Interaction of Sertraline and Nimodipine on Some Behavioural Tests in Rats

Department of Pharmacology, Eskisehir Osmangazi University, Medical Faculty, Turkey

Abstract

Background. Intracellular calcium contributes to the development of affective disorders. Also, calcium channel inhibitors influence the activity of many neurotransmitters and exert antidepressant and anxiolytic properties.

Objectives. The aim of this study was to examine the effects of sertraline on anxiety and depressive behaviors and the role of nimodipine, a calcium channel antagonist, on these effects.

Material and Methods. Forced swimming and elevated plus maze tests were used to assess depression and anxiety respectively in rats. Sertraline (10 mg/kg) was administered repeatedly for 7 days both alone and in combination with single (0.5 mg/kg) and repeated (0.5 mg/kg/7 days) nimodipine administrations.

Results. Both repeated sertraline (S) and its combination with single nimodipine administration (S + N) significantly decreased the immobility time compared to control. The combination of (S) with repeated doses of nimodipine (N/7d), significantly increased the immobility time compared to (S) and (S + N). Single dose of nimodipine (N) significantly increased the immobility time compared to (S) and (S + N), and decreased the number of divings compared to control. There was no significant difference between groups in terms of struggle and the time spent in closed arms of the elevated plus maze.

Conclusions. There was no interaction between a single dose of sertraline and nimodipine when administered in combination, while repeated nimodipine administration reversed the antidepressant-like effect of sertraline. We suggest that L-type calcium channels are involved in the antidepressant-like effect of sertraline. Neither single nor repeated nimodipine administration had a significant effect on both depressive behaviour and anxiety. We also propose that there is no interaction between the effects of sertraline and nimodipine on anxiety behavior (Adv Clin Exp Med 2014, 23, 2, 169–175).

Key words: sertraline, nimodipine, forced swimming test, elevated plus maze test.
display adaptive alterations in the ligand binding of receptors which are similar to the chronic actions of antidepressants [9]. It was found that nimodipine, an L-type Ca\(^{2+}\) channel antagonist, affected brain serotonin metabolism and activated serotonergic transmission [10]. Ca\(^{2+}\) and VACC also have a significant role in anxiety-related behavior. In support of this role, the anxiogenic effect of nicotine was alleviated by CCAs in the elevated plus maze in mice [11]. The finding that fear conditioning, an animal model of fear and anxiety, was blocked by nimodipine, suggests the significance of L-type Ca\(^{2+}\) channels in the treatment of anxiety [12]. The suggested role of VACC in anxiety was supported by the observation that diazepam exerts an inhibitor effect on Ca\(^{2+}\) channels like nicardipine [13].

Surprisingly, neurotransmitters including serotonin inhibit Ca\(^{2+}\) current through Ca\(^{2+}\) channels. It has been indicated that fluoxetine, which is a member of the selective serotonin re-uptake inhibitors (SSRIs), inhibited T, N, and L-type calcium channels in hippocampal pyramidal cells [14]. It has been reported that the therapeutic actions of antidepressants require adaptation of Ca\(^{2+}\) signaling in addition to their effects on monoamines [15].

The aim of this study is to investigate the effects of sertraline, an SSRI, and nimodipine, on animal models of depression and anxiety to explore the relationship between Ca\(^{2+}\) channels and serotonergic systems and the role of L-type Ca\(^{2+}\) channels in the effects of sertraline on depressive and anxiety-like behaviors. The present study investigated the role of L-type Ca\(^{2+}\) channels by using nimodipine, a dihydropyridine derivate L-type Ca\(^{2+}\) channel antagonist which passes through the blood-brain barrier by means of its lipophilic feature which allows access to the central nervous system.

### Material and Methods

#### Animals

Female Wistar rats, weighing 200–250 g, were sheltered under a controlled environment (21 ± 2°C; 12 hr light/dark cycle, free access to standard food and tap water).

#### Drugs

Sertraline HCl (Sanovel) and nimodipine (Bay-er) were used in the study. Both of the drugs were dissolved in saline. Sertraline was used at a dose of 10 mg/kg and nimodipine was used at a dose of 0.5 mg/kg. Saline 0.9% was used as the vehicle solution. Both of the drugs and saline were administered intraperitoneally.

#### Experimental Groups

48 rats were randomly divided into 6 groups (n: 8 in each) as below:

- **Group 1 – control:** treated with saline for 7 days
- **Group 2 – repeated doses of sertraline group:** treated with sertraline 10 mg/kg for 7 days
- **Group 3 – repeated doses of sertraline and single dose of nimodipine group:** treated with sertraline 10 mg/kg for 7 days and received nimodipine 0.5 mg/kg 15 min before the tests
- **Group 4 – single dose of nimodipine group:** treated with saline for 7 days and nimodipine 0.5 mg/kg 15 min before the tests
- **Group 5 – repeated doses of sertraline and repeated doses of nimodipine group:** treated with sertraline 10 mg/kg and nimodipine 0.5 mg/kg for 7 days
- **Group 6 – repeated nimodipine group:** treated with nimodipine 0.5 mg/kg for 7 days

#### Study Design

Sertraline was injected to the rats i.p. for 7 days. Nimodipine was administered i.p. 15 min before the experiment procedure as a single injection with a dose of 0.5 mg/kg on the experiment day in groups 3 and 4 and repeatedly for 7 days in groups 5 and 6. The rats in the control group were given saline i.p. for 7 days. The experiments were carried out on the 7th day, 1 h after the last injections of sertraline or saline. Firstly, the rats were assessed with the elevated plus maze and then immediately evaluated with the forced swimming test.

All the experiments were carried out with the permission of the Local Ethics Committee for Experimentation of Eskisehir Osmangazi University, numbered as 191 in accordance with the Guide for the Care and Use of Laboratory Animals, and were conducted between the hours of 9:00 am and 1:00 pm.

#### Forced Swimming Test

The test was performed as described by Porsolt et al. [17]. The rats were forced to swim in a transparent plexyglass cylinder containing 15 cm and 25.0 ± 0.5°C of water. They were exposed to a training session for 15 min without any observations 24 h before the experimental session. In the experimental session, they were forced to swim for 5 min and the time of immobility, the time of struggle and the number of divings was recorded. An immobile posture was accepted as the position that rats use to float in the water motionless with only small movements and their heads just above the surface of the water.
Elevated Plus Maze

The test was performed as described by Pellow et al. [16]. The rats were put in the center of the elevated construction, 50 cm above the floor, and which has 2 open (50 cm × 10 cm) and 2 closed (50 cm × 10 cm × 50 cm) arms with an area (10 cm × 10 cm) binding these 4 arms. The times spent in open and closed arms were recorded in seconds for 5 min.

Statistical Analysis

The results of all the experiments are expressed as mean ± SEM. The results were analyzed with a One Way ANOVA for normally distributed data and with a Kruskal-Wallis test for abnormally distributed data, by using Sigma Stat 3.5 and SPSS 21 statistical programs. The normality tests were performed with a Kolmogrov-Smirnov and a Shapiro-Wilk test. The equality of variance was analyzed with a homogeneity test. A value of p < 0.05 was accepted as statistically significant.

Results

Results of the Forced Swimming Test

Repeated doses of sertraline (10 mg/kg, i.p. for 7 days) significantly decreased the immobility time compared to the control (Fig. 1). A similar observation was achieved when sertraline (10 mg/kg, i.p. for 7 days) was given in combination with a single dose of nimodipine (0.5 mg/kg, i.p.). This combination also significantly reduced the immobility time compared to the control (Fig. 1) and slightly decreased the immobility time compared to repeated sertraline administration alone, but this was not statistically significant. On the other hand, when both sertraline (10 mg/kg, i.p. for 7 days) and nimodipine (0.5 mg/kg, i.p. for 7 days) were administered repeatedly in combination, a significant increase in the immobility time (Fig. 1) was observed compared to the repeated doses of sertraline (10 mg/kg, i.p. for 7 days) alone and to the combination of repeated doses of sertraline (10 mg/kg, i.p. for 7 days) with a single dose of nimodipine (0.5 mg/kg, i.p.). A single dose of nimodipine (0.5 mg/kg, i.p.) significantly increased the immobility time compared to the repeated doses of sertraline (10 mg/kg, i.p. for 7 days) alone and to the combination of repeated doses of sertraline (10 mg/kg, i.p. for 7 days) with a single dose of nimodipine (0.5 mg/kg, i.p.), however repeated doses of nimodipine (0.5 mg/kg, i.p. for 7 days) made no significant alteration in the immobility time (Fig. 1). There were no significant differences between groups in terms of struggle time (Fig. 2). The number of davings was significantly less in single doses of nimodipine (0.5 mg/kg, i.p.) compared to the control group (Fig. 3).
Results of the Elevated Plus Maze Test

There were no significant differences between the experimental groups in the time spent in closed arms of the elevated plus maze (Fig. 4).

Discussion

In this study, we investigated the interaction between the effects of sertraline and nimodipine on depressive and anxiogenic behaviors in the forced swimming and elevated plus maze tests in rats. The results of the forced swimming test showed that repeated sertraline administration decreased the immobility time, so that our results confirmed the antidepressant effect of sertraline. Similarly, the combination of repeated doses of sertraline and a single dose of nimodipine also decreased the immobility time, but the decrease in the combination group was not significantly more than the decrease observed with repeated doses of sertraline administration alone. Therefore, this finding demonstrates that an interaction does not occur between repeated doses of sertraline and a single dose of nimodipine administration. In contrast, the combination of repeated doses of sertraline and repeated doses of nimodipine administrations increased the immobility time to an insignificant extent compared to the control but to a significant extent compared to repeated doses of sertraline administration alone and to the combination of repeated doses of sertraline and a single dose of nimodipine administration. This result indicates an inhibitory effect on the antidepressant effect of sertraline by repeated doses of nimodipine administration. The inhibition revealed by repeated doses of nimodipine administration may be the consequence of the reported role of L-type calcium channels on the release of neurotransmitters [18] and the complex effects of CCAs on serotonin functions in rodents [19]. In this study, we also observed that there was no significant difference between groups in the time spent in closed arms in the elevated plus maze test. This reflects that there is no antianxiety-like effect with repeated doses of sertraline alone, with single or repeated administrations of nimodipine alone and with combinations of repeated sertraline with single or repeated nimodipine administrations.

Several studies have researched the effects of CCAs in combination with antidepressant drugs. The acute effects of the CCAs nimodipine (5 mg/kg, p.o.), nifedipine (5 mg/kg, p.o.), and nitrendipine (5 mg/kg, p.o.) were investigated in the mice forced swimming test given alone or in combination with acute administration of the antidepressants imipramine, citalopram, mianserin, and amitriptyline [20]. In that study, Czyrak et al. found that nimodipine had no effect on immobility. However, when nimodipine was combined with the antidepressants above, a decrease in the immobility time was observed. In contrast, nifedipine
and nitrendipine reduced the immobility time and the reduction in the immobility time was greater in joint administration of nifedipine and nitrendi- 
pine with imipramine, citalopram, and mianserin. Similarly, Srivastava et al. studied the acute effects of the CCA verapamil, diltiazem and nifedipine in a behavior despair test in mice both alone and in combination with acute administration of the antidepressant drugs desipramine, clomipramine, mianserin, and tranylcypromine. They found that the non-dihydropyridine CCAs, verapamil, mianserin, and tranylcypromine inhibited the effects of the antidepressants above. Aburawi et al. also investigated the use of nifedipine and verapamil in combination with acute administration of the drugs alprazolam and imipramine in the mice forced swimming test. In that study, both nifedipine (5 mg/kg) and verapamil (10 mg/kg) showed antidepressant effects and potentiated the antidepressant effect of imipramine and alpro- zolam. The results of the three studies mentioned above are in accordance with our findings that the combination of repeated sertraline and single nimodipine administration decreased the immobility time. However, we did not find an antidepressant-like effect with single or repeated nimodipine administrations. This is similar to the findings of Czyrak et al., as they found that nimodipine had no effect on immobility, but different from the data of the studies of Srivastava et al. and Aburawi et al. in which they observed an antidepressant-like effect with nifedipine. In our study, we assessed the depression-like state in the forced swimming test, which is a common method shared by those three studies. But still there is a difference in dose regimen and the class of the antidepressants that those researchers used acute administrations of, while we repeatedly administrated sertraline. We used an SSRI (sertraline) as an antidepressant drug, which is only similar to the study of Czyrak et al., in which they used citalopram which is also an SSRI. The dose of nimodipine and the experimental animals are different in our study, in which we used nimodipine at a dose of 0.5 mg/kg and we performed experiments in rats while those three studies used mice as the experimental animal. Furthermore, Srivastava et al. and Aburawi et al. did not use nimodipine in their study, instead they used nifedipine as an L-type dihydropyridine derivate CCA. Although both nifedipine and nimodipine are dihydropyridine derivate L-type CCAs, they may have different effects on neurotransmitter functions.

In various studies, CCAs were assessed according to their behavioral effects. In one of them, Czyrak et al. studied the effect of both single and repeated administration of the CCAs nifedipine, nimodipine, and diltiazem (5 mg/kg, i.p.) in the forced swimming test in rats, and they observed a decrease in the immobility time only with repeated administrations of all three drugs. Their data is inconsistent with our findings. In our study, we found that neither a single dose of nimodipine nor repeated doses of nimodipine administration decreased the immobility time. However, there is a methodological difference, that they used nifedipine and nimodipine at a dose of 10 mg/kg p.o. while we utilized nimodipine at a dose of 0.5 mg/kg i.p. The effect of the L-type calcium channel antagonist (CCA) nifedipine on depression was studied in the forced swimming test by Tazi et al. and it was observed that nifedipine (5 mg/kg) reduced the immobility time. In another study, Biala studied the effects of nifedipine (10 mg/kg) and verapamil (10 and 20 mg/kg) in the forced swimming test in mice and found that nifedipine decreased the immobility time while verapamil had no effect on the immobility time. Cohen et al. showed that acute nifedipine administration reduced the immobility time in the mouse forced swimming (30 mg/kg) and tail suspension test (10 and 30 mg/kg) while the other dihydropyridine drugs, nicardipine (30 and 60 mg/kg), nitrendipine (10 and 30 mg/kg), isradipine (3 mg/kg), felodipine (30 mg/kg) and nimodipine (60 mg/kg), also exerted antidepressant-like features, but only in the tail suspension test. However, the phenylalkylamine derivate verapamil, the benzothiazepine derivate diltiazem and the non-selective drug flunarizine had no effect in both the tail suspension test and the forced swimming test. These results are inconsistent with the findings of our study that neither a single dose nor repeated doses of nimodipine administration (0.5 mg/kg, i.p.) decreased the immobility time. The difference between the doses and type of the experimental animal and model may contribute to these inconsistencies.

In the present study, the results of the elevated plus maze test demonstrated that there was no significant difference between experimental groups in terms of the time spent in closed arms. Repeated doses of sertraline administration showed no effect on anxiety-like behavior both alone and in combination with single and repeated doses of nimodipine administrations. Bagdy et al. reported that acute sertraline administration showed an anxiety-like behavior in the elevated plus maze in rats. In addition, it has been observed that SSRIs present
an anxiolytic-like effect with chronic administration [27]. In our study, sertraline was administered for 7 days. This may be accepted as a subchronical administration and may be an explanation for our finding that sertraline had no effect on anxiety behavior. A number of researchers have examined the effects of CCAs in anxiety models. Tazi et al. found that nifedipine (2.5 and 5.0 mg/kg) administration showed an anxiolytic effect in the water consumption test [23]. In another animal model of anxiety, Matsumoto et al. used a Vogel-type conflict test to investigate the acute effects of the CCAs flunarizine, nicardipine and verapamil and the chronic effect of diltiazem in rats. They found that flunarizine (10 and 20 mg/kg), nicardipine (20 mg/kg), verapamil (20 mg/kg) and diltiazem (20 mg/kg/8 days) showed anti-anxiety effects [28]. These findings are different from the results of our study, that neither single nor repeated doses of nimodipine administration had a significant effect on the elevated plus maze test. On the other hand, this difference may be the consequence of the differences in the type of the CCA (nifedipine, nicardipine vs nimodipine) and experimental model (water consumption and Vogel-type conflict test vs elevated plus maze). Shinnick-Gallagher et al. studied the effects of nimodipine (1.5, 2.5, 10 and 20 mg/kg) in a fear conditioning model in rats and they found that it dose-dependently inhibited fear conditioning responses. According to this finding, the researchers suggested that nimodipine might be effective in the treatment of anxiety [12]. In that study, nimodipine was acutely administered and used at doses of 1.5, 2.5, 10 and 20 mg/kg. In our study, we found that neither single nor repeatedly administered nimodipine reflected an anxiolytic-like effect. However, there is diversity in terms of the doses and the experimental model (fear conditioning vs. elevated plus maze). In another study, both acute and chronic administrations of the CCAs nimodipine, flunarizine, verapamil and diltiazem were assessed for their effects on nicotine-related anxiogenic responses in an elevated plus maze in mice [11]. The researchers found that all of the CCAs they used dose-dependently alleviated the anxiogenic effects of nicotine. The drugs they used belonged to different classes of Ca²⁺ channel antagonists. They also used nimodipine, however with a different dose regimen (5 and 10 mg/kg, i.p.) from that of our study. The elevated plus maze was a common feature of their and our study. In a similar study, Viveros et al. investigated both single and repeated administrations of nimodipine (2.5 and 5 mg/kg, i.p.) and nifedipine (2.5 and 5 mg/kg, i.p.) in the plus-maze in rats [29]. They found that both single and repeated administrations of nifedipine and nimodipine showed an anxiety-like behavior. This is partially well-matched with our results, that we did not observe an antianxiety-like effect with single or repeated nimodipine administrations in the time spent in closed arms, although there is a difference in dose regimen.

In our study, we used nimodipine at a dose of 0.5 mg/kg. This dose is relatively lower than the doses used in the studies that we discussed above. In the present study, one of our aims was to explore the involvement of L-type calcium channels in the effects of sertraline so that we used a relatively low dose of nimodipine. Urani et al. studied the role of the modulators of intracellular Ca²⁺ mobilization in the antidepressant-like effects of imgesine. In the same way, they used the modulators at ineffective doses alone [30].

In conclusion, we suggest that there is an interaction between sertraline and nimodipine, reflecting a reversal in the antidepressant effect of sertraline by nimodipine, and L-type calcium channels are involved in the antidepressant effects of sertraline. This kind of interaction seems to appear with repeated doses of nimodipine administration but not with a single dose of nimodipine administration. We also propose that there is no interaction between the effects of sertraline and nimodipine on anxiety behavior and neither single nor repeated doses of nimodipine administration have an effect on anxiety behavior. As a result, this study contributes to the data on the role of L-type calcium channels in the antidepressant effects of sertraline.

**References**


Sertraline and Nimodipine Interaction on Behavior

Address for correspondence:

Bilgin Kaygisiz
Medical Faculty, Department of Pharmacology
Eskisehir Osmangazi University
Meselik Kampusu
26480 Eskisehir
Turkey

Conflict of interest: None declared

Received: 23.08.2012
Revised: 22.11.2013
Accepted: 7.04.2014