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Modulation of the Antipsychotic Effect of Ziprasidone with Nimodipine

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ÖZET:

Ziprasidon'un antipsikotik etkisinin nimodipin ile düzenlenmesi

Amaç: Bu çalışmanın amacı bir atipik antipsikotik ilaç olan ziprasidon'un kronik olarak verilmesinin farelerde oluşturulan deneysel psikoz modellerindeki etkilerinin araştırılması ve bu etkilerde bir dihidropiridin türevi kalsiyum kanal blokörü olan nimodipin'in rolünün incelenmesidir.

Yöntem: Deneysel psikoz modelleri farelerde amfetamin ile indüklenmiş lokomotor aktivite, haloperidol ile indüklenmiş katalepsi ve apomorfin ile indüklenmiş tırmanma testleri kullanılarak oluşturulmuştur. Çalışmamızda, ziprasidon'un 1mg/kg ve 10mg/kg dozları farelere 10 gün boyunca kronik enjeksiyon şeklinde günde bir kere periton içinden verilmiştir. Nimodipin ise tek enjeksiyon şeklinde 0.5mg/kg dozunda ve deney gününde periton içinden uygulanmıştır. Ayrıca nimodipin, ziprasidon'un 10mg/kg dozu ile de kombine edilerek verilmiştir. Kontrol grubundaki farelere de 10 gün boyunca periton içinden serum fizyolojik enjekte edilmiştir. Lokomotor aktivite testi bulguları istatistiksel olarak tek yönlü varyans analizi kullanılarak değerlendirilmiştir ve grupların karşılaştırmasında Tukey çoklu karşılaştırma testi kullanılmıştır. Tırmanma testi ve katalepsi testi bulguları istatistiksel olarak tek yönlü varyans analizi ile değerlendirilmiştir.

Bulgular: Ziprasidon'un 10mg/kg dozunda amfetamin ile indüklenmiş lokomotor aktivitede amfetamin grubuna göre anlamlı bir azalma saptandığı halde ziprasidon'un 1mg/kg dozunda anlamlı bir farklılık saptanmamıştır. Haloperidol ile indüklenmiş katalepsi sürelerinde ziprasidon'un 1mg/kg dozu ile anlamlı bir azalma gözlenirken, 10mg/kg dozunda ise anlamlı bir değişiklik gözlenmemiştir. Ziprasidon'un her iki dozunda da tırmanma sürelerinde diğer gruplara göre anlamlı bir azalma saptanmıştır. Nimodipin amfetamin ile indüklenmiş lokomotor aktivitede, haloperidol ile indüklenmiş katalepsi sürelerinde ve apomorfin ile indüklenmiş tırmanma sürelerinde kontrol grubuna göre anlamlı bir değişiklik yapmamıştır. Ancak nimodipin, ziprasidon'un 10mg/kg dozuyla kombine edildiğinde, lokomotor aktivite ve tırmanma sürelerinde ziprasidon 10 mg/kg dozuna göre anlamlı bir artış saptanmış ancak katalepsi sürelerinde ise anlamlı bir değişiklik yapmamıştır.

Sonuçlar: Nimodipin ziprasidon ile kombine edildiğinde, ziprasidon'un lokomotor aktivite ve tırmanma sürelerindeki azaltıcı yönde olan etkisini tersine çevirmiş ancak ziprasidon'un katalepsi süreleri üzerindeki etkisinde bir değişiklik yapmamıştır. Bu sonuçlara göre ziprasidon'un antidopaminerjik etkisinde, dolayısıyla da antipsikotik etkisinde kalsiyum kanallarının rolünün olabileceğini ancak kataleptojenik etkisinde kalsiyum aracılı mekanizmaların rolünün olmadığını ileri sürmekteyiz.

Anahtar sözcükler: Ziprasidon, nimodipin, kalsiyum kanalları, deneysel hayvan modelleri

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ABSTRACT:

Modulation of the antipsychotic effect of ziprasidone with nimodipine

Objective: The aim of this study was to examine the effects of chronic administration of ziprasidone, an atypical antipsychotic drug, on experimental models of psychosis and the role of nimodipine, a dihydropyridine calcium channel blocker, on these effects in mice.

Methods: Experimental models of psychosis were studied in mice. Amphetamine-induced hyperlocomotion, haloperidol-induced catalepsy, and apomorphine-induced climbing tests were used as experimental models of psychosis. One and 10mg/kg doses of ziprasidone were given to mice i.p. for 10 days. Nimodipine was given as a single injection at a dose of 0.5mg/kg i.p. on the day of the experiment. Nimodipine 0.5mg/kg was also combined with the 10mg/kg dose of ziprasidone. Mice in control groups were also given saline i.p. for 10 days. A one-way ANOVA test was used as the statistical method to assess the results of the locomotor activity test and the Tukey multiple comparison test was used to compare groups. Outcomes of the climbing and catalepsy tests were analysed using the one-way ANOVA.

Results: Ten mg/kg but not 1mg/kg ziprasidone significantly decreased amphetamine-induced hyperlocomotion compared to the amphetamine group. One mg/kg but not 10mg/kg ziprasidone significantly alleviated catalepsy time compared to the haloperidol group. Both doses of ziprasidone significantly reduced climbing time compared to all other groups. Nimodipine had no significant effect on amphetamine-induced hyperlocomotion, climbing and catalepsy time compared to controls, however when combined with ziprasidone, a significant increases in locomotor activity and climbing time, but no significant difference in catalepsy time were observed compared to 10mg/kg ziprasidone.

Conclusion: Nimodipine when combined with ziprasidone, reversed the effect of ziprasidone on locomotor activity and climbing time but didn't change its effect on catalepsy time. We suggest that calcium channels might mediate antidopaminergic pathways and thereby the antipsychotic effect of ziprasidone, but that there is no involvement of calcium-dependent mechanisms in the cataleptogenic effect of ziprasidone.

Key words: Ziprasidone, nimodipine, calcium channels, experimental animal models

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INTRODUCTION

Intracellular calcium evokes many processes as well as secretion of neurotransmitters (1) and has been suggested to play a role in the regulation of dopaminergic and cholinergic activity (2); thus, voltage-gated calcium channels have a key role in controlling these processes. This feature makes voltage-gated calcium channels new targets to control dopaminergic mechanisms (1). It is suggested that an increase in mesolimbic dopaminergic transmission is involved in the etiopathogenesis of schizophrenia (3).

Calcium channels are classified into T-, N-, L-, P/Q- and R-types in terms of their different electrophysiological and pharmacological properties. T-type channels are low voltage- activated whereas N-, L-, P/Q- and R-types are high voltage-activated (4). It has also been reported that L-type channels have strong effects on neuronal cell bodies. Calcium channel inhibitors (CCIs) can be categorized as: dihydropyridines, e.g. nifedipine, nimodipine, nicardipine; phenylalkylamines, e.g. verapamil; or benzothiozepines, e.g. diltiazem (5).

Interestingly, it has been suggested that many of the antipsychotics have calcium channel blocking activity and that the diphenylbutylpiperidine class of neuroleptics have a similar structure to the verapamil-type CCIs and bind to the verapamil recognition site, which is associated with voltage-dependent calcium channels of the L-type in neuronal tissue (6,7).

On the other hand, it has been suggested that CCIs have potential antipsychotic effects. It is thought that the antipsychotic activity of neuroleptics is partly associated with their antidopaminergic effects (8). Accordingly, CCIs have beenexamined for their antidopaminergic activity in clinical studies and in animals. In clinical studies, some of the CCIs have been found to be effective in improving psychotic symptoms while some of the CCIs were found to have antidopaminergic effects in experimental animal studies (9-13); however, the idea that CCIs display antidopaminergic activity is not totally accepted because of some conflicts in the literature (8).

The issue of benefits from synergistic activity of dopamine and calcium in the treatment of psychosis has been examined and it has been reported that L-type calcium channel blockade and antagonism of D2 receptors had useful effects in the treatment of chronic schizophrenia and negative schizophrenic symptoms (14).

In this study, we assessed the effects of ziprasidone, an atypical antipsychotic drug combined with nimodipine, a calcium channel blocker, on experimental psychosis models. Ziprasidone has a low affinity for dopamine (D2) receptors, a much higher affinity for serotonin (5HT2) receptors, and a higher 5HT2A/D2 receptor affinity than other antipsychotics. It also acts on adrenergic (α-1) and histaminergic (H1) receptors with a low affinity and inhibits noradrenaline and serotonin re-uptake (15). Nimodipine is an L-type dihydropyridine calcium channel blocker with an ability to cross the blood-brain barrier (16).

The aim of this study is to explore the modulatory effects of nimodipine on the antipsychotic effect of ziprasidone.

METHODS

Animals

Male, adult Swiss albino mice (weighing 20-30g) were used for the study and sheltered in standard laboratory conditions of light (12 hours light/dark cycle) and temperature (21±1 °C) with free access to standard food and tap water. All the experiments were carried out with the permission of the Local Ethics Committee for Experimentation of Eskisehir Osmangazi University (18.02.2009/97-1) in line with Declaration of Helsinki.

Drugs

Ziprasidone (Pfizer), haloperidol (Aris), amphetamine (Sigma), apomorphine (Gen) and nimodipine (Bayer) were dissolved in saline.

Experimental Design

108 mice were included in the study, however 100 of them completed the experiments. Groups and the number of animals used in the experiments are as below:

Experimental Protocol

Ziprasidone was injected i.p. into mice chronically for 10 days and experimental psychosis models were carried out as described below on the 10th day 1 hour after the last injection of ziprasidone or vehicle. Ziprasidone was administered to the mice at doses of 1mg/kg or 10mg/kg.

Table 1: Groups and the number of animals used in the experiments are as below

Groups	Experiment	n
Group 1a: Control group: injected with saline for 10 days (sal.+sal.+sal.)	Amphetamine induced hyperlocomotion	5
Group 1b: Control group: injected with saline for 10 days (sal.+sal.+sal.)	Apomorphine induced climbing	6
Group 1c: Control group: injected with saline for 10 days (sal.+sal.+sal.)	Haloperidol induced catalepsy	5
Group 2a: injected with ziprasidone 1 mg/kg for 10 days (zip1mg/kg+sal.+amph.)	Amphetamine induced hyperlocomotion	6
Group 2b: injected with ziprasidone 1 mg/kg for 10 days (zip1mg/kg+sal.+apo.)	Apomorphine induced climbing	5
Group 2c: injected with ziprasidone 1 mg/kg for 10 days (zip1mg/kg+sal.+hal.)	Haloperidol induced catalepsy	6
Group 3a: injected with ziprasidone 10 mg/kg for 10 days (zip10mg/kg+sal.+amph.)	Amphetamine induced hyperlocomotion	6
Group 3b: injected with ziprasidone 10 mg/kg for 10 days (zip10mg/kg+sal.+apo.)	Apomorphine induced climbing	5
Group 3c: injected with ziprasidone 10 mg/kg for 10 days (zip10mg/kg+sal.+hal.)	Haloperidol induced catalepsy	5
Group 4a: Ziprasidone 10mg/kg+nimodipine combination: injected with ziprasidone 10 mg/kg for 10 days (zip10mg/kg+nim.0,5mg/kg+amph.)	Amphetamine induced hyperlocomotion	6
Group 4b: Ziprasidone 10mg/kg+nimodipine combination: injected with ziprasidone 10 mg/kg for 10 days (zip10mg/kg+nim.0,5mg/kg+apo.)	Apomorphine induced climbing	5
Group 4c: Ziprasidone 10mg/kg+nimodipine combination: injected with ziprasidone 10 mg/kg for 10 days (zip10mg/kg+nim.0,5mg/kg+hal.)	Haloperidol induced catalepsy	6
Group 5a: Nimodipine group: injected with saline for 10 days (sal.+nim.0,5mg/kg+amph.)	Amphetamine induced hyperlocomotion	6
Group 5b: Nimodipine group: injected with saline for 10 days (sal.+nim.0,5mg/kg+apo.)	Apomorphine induced climbing	5
Group 5c: Nimodipine group injected with saline for 10 days (sal.+nim.0,5mg/kg+hal.)	Haloperidol induced catalepsy	6
Group 6: Amphetamine group: injected with saline for 10 days (sal.+sal.+amph..)	Amphetamine induced hyperlocomotion	5
Group 7: Apomorphine group: injected with saline for 10 days (sal.+sal.+apo..)	Apomorphine induced climbing	6
Group 8: Haloperidol group: injected with saline for 10 days (sal.+sal.+hal.)	Haloperidol induced catalepsy	6

Sal.: saline, amph.: amphetamine, apo.: apomorphine, hal.: haloperidol, zip.: ziprasidone, nim.: nimodipine

Nimodipine was administered 15 minutes before the experimental procedure as a single injection at a dose of 0.5mg/kg. Mice in the control, amphetamine, apomorphine, haloperidol and nimodipine groups were also given saline i.p. for 10 days. Saline was also injected on the experimentation day instead of nimodipine, amphetamine, apomorphine, and haloperidol in other groups according to the standardized injection protocol.

Experimental Psychosis Model

This model consisted of 3 different tests:

1. Amphetamine-induced hyperlocomotion:

Amphetamine is an indirect dopamine agonist. Amphetamine-induced hyperlocomotion is considered to be a pharmacological model of schizophrenia and has a predictive validity for identification of antipsychotic agents. The amphetamine method has been predominantly used, compared to other models that explore probable antipsychotic activity of new substances in animals. This model has been also reported to increase dopaminergic activity in patients with schizophrenia which improves its value (17).

On the 10th day of chronic administration of ziprasidone, 3mg/kg of amphetamine was injected i.p. into the mice 1 hour after the last dose of ziprasidone or vehicle and the mice were put on the device (MAY AMS 02 animal activity monitoring system, COMMAT, Ankara), a square plexiglass box (40x40x40cm) that was set to record total movements automatically by a video-computerized system (18). Total movements were recorded for 5 min in every 30 minutes for a total 3 hour period.

2. Apomorphine-induced climbing test:

Apomorphine, a dopamine receptor agonist, evokes climbing behaviour. It is known that climbing behaviour is induced via stimulation of dopaminergic receptors in the striatum (19). Activation of both D1 and D2 receptors needed to evoke climbing behaviour; however, it has been suggested that new generation antipsychotics show their effects on climbing behaviour via D2 receptors (20).

On the 10th day of chronic administration of ziprasidone, 1.5mg/kg of apomorphine was injected s.c. into the mice 1 hour after the last dose of ziprasidone or vehicle and the mice were immediately placed in cylindrical wire mesh cages (height 13 cm, diameter 14 cm, mesh size 3 mm). The total climbing time on the inside of the cage was recorded for 30 min. (19).

3. Haloperidol-induced catalepsy test:

It has been noted that blockage of striatal dopamine receptors by haloperidol and haloperidol-like neuroleptics, evokes cataleptic behaviour in rodents. In addition, it has been demonstrated that the haloperidol-induced catalepsy test is a useful method to assess the effects of drugs on

central dopaminergic transmission and their extrapyramidal side-effects (21).

On the 10th day of chronic administration of ziprasidone, 1mg/kg haloperidol was injected i.p. into the mice 1 hour after the last dose of ziprasidone or vehicle and the mice were observed in atone, two and three hours after haloperidol injection for 5 min each hour. The mice were positioned with both front limbs on a 4cm high bar and the total time that the mice kept this position was recorded for a maximum period of 300 s. (19,22).

Data Analysis

Data of the amphetamine-induced hyperlocomotion test are presented as mean ± SD for the number of total movements recorded at each time point over 3 hours for each animal in each group. Statistical analyses were performed using SPSS version 15.0 statistical pack software 15.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was applied to examine normal distribution (χ^2=0,14, P=0,090). Numeric variables were compared using a One-Way ANOVA and the Tukey Multiple Comparison Test. P<0.05 was considered for statistical significance. A One-Way ANOVA was used for statistical analysis of results of the climbing test (total climbing time as seconds). The catalepsy test results (catalepsy time as seconds) were statistically analysed with a One-Way ANOVA.

RESULTS

Results of the Amphetamine-induced Hyperlocomotion Test

Total movements were recorded for the locomotor activity test for 5 minutes in every 30 minutes for a 3 hours period and data were reported as the number of total movements recorded at each time point over 3 hours for each animal in each group. The dose of 1mg/kg ziprasidone, a relatively low dose in this study, significantly enhanced amphetamine-induced hyperlocomotion compared to the controls (p<0.001), the 10mg/kg ziprasidone group (p<0.001), the 10mg/kg ziprasidone and nimodipine combined group (p=0.020) and the nimodipine group (p=0.014) but not compared to the amphetamine group (p=0.996). There was no significant difference between the 10mg/kg ziprasidone group and controls (p=0.165); however, the dose of 10mg/kg ziprasidone significantly reduced amphetamine-induced hyperlocomotion compared to amphetamine (p<0.001), the 1mg/kg ziprasidone group (p<0.001), the 10mg/kg ziprasidone and nimodipine combined group (p=0.001), and the nimodipine group (p=0.001). There was no significant difference in total movements between the nimodipine group and the control (p=0.403) or amphetamine groups (p=0.065). Nimodipine increased the number of total movements compared to the 10mg/kg ziprasidone group (p=0.001). However when the 10mg/kg dose of ziprasidone was given with nimodipine, this combination showed a reversal of the effects of the dose of 10mg/kg ziprasidone on total movements. Total movements in the combination group of ziprasidone 10mg/kg and nimodipine were enhanced compared to the 10mg/kg ziprasidone group (p=0.001). The results are shown in figure 1.

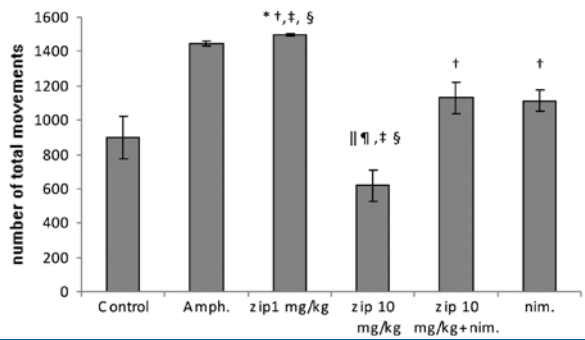

Figure 1: Effects of ziprasidone, nimodipine, and the combined use of ziprasidone and nimodipine on amphetamine-induced hyperlocomotion in mice.
*: compared to control , †: compared to 10mg/kg zip., ‡: compared to the 10mg/kg zip. and nim. combined group, §: compared to nim., ‖: compared to the amphetamine group, ¶: compared to 1mg/kg zip. Amph.: amphetamine, zip: ziprasidone; nim: nimodipine.

Results of the climbing test

The 1mg/kg dose of ziprasidone significantly reduced climbing time compared to the apomorphine (p=0.007), control (p=0.001) and combination of 10mg/kg ziprasidone and nimodipine groups (p=0.032). The 10mg/kg dose of ziprasidone also significantly reduced climbing time compared to the apomorphine (p=0.001), control (p=0.001), combination of 10mg/kg ziprasidone and nimodipine (p=0.003) and nimodipine alone groups (p=0.025). There was no significant difference between the nimodipine group and the apomorphine (p=0.660) and control groups (p=0.881) respectively. However when the 10mg/kg dose

of ziprasidone was combined with nimodipine, the climbing time was greater in the combination group than in the 10mg/kg ziprasidone group (p=0.003) indicating a reversal in the effects of 10mg/kg ziprasidone on climbing behaviour. The results are shown in figure 2.

Results of catalepsy test

There was a significant difference between groups in terms of the first hour catalepsy test results (p<0.001) but not in the second (p=0.704) and the third hour catalepsy tests (p=0.287). The 1mg/kg dose of ziprasidone significantly reduced catalepsy time compared to the haloperidol (p=0.001), ziprasidone 10mg/kg (p=0.009), ziprasidone 10mg/kg and nimodipine combination (p=0.005) and nimodipine alone groups (p=0.001). However 10mg/kg ziprasidone didn't significantly reduced catalepsy time compared to the haloperidol (p=0.994), control (p=0.757), ziprasidone 10mg/kg and nimodipine combination (p=1.000) and nimodipine alone groups (p=0.755). It was observed that nimodipine didn't change catalepsy time compared to the control (p=0.095) and haloperidol groups (p=0.953). There was also no change in the effects of the 10mg/kg dose of ziprasidone when it was combined with nimodipine (p=1.000). The results are shown in figure 3.

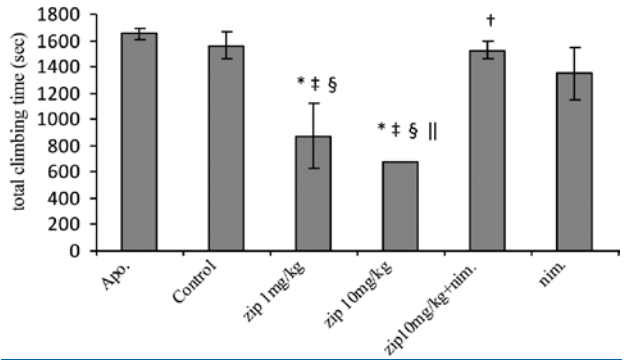

Figure 2: Effects of ziprasidone, nimodipine, and the combined use of ziprasidone and nimodipine on the climbing test in mice. *: compared to control , †: compared to 10mg/kg zip., ‡: compared to the 10mg/kg zip. and nim. combined group, §: compared to nim., ||: compared to the apo group. apo=apomorphine; zip: ziprasidone; nim: nimodipine.

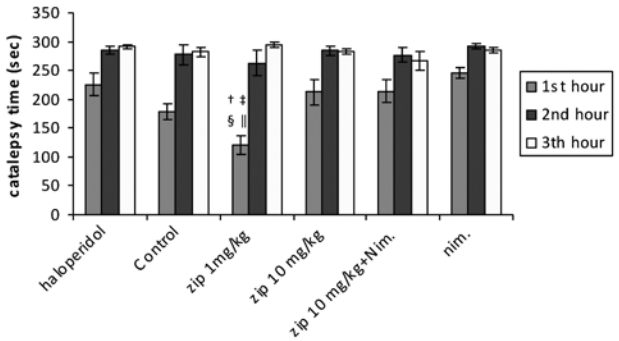

Figure 3: Effects of ziprasidone, nimodipine, and the combined use of ziprasidone and nimodipine on catalepsy test in mice. †: compared to 10mg/kg zip., ‡: compared to the 10mg/kg zip. and nim. combined group, §: compared to nim., ||: compared to the haloperidol group, zip: ziprasidone; nim: nimodipine.

DISCUSSION

In this study, we found that ziprasidone, at a relatively low dose (1mg/kg), enhanced amphetamine-induced hyperlocomotion and reduced catalepsy time while at a relatively high dose (10mg/kg) reduced amphetamine-induced hyperlocomotion but not catalepsy time and at both doses (1mg/kg and 10mg/kg) reduced climbing time. We also found that nimodipine alone made no change in amphetamine-induced hyperlocomotion, climbing time and catalepsy time. However, when nimodipine was combined with a dose of 10mg/kg ziprasidone, nimodipine reversed the effect of a dose of 10mg/kg ziprasidone on locomotor activity and climbing time but didn't alter the effect on catalepsy time.

It has been suggested that dihydropyridine calcium channel inhibitors could reach high levels in the central nervous system as they have the ability to cross the blood-brain barrier. It has also been suggested that these substances are closely associated with emotional processes. It has been shown that dihydropyridine calcium channel inhibitors play a role in release of neurotransmitters like acetylcholine, serotonin, dopamine and noradrenaline in the brain and that they activate serotonergic systems in rat brain (23,24). It has been reported that nimodipine activates serotonergic transmission via 5-HT1A receptor blockade and also that activation of 5-HT1A receptors inhibits the calcium current through calcium channels (23,25). Hence it is possible to suggest that there is an interaction between calcium channels and neurotransmitter systems. Ziprasidone acts as an antagonist at D2, 5-HT2A, 2C, 1D receptors and as an agonist at 5-HT1A receptors. These complex interactions in the central nervous system might suggest a role for nimodipine in modifying ziprasidone's effect on dopaminergic systems.

Calcium channel inhibitors (CCIs) have been assessed for their effects on amphetamine-induced hyperlocomotion. It has been found that nimodipine (10mg/kg sc) alone didn't

result in a decrease in amphetamine-induced hyperlocomotion (14). Although in that study nimodipine was used at a dose of 10mg/kg s.c. for 10 days in rats and we used nimodipine 0.5mg/kg i.p. in a single injection in mice, this result is consistent with our findings in which we found that nimodipine (0,5mg/kg ip) alone didn't result in any change in amphetamine-induced hyperlocomotion. In the same study it was also found that a nimodipine and haloperidol combination reduced amphetamine-induced hyperlocomotion. This result is not consistent with our results, in which we found that a nimodipine and ziprasidone combination reversed the effect of ziprasidone 10mg/kg on amphetamine-induced hyperlocomotion. This difference may be due to the distinct receptor binding profiles of haloperidol and ziprasidone, where haloperidol is a potent dopamine 2 receptor blocker while ziprasidone is not only a weak dopamine 2 receptor blocker but also blocks serotonin, histamine, and adrenergic receptors. However, the results of some other studies are not consistent with our results. In a study which assessed the effects of calcium channel blockers such as nifedipine, nimodipine, and diltiazem, it was observed that nimodipine and nifedipine reduced amphetamine-induced hyperlocomotion (26) while in our study, we observed no change in amphetamine-induced hyperlocomotion with nimodipine. However, in that study nimodipine was orally administered to rats for 4 days at a dose of 10mg/kg while we injected nimodipine to mice intraperitoneally at a single dose of 0.5mg/kg. The methodological differences may be the cause of the inconsistency between these studies. In another study assessing the effects of calcium channel blockers, nimodipine, verapamil and diltiazem, on nicotine, morphine, and MK-801 induced hyperlocomotion, it was found that nimodipine reduced MK-801 induced hyperlocomotion (27). These results are not in agreement with our findings; however, in that study, nimodipine was administered i.p. at a dose of 20mg/kg to mice and assessed on MK-801 induced hyperlocomotion while in our study we injected nimodipine i.p. at a dose of 0.5mg/kg to mice and observed its effects on amphetamine-induced hyperlocomotion. It has been reported that nimodipine decreased pargyline-induced hyperlocomotion (28). This study is not in accordance with our results; however, in that study, nimodipine was used s.c. at a dose of 50mg/kg to mice and locomotor activity was induced with pargyline while in our study, we injected nimodipine i.p. at a dose of 0.5mg/kg to mice and amphetamine-induced hyperlocomotion was used. It has been reported that flunarizine inhibited amphetamine-induced hyperlocomotion (17). This result is not in accordance with our results; however, in that study flunarizine was used as a calcium channel blocker which is a non-selective agent for T-type, N-type and L-type calcium channels while we used nimodipine which blocks L-type calcium channels selectively.

In a study, the researchers examined the effects of nimodipine, nifedipine, nitrendipine on apomorphine-induced hypothermia test and found that all of them reduced apomorphine-induced hypothermia (29). In our study, we observed that nimodipine had no effect on the results of the apomorphine-induced climbing test. However, in that study, nimodipine was used p.o. at doses of 5mg/kg and 20mg/kg and apomorphine-induced hypothermia was used as the experimental method while in our study, nimodipine was used i.p. at a dose of 0.5mg/kg and apomorphine-induced climbing test was used as the experimental method.

It has been reported that cholinergic, serotonergic, histaminergic, angiotensinergic, and glutamergic systems have effects on neuroleptic catalepsy by affecting dopaminergic transmission. In addition, a large volume of evidence has pointed out that neuronal voltage-sensitive calcium channels are involved in the modulation of dopaminergic transmission in both animals and humans (21). It has been found that nimodipine enhanced (5) and potentiated (21) haloperidol-induced catalepsy and this is thought to be related to the effects of dihydropyridine calcium channel blockers on dopamine neurotransmission (5). These results are not consistent with the results of our study in which we found that nimodipine had no effect on haloperidol-induced catalepsy. However, in those studies nimodipine was used at a dose of 20mg/kg i.p. given to rats (5) and at doses of 3mg/kg, 10mg/kg, 30mg/kg (21) while we gave nimodipine at a dose of 0.5mg/kg i.p. to mice.

CONCLUSIONS

Considering the results of the amphetamine-induced hyperlocomotion and apomorphine-induced climbing tests, we suggest that calcium channels might play a role in the production of antidopaminergic effects and thus the antipsychotic effects of ziprasidone might be eliminated by calcium channel blockers. No involvement of calcium-dependent mechanisms was found in the cataleptogenic effect

of ziprasidone. In the light of these results, nimodipine, an L-type dihydropyridine calcium channel blocker, decreased the antipsychotic effects of ziprasidone. However, in this study, we only used nimodipine as a calcium channel blocker, tested it with a single dose and combined it with one dose of ziprasidone. These are limitations of our findings which may be the subject of further studies.

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