc* test).

Table 2
Effect of DPCPX and DMPX on the concentration of agomelatine and tianeptine in mouse serum and brain.

Treatment	Antidepressants concentration in serum		Antidepressants concentration in brain	
(mg/kg)	(ng/ml)		(ng/g)	
agomelatine 20 + saline	51.05 ± 6.129		53.60 ± 5.389	
agomelatine 20 + DPCPX 1	29.75 ± 4.621 *	$p = 0.0125$	43.34 ± 4.703	$p = 0.9705$
agomelatine 20 + DMPX 3	80.69 ± 6.248 **	$p = 0.0033$	125.2 ± 9.520 ****	$p < 0.0001$
tianeptine 15 + saline	104.8 ± 7.633		30.35 ± 2.720	
tianeptine 15 + DPCPX 1	59.58 ± 5.995 ^^^	$p = 0.0002$	22.18 ± 4.163	$p = 0.1168$
tianeptine 15 + DMPX 3	73.87 ± 6.520 ^^	$p = 0.0062$	44.23 ± 5.735 ^	$p = 0.0426$

Antidepressants and saline were administered *ip* 60 min, whereas DPCPX and DMPX *ip* 30 min before decapitation. n = 10 animals. Results are presented as mean values ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{**}p < 0.01$, $^{****}p < 0.0001$ *vs.* agomelatine-treated group. $^{\wedge}p < 0.05$, $^{\wedge\wedge}p < 0.01$, $^{\wedge\wedge\wedge}p < 0.1$ *vs.* tianeptine-treated group (Student's *t*-test).

animals [20,21]. However, the antidepressant-like effect in the animal behavioral despair tests has also been observed following administration of adenosine [22]. The stimulation of adenosine receptors induces the depressive-like behavior [20,21], while the inhibition of adenosine receptors reduces [6,8,23–25] this type of behavior in laboratory animals. Nevertheless, opposite results can also be found, *e.g.*, Kaster et al. [22,26–28] have shown that adenosine and non-selective adenosine receptor agonists shorten the duration of immobility time in the FST and the TST. Moreover, this effect was reversed by A_1 and A_{2A} antagonists and both A_1 and A_{2A} receptor agonists CHA and DPMA were demonstrated to cause antidepressant-like effect in the FST [22]. Based on the above-mentioned findings, it has been suggested that adenosine A_1 and/or A_{2A} receptor antagonists may play an important role in the treatment of depressive disorders [5–9].

We have previously found that a non-selective inhibition of A_1 and A_{2A} adenosine receptors by caffeine increased the activity of two atypical antidepressants, *i.e.*, agomelatine and mianserin in the FST and TST. Moreover, the observed synergistic antidepressant-like effect between caffeine and agomelatine/mianserin was associated with summative impact of these agents on monoamine neurotransmission but not with changes in the concentration of the tested drugs in the blood or brain tissue of mice [12]. Similarly, the antidepressant-like potential of DMPX-agomelatine and DMPX-tianeptine combination that was observed in the present study is presumably the consequence of their joint impact on the monoaminergic transmission. Both agomelatine and tianeptine indirectly enhances the level of DA in brain structures. Agomelatine also enhances NA concentration [13,29]. Additionally, DMPX stimulates the monoaminergic system [14].

An important observation is the increase in the level of the studied antidepressants in brain tissue following their concomitant administration with DMPX. It may be explained by an interaction in the transport across the blood-brain barrier. The decrease in tianeptine concentration in the blood may be caused by the shift of the pool of drugs to the brain. The increase in agomelatine concentration in the biological materials may be a result of an interaction at the level of hepatic biotransformation. In the literature there is lack of information about the biotransformation of DPCPX or DMPX in either animals or in humans. Since DPCPX and DMPX are analogues of xanthine [30], it can be assumed that their metabolisms are similar, *i.e.*, they are mainly metabolized by the cytochrom P450 isoenzymes, which are also involved in the metabolism of most antidepressants, for example mianserin, imipramine, citalopram, paroxetine, *etc.* [30,31]. Therefore, there is a high probability of pharmacokinetic interaction between the tested compounds.

In summary, our results show that selective antagonist of A_{2A} receptor, but not selective antagonist of A_1 receptor, augmented the antidepressant-like activity of agomelatine and tianeptine. Furthermore, the interaction between DMPX and agomelatine/tianeptine at least partly occurred in the pharmacokinetic phase. It seems plausible that a combination of selective A_{2A} receptor antagonist and an atypical antidepressant may be a new strategy for treating depression.

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Conflict of interest

The authors declare that they have no conflict of interest.

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