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Short communication

Effect of citalopram in the modified forced swim test in rats

Maciej Kuśmider, Joanna Solich, Paulina Pałach, Marta Dziedzicka-Wasylewska

Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Correspondence: Maciej Kuśmider, e-mail: kusmider@if-pan.krakow.pl

Abstract:
The present study examined the effect of citalopram (7.5 and 15 mg/kg) in the modified forced swim test (FST) in Wistar rats, in comparison to the effect of desipramine at the same doses. The citalopram at both doses increased swimming behavior, at the cost of climbing and immobility. The administration of desipramine increased climbing behavior while immobility counts were decreased. The modified FST is indeed more sensitive than the conventional FST in describing precisely the behavioral effects of antidepressant drugs, allowing to roughly estimate the contribution of individual neurotransmitter system to the mechanism of action of the studied drug.

Key words:
desipramine, citalopram, FST, rats

Abbreviations: CIT – citalopram, DMI – desipramine, FST – forced swim test, SSRI – selective serotonin reuptake inhibitor

Introduction

The forced swim test (FST), described originally by Porsolt et al. [18], is widely used as an animal test to assess the antidepressant action [2, 3, 10, 17]. The test is relatively simple to perform and has ability to measure behavioral effects common to antidepressant treatments that have diverse pharmacological and physiological effects. That test can also distinguish drugs that are not antidepressants. Nonetheless, almost all members of an important group of antidepressants – the selective serotonin reuptake inhibitors (SSRIs) – had been found not to be active in classic Porsolt's test in rats [1, 3]. Therefore, certain procedural modifications had to be introduced in order to measure the behavioral effects of those drugs [6, 8, 13].

The modifications that have been introduced concerned the water depth – in the modified procedure it was increased from 15–18 cm to 30 cm resulting in worse support of floating animals, and the scoring – not only the immobility time has been measured, but also the mode of active behavior (climbing, swimming, diving or head shaking) [7, 8]. The modified FST, beside allowing to observe the effects of SSRIs in rats, was found to be very useful in distinguishing that group of compounds from the compounds acting *via* the inhibition of noradrenaline reuptake. The latter

group, as for example reboxetine or desipramine, increases rather climbing, while SSRIs – rather swimming behavior.

Despite numerous studies using that modified FST procedure to assess the behavioral effects of SSRIs in rats, citalopram has not been studied extensively. The available data are not only scanty but also uncertain [11, 14, 16, 20]. Therefore, we decided to examine the effect of citalopram in the modified FST and compare its effect with that of desipramine, a noradrenaline reuptake inhibitor – an antidepressant with well established impact on behavior in FST.

Materials and Methods

Subjects

The experiments were carried out on male Wistar rats (ca. 80 days old, weighing 220–230 g). The animals had free access to food and water and were kept at a constant room temperature (22 ± 1°C), under a 12 h light/dark cycle (light on at 7 a.m.). Experimental protocols were approved by the local Ethics Committee and met guidelines of the responsible agency.

Drug administration

Citalopram (CIT), which was kindly provided by Lundbeck, and desipramine (DMI, Sigma) were dissolved in saline and administered at two doses 7.5 and 15 mg/kg intraperitoneally (*ip*) three times: at 24, 5 and 1 h before the FST. Control animals received 3 injections of vehicle. All animals were handled in the same manner. Each group consisted of 8 subjects.

Forced swim test

The modified FST procedure was used [8, 11]. During initiation session, the rats were forced to swim for 15 min in the opaque cylinders (21 cm in diameter), filled with water (23–25°C) to a 30 cm depth. Then, they were removed from the water, dried with towels and placed in a warm enclosure, and afterwards returned back to their home cages. The cylinders were emptied and cleaned between the rats. The animals started to receive the CIT or DMI on the next day after this pre-test.

One hour after the last dose of the drug animals were again put in the cylinders filled in the same way as during the pre-test, and their behavior was videotaped with videorecorder placed above the cylinders. The quantification has been done by means of behavioral sampling, i.e. the 5 min of the test session was divided into 60 intervals lasting 5 s each. An experienced observer qualified the period as climbing, swimming or immobility on the basis of activity predominant in each interval. Climbing behavior was defined as upward directed movements of the forepaws, usually along the wall of the chamber; swimming – as movement throughout the chamber, and immobility – when no additional activity was observed other than that required to keep the rat afloat.

In parallel, locomotor activity for the same doses and the same time schedule was measured in the Columbus actometers. Distance traveled, resting time and ambulations during 5 min of experiment were recorded.

Statistics

Data were analyzed by one-way ANOVA followed by Dunnett's test. Effects were considered significant when $p < 0.05$.

Results

The parameters describing control groups were comparable between both experiments. The immobility counts (in behavioral sampling) were of about 30 what corresponds to about 150 s. The climbing and swimming behavior was scored as about 13 and 17 counts (65 and 85 s), respectively, during 5 min of experiment.

The administration of CIT at both doses increased swimming behavior by about 50% [ANOVA: $F(2, 21) = 4.619$, $p = 0.0217$]. It looks like it was changed at the cost of climbing [a nonsignificant decrease of about 15%, $F(2, 21) = 0.7747$, $p = 0.4738$] and immobility [a nonsignificant decrease of about 11%, $F(2, 21) = 0.6141$, $p = 0.5506$] (Fig. 1).

The administration of DMI increased climbing behavior by about 30% at the dose of 7.5 mg/kg and by about 100% at the dose of 15 mg/kg [ANOVA: $F(2, 21) = 4.573$, $p = 0.0225$]. Neither dose of DMI

changed swimming counts [F(2, 21) = 0.0008, p = 0.9918]. Immobility was decreased by about 30% and by about 50% at the doses of 7.5 mg/kg and 15 mg/kg, respectively [F(2, 21) = 6.44, p = 0.006] (Fig. 2).

Locomotor activity expressed as distance traveled, resting time or ambulations was not affected by either drug [F(2, 21) statistics values ranged from 0.048 to 0.391, what corresponds to p values between 0.95 and 0.68, data not shown].

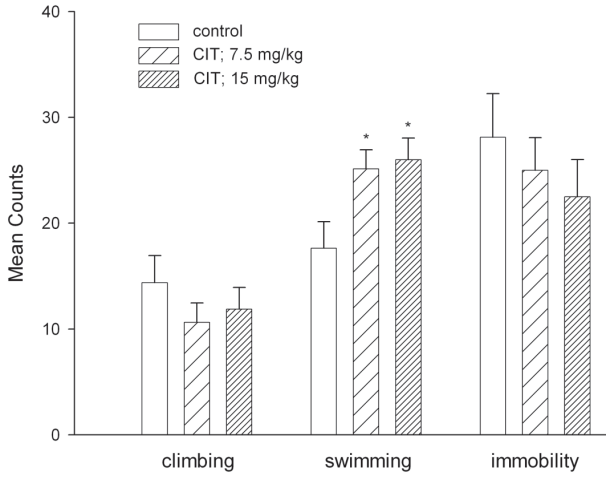

Fig. 1. Effect of citalopram (CIT) at the doses of 7.5 mg/kg and 15 mg/kg on behavioral parameters in the modified forced swim test in rats. Results are the mean counts ± SEM acquired by behavioral sampling (each count corresponds to a 5 s interval). The groups, consisting 8 animals each, received treatment (appropriate dose of the drug or mere vehicle) 24 h, 5 h and 1 h before the test, *ip* in 2 ml/kg of saline. Asterisks mark significance according to ANOVA followed by Dunnett's test. * $p < 0.05$

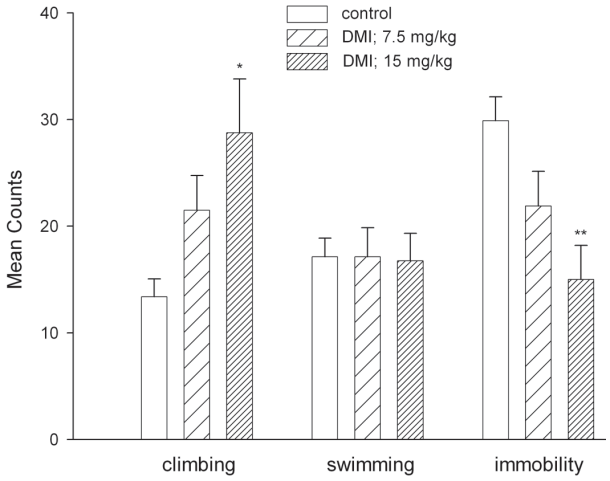

Fig. 2. Effect of desipramine (DMI) at the doses of 7.5 mg/kg and 15 mg/kg on behavioral parameters in the modified forced swim test in rats. Results are the mean counts ± SEM acquired by behavioral sampling (each count corresponds to 5 s interval). The groups, consisting 8 animals each, received treatment (appropriate dose of drug or mere vehicle) 24 h, 5 h and 1 h before the test, *ip* in 2 ml/kg of saline. Asterisks mark significance according to ANOVA followed by Dunnett's test. * $p < 0.05$, ** $p < 0.01$

Discussion

The present study characterized the effect of two antidepressant drugs with different pharmacological profile, using the modified FST. The behaviors selected for scoring were climbing and swimming behaviors as well as immobility.

CIT belongs to SSRIs, which, with few exceptions (e.g. high doses of sertraline or paroxetine [1]), do not show any significant effects in the conventional FST. However, as can be seen in Figure 1, both doses of the drug used in the present study, increased the swimming behavior, in comparison to the control group. Similar effects have been presented for other SSRIs, e.g. swimming behavior was the most sensitive behavioral response to fluoxetine [4, 5], paroxetine or sertraline [8], still in our study immobility parameter was not changed significantly.

On the other hand, DMI, the noradrenaline reuptake inhibitor, significantly augmented the climbing behavior, without any effect on the swimming component (Fig. 2). The effect remains in agreement with the data published previously [8, 9, 12, 19], which indicated that drugs affecting noradrenergic system modify rather climbing behavior, without any significant changes in the swimming. Lower dose (7.5 mg/kg) of DMI failed to exert statistically significant effect. Inconsistency of these data with other reports [14], may be due to different vulnerability of rat strains.

Indeed, the involvement of serotonin *vs.* noradrenaline systems in the mechanism of action of SSRIs *vs.* noradrenaline reuptake inhibitors in the modified FST was shown by Page et al. [15], who have shown that swimming behavior produced by fluoxetine but not the climbing behavior produced by DMI, was prevented by pretreatment with the tryptophan hydroxylase inhibitor, para-chlorophenylalanine. Additionally, Cryan et al. [5]. have shown that effects of reboxetine were blocked by selective chemical lesions

of the ventral noradrenergic bundle. However, one has to remember that the sole depletion of serotonin or noradrenaline failed to change the responses in the modified FST [5, 15].

Nevertheless, from the results presented here it may be concluded that the modified FST is indeed more sensitive that the conventional FST in describing precisely the behavioral effects of antidepressant drugs. Behavioral sampling following the videotaping of the animal performance is relatively easy. It can be used to study new compounds with antidepressant potential, allowing to roughly estimate the contribution of individual neurotransmitter system to the mechanism of action of the studied drug.

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