ORIGINAL PAPERS

Adv Clin Exp Med 2014, **23**, 2, 169–175
ISSN 1899–5276

Bilgin Kaygisiz[B, D], Fikriye Yasemin Ozatik[B], Kevser Erol[A, C, E, F]

Interaction of Sertraline and Nimodipine on Some Behavioural Tests in Rats

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

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

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 anxitey behavior (**Adv Clin Exp Med 2014, 23, 2, 169–175**).

Key words: sertraline, nimodipine, forced swimming test, elevated plus maze test.

Calcium (Ca^{+2}) plays a crucial physiological role in the functions of excitable and non-excitable cells. Moreover, it has been reported that Ca^{+2} dependent mechanisms are involved in neurotransmitter release and Ca^{+2} influx into the presynaptic terminal of the nerve via voltage-activated Ca^{+2} channels (VACC) is essential for neurotransmitter release [1, 2]. VACC are categorized as low-voltage activated (T-type) and high-voltage activated (L, N, P/Q and R-types) channels [3]. Although neurotransmitter release is fundamentally controlled by the P/Q type channels at neuromuscular junctions (NMJs) and many synapses, the process can include the other channels. It has been reported that L-type Ca^{+2} channels are also present in NMJs and contribute to neurotransmitter release [4]. There is growing data on the involvement of intracellular Ca^{+2} in the pathophysiology of mood disorders. It has been observed that blockage of intracellular Ca^{+2} release presents an antidepressant-like effect in the forced swimming test [5] and CaV1.3 L-type Ca^{2+} channels-deficient mice (CaV1.3–/–) exhibited antidepressant-like effects in the forced swimming and tail suspension tests, and an anxiolytic-like effect in the elevated plus maze [6]. Accordingly, it has been suggested that Ca^{+2} channel antagonists (CCAs) have behavioral effects and show anxiolytic-like features [7]. The behavioral effects of CCAs may be related to their influence on central nervous system functions via affecting the release of neurotransmitters including norepinephrine, serotonin and dopamine [8]. CCAs also

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 serotoninergic 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 ($21 \pm 2^{o}C$; 12 hr light/dark cycle, free access to standard food and tap water).

Drugs

Sertraline HCl (Sanovel) and nimodipine (Bayer) 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 7^{th} 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 15cm and $25.0 \pm 0.5^{o}C$ 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 homogenity 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 divings was significantly less in single doses of nimodipine (0.5 mg/kg, i.p.) compared to the control group (Fig. 3).

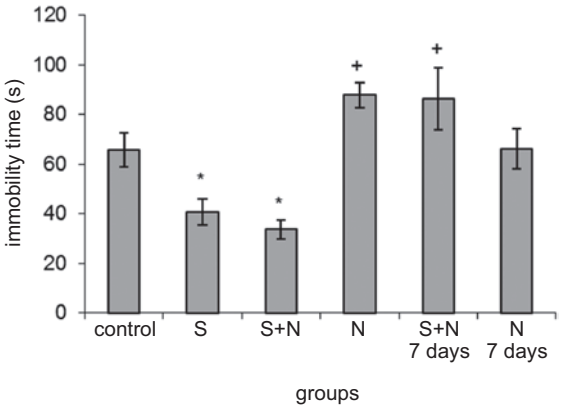

Fig. 1. Effects of sertraline and nimodipine on immobility time in the forced swimming test in rats

İmmobility time was recorded in seconds for 5 min. Values are given as mean ± SEM**.** (* = $p < 0.05$ vs. control; + = $p < 0.05$ vs. S + N). The abbreviations represent: S = sertraline 10 mg/kg for 7 days; S + N = sertraline 10 mg/kg for 7 days + single dose of nimodipine 0.5 mg/kg; N = single dose of nimodipine 0.5 mg/kg administration; S + N 7 days = combination of sertraline 10 mg/kg for 7 days + nimodipine 0.5 mg/kg for 7 days; N 7 days = nimodipine 0.5 mg/kg for 7 days.

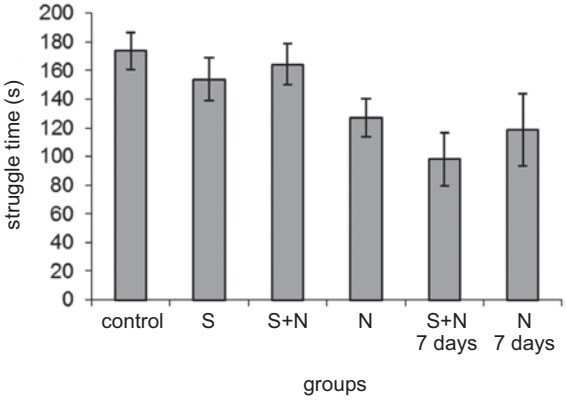

Fig. 2. Effects of sertraline and nimodipine on struggle time in the forced swimming test in rats

Struggling time was recorded in seconds for 5 min. Values are given as mean ± SEM. The abbreviations represent: S = sertraline 10 mg/kg for 7 days; S + N = sertraline 10 mg/kg for 7 days + single dose of nimodipine 0.5 mg/kg; N = single dose of nimodipine 0.5 mg/kg; S + N 7 days = combination of sertraline 10 mg/kg for 7 days + nimodipine 0.5 mg/kg for 7 days; N 7 days = nimodipine 0.5 mg/kg for 7 days.

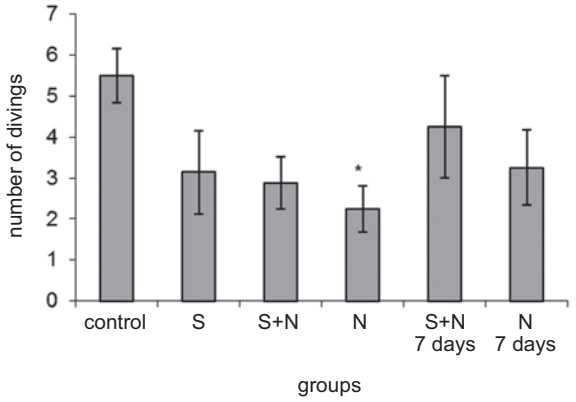

Fig. 3. Effects of sertraline and nimodipine on the number of divings in the forced swimming test in rats

Number of divings were observed for 5 min. Values are given as mean ± SEM. (* = $p < 0.05$ vs. control). The abbreviations represent: S = sertraline 10 mg/kg for 7 days; S + N = sertraline 10 mg/kg for 7 days + single dose of nimodipine 0.5 mg/kg; N = single dose of nimodipine 0.5 mg/kg; S + N 7 days = combination of sertraline 10 mg/kg for 7 days + nimodipine 0.5 mg/kg for 7 days; N 7 days = nimodipine 0.5 mg/kg for 7 days.

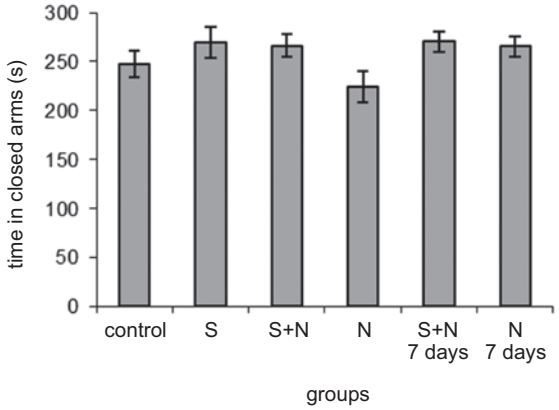

Fig. 4. Effects of sertraline and nimodipine on time spent in closed arms in the elevated plus maze test in rats

Time in closed arms was recorded in seconds for 5 min. Values are given as mean ± SEM. The abbreviations represent: S = sertraline 10 mg/kg for 7 days; S + N = sertraline 10 mg/kg for 7 days + single dose of nimodipine 0.5 mg/kg; N = single dose of nimodipine 0.5 mg/kg; S + N 7 days = combination of sertraline 10 mg/kg for 7 days + nimodipine 0.5 mg/kg for 7 days; N 7 days = nimodipine 0.5 mg/kg for 7 days.

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 sertaline 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 nitrendipine with imipramine, citalopram, and mianserin. Similarly, Srivastava et al. studied the acute effects of the CCAs verapamil, diltiazem and nifedipine in a behavioral despair test in mice both alone and in combination with acute administration of the antidepressant drugs desipramine, clomipramine, mianserin, and tranylcypromine [8]. They found that the non-dihydropyridine CCAs, verapamil (5, 10, 20, and 40 mg/kg, i.p.) and diltiazem (10, 20, and 40 mg/kg, i.p.) dose-dependently increased the immobility time, reflecting a depressive-like state while the dihydropyridine CCA nifedipine (12.5, 25, and 50 mg/kg, i.p.) decreased the immobility time indicating an antidepressant-like effect. They also observed that verapamil and diltiazem 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 alprozolam and imipramine in the mice forced swimming test [21]. In that study, both nifedipine (5 mg/kg) and verapamil (10 mg/kg) showed antidepressant effects and potentiated the antidepressant effect of imipramine and alprozolam. 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 antidepressive-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 [19].

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 (10 mg/kg, p.o.) in the forced swimming test in rats, and they observed a decrease in the immobility time only with repeated administrations of all three drugs [22]. This 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 [23]. 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 [24]. 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 [25]. 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 [26]. 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 classess of Ca^{+2} channel antagonists. They also used nimodipine, however with a different dose regimen (5 and 10mg/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 Ca^{+2} 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 anxitey 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

[1] **Li H, Foss SM, Dobryy YL, Park CK, Hires SA, Shaner NC, Tsien RY, Osborne LC, Voglmaier SM:** Concurrent imaging of synaptic vesicle recycling and calcium dynamics. Front Mol Neurosci 2011, 4, 34.

[2] **Giugovaz-Tropper B, González-Inchauspe C, Di Guilmi MN, Urbano FJ, Forsythe ID, Uchitel OD:** P/Q-type calcium channel ablation in a mice glycinergic synapse mediated by multiple types of Ca^{2+} channels alters transmitter release and short term plasticity. Neuroscience 2011, 192, 219–230.

[3] **Scott VE, Vortherms TA, Niforatos W, Swensen AM, Neelands T, Milicic IBanfor PN, King A, Zhong C, Simler G, Zhan C, Bratcher N, Boyce-Rustay JM, Zhu CZ, Bhatia P, Doherty G, Mack H, Stewart AO, Jarvis MF:** A-1048400 is a novel, orally active, state-dependent neuronal calcium channel blocker that produces dose-dependent antinociception without altering hemodynamic function in rats. Biochem Pharmacol 2012, 83, 406–418.

[4] **Urbano FJ, Rosato-Siri MD, Uchitel OD:** Calcium channels involved in neurotransmitter release at adult, neonatal and P/Q-type deficient neuromuscular junctions (Review). Mol Membr Biol 2002, 19, 293–300.

[5] **Galeotti N, Bartolini A, Ghelardini C:** Blockade of intracellular calcium release induces an antidepressant-like effect in the mouse forced swimming test. Neuropharmacology 2006, 50, 309–316.
[6] **Busquet P, Nguyen NK, Schmid E, Tanimoto N, Seeliger MW, Ben-Yosef T, Mizuno F, Akopian A, Striessnig J, Singewald N:** CaV1.3 L-type Ca2+ channels modulate depression-like behaviour in mice independent of deaf phenotype. Int J Neuropsychopharmacol 2010, 13, 499–513.
[7] **El Ganouni S, Tazi A, Hakkou F:** Potential serotonergic interactions with the anxiolytic-like effects of calcium channel antagonists. Pharmacol Biochem Behav 1998, 60, 365–369.
[8] **Srivastava SK, Nath C:** The differential effects of calcium channel blockers in the behavioural despair test in mice. Pharmacol Res 2000, 42, 293–297.
[9] **Nowak G, Paul IA, Popik P, Young A, Skolnick P:** Ca2+ antagonists effect an antidepressant-like adaptation of the NMDA receptor complex. Eur J Pharmacol 1993, 247, 101–102.
[10] **Gaggi R, Dall'olio R:** Actions of nimodipine on the serotonergic systems of rat brain. Gen Pharmac 1997, 29, 415–419.
[11] **Biala G, Budzynska B:** Effects of acute and chronic nicotine on elevated plus maze in mice: involvement of calcium channels. Life Sci 2006, 79, 81–88.
[12] **Shinnick-Gallagher P, McKernan MG, Xie J, Zinebi F:** L-type voltage-gated calcium channels are involved in the *in vivo* and *in vitro* expression of fear conditioning. Ann N Y Acad Sci 2003, 985, 135–149.
[13] **Nakazawa K, Inoue K, Ohara-Imaizumi M, Fujimori K, Takanaka A:** Inhibition of Ca-channels by diazepam compared with that by nicardipine in pheochromocytoma PC12 cells. Brain Res 1991, 553, 44–50.
[14] **Deák F, Lasztóczi B, Pacher P, Petheö GL, Valéria Kecskeméti, Spät A:** Inhibition of voltage-gated calcium channels by fluoxetine in rat hippocampal pyramidal cells. Neuropharmacology 2000, 39, 1029–1036.
[15] **Paul IA:** Antidepressant activity and calcium signaling cascades. Hum Psychopharmacol 2001, 16, 71–80.
[16] **Pellow S, Chopin P, File SE, Briley M:** Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods 1985, 14, 149–167.
[17] **Porsolt RD, Anton G, Blavet N, Jalfre M:** Behavioural despair in rats: a new model sensitive to antidepressant treatments. Eur J Pharmacol 1978, 47, 379–391.
[18] **Calin-Jageman I, Lee A:** Ca(v)1 L-type Ca^{2+} channel signaling complexes in neurons. J Neurochem 2008, 105, 573–583.
[19] **Green AR, DeSouza RJ, Davies EM, Cross AJ:** The effects of Ca2+ antagonists and hydralazine on central 5-hydroxytryptamine biochemistry and function in rats and mice. Br J Pharmacol 1990, 99, 41–46.
[20] **Czyrak A, Mogilnicka E, Maj J:** Dihydropyridine calcium channel antagonists as antidepressant drugs in mice and rats. Neuropharmacology 1989, 28, 229–233.
[21] **Aburawi S, Al-Tubuly R, Alghzewi E, Gorash Z:** Effects of calcium channel blockers on antidepressant action of Alprazolam and Imipramine. Libyan J Med 2007, 2, 169–175.
[22] **Czyrak A, Mogilnicka E, Siwanowicz J, Maj J:** Some behavioral effects of repeated administration of calcium channel antagonists. Pharmacol Biochem Behav 1990, 35, 557–560.
[23] **Tazi A, Farh M, Hakkou F:** Behavioral effects of a calcium channel antagonist: nifedipine. Fundam Clin Pharmacol 1991, 5, 229–236.
[24] **Biała G:** Antidepressant-like properties of some serotonin receptor ligands and calcium channel antagonists measured with the forced swimming test in mice. Pol J Pharmacol 1998, 50, 117–124.
[25] **Cohen C, Perrault G, Sanger DJ:** Assessment of the antidepressant-like effects of L-type voltage-dependent channel modulators. Behav Pharmacol 1997, 8, 629–638.
[26] **Bagdy G, Graf M, Anheuer ZE, Modos EA, Kantor S:** Anxiety-like effects induced by acute fluoxetine, sertraline or m-CPP treatment are reversed by pretreatment with the 5-HT2C receptor antagonist SB-242084 but not the 5-HT1A receptor antagonist WAY-100635. Int J Neuropsychopharmacol 2001, 4, 399–408.
[27] **To CT, Bagdy G:** Anxiogenic effect of central CCK administration is attenuated by chronic fluoxetine or ipsapirone treatment. Neuropharmacology 1999, 38, 279–282.
[28] **Matsumoto Y, Kataoka Y, Watanabe Y, Miyazaki A, Taniyama K:** Antianxiety actions of Ca^{++} channel antagonists with Vogel-type conflict test in rats. Eur J Pharmacol 1994, 264, 107–110.
[29] **Viveros MP, Martín S, Ormazabal MJ, Alfaro MJ, Martín MI:** Effects of nimodipine and nifedipine upon behavior and regional brain monoamines in the rat. Psychopharmacology (Berl) 1996, 127, 123–132.
[30] **Urani A, Romieu P, Portales-Casamar E, Roman FJ, Maurice T:** The antidepressant-like effect induced by the sigma(1) (sigma(1)) receptor agonist igmesine involves modulation of intracellular calcium mobilization. Psychopharmacology (Berl) 2002, 163, 26–35.

Address for correspondence:

Bilgin Kaygisiz
Medical Faculty, Department of Pharmacology
Eskisehir Osmangazi University
Meselik Kampusu
26480 Eskisehir
Turkey
E-mail: bilginkay@yahoo.com
Tel: +90 222 239 2979/45 63

Conflict of interest: None declared

Received: 23.08.2012
Revised: 22.11.2013
Accepted: 7.04.2014