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Some Behavioral Effects of Repeated Administration of Calcium Channel Antagonists

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CZYRAK, A., E. MOGILNICKA, J. SIWANOWICZ AND J. MAJ. *Some behavioral effects of repeated administration of calcium channel antagonists.* PHARMACOL BIOCHEM BEHAV **35**(3) 557–560, 1990.—The effect of the calcium channel antagonists nifedipine, nimodipine, and diltiazem (10 mg/kg PO) was studied after single and repeated administration to rats. All the compounds administered repeatedly reduced significantly the duration of immobility in the forced swimming test. At the same time the locomotor activity of rats was reduced (nifedipine, nimodipine) or unchanged (diltiazem). All the calcium channel antagonists studied did not modify the behavior of normal or phenylephrine-stimulated rats in the open field test. Only nimodipine, given repeatedly, was able to antagonize the clonidine-induced behavioral inhibition in the latter test. The results indicate that, like antidepressants, calcium channel antagonists given repeatedly to rats reduce the immobility time in the forced swimming test, but do not change the responsiveness of α_1- and α_2-adrenoceptors to their agonists.

Calcium channel antagonists Repeated treatment Forced swimming test Exploration Rats

OUR earlier experiments demonstrated that calcium channel antagonists of the dihydropyridine (DHP) type show an action similar to that of antidepressant drugs (ADs) in the forced swimming test (FST) in mice, i.e., they shorten the immobility time (17). Conversely, the calcium channel agonist BAY K 8644 lengthens the immobility time, this effect being blocked by nifedipine (18). Calcium channel antagonists also potentiate the activity of ADs in the FST (3,17). Furthermore, in some other tests used for evaluation of the antidepressant action these compounds act like ADs (3). All these data permitted us to put forward a hypothesis that calcium channel antagonists may have an antidepressant action or may enhance such an action when they are administered jointly with ADs.

The present paper was aimed at determining whether the antidepressant activity of calcium channel antagonists in the FST is also observed in rats, which—as has been recently reviewed by Borsini and Meli (1)—appear to be more suitable than mice for detection of antidepressant activity. Calcium channel antagonists were used in the latter test both in the single dose and repeatedly. The antidepressant activity in the FST may be due to the locomotor hyperactivity of rats; hence, we attempted to find out whether calcium channel antagonists induce locomotor hyperactivity.

When used repeatedly, ADs evoke adaptive changes in, e.g., α_1- and α_2-adrenoceptors, which manifest themselves by an increased responsiveness to α_1-adrenoceptor agonists (e.g., phenylephrine and methoxamine), as well as by a decreased responsiveness to α_2-adrenoceptor agonists (e.g., clonidine) (4–6, 12–14, 19, 20, 22, 26). Therefore, in the present paper, we tried to determine whether calcium channel antagonists administered repeatedly (twice a day for 4 days), i.e., under conditions of their antidepressant activity in the FST, modify the behavioral response to phenylephrine (PHE) and clonidine (CLO), both these effects being assessed in the open field test.

METHOD

The experiment was carried out on male Wistar rats weighing 180–200 g, kept under standard laboratory conditions, with free access to food and water. The experiment was always performed between 9 a.m. and noon.

Studies on the effect of the drugs on animal activity in the FST were conducted according to Porsolt *et al.* (24). Briefly, the rats were given 2 trials in which they were forced to swim in a cylinder from which escape was impossible. There was a 24-hr interval between the first and the second trial. The first trial lasted 15 min and the second one 5 min. The total duration of immobility was measured in the 5-min test of the second trial.

Separate groups of rats (n = 10 per group) were given the following drugs: nifedipine (NIF), nimodipine (NIM) and diltiazem (DIL) or vehicle (1% aqueous solution of Tween 80) per os, according to two different procedures. Under the acute schedule the rats were given the drug (10 mg/kg PO) once: 1 hr before the test, or twice: 19 and 1 hr before the test (the first dose was administered 4 hr after the first trial). Under the repeated schedule the rats were given the drug or vehicle twice daily for 4 consecutive days. On the 3rd day from the beginning of treatment, 2 hr after the last dose, the rats were subjected to the first trial. Afterwards, they were given 2 more doses of the drug 19 and 1 hr

before the test. The groups treated repeatedly were given 8 doses of the drug in all.

The locomotor activity of rats (single animals) was measured for 30 min in photoresistor actometers (two light beams, two photoresistors) 24 hr after the last dose of the calcium channel antagonist or vehicle. Calcium channel antagonists were given in a dose of 10 mg/kg PO twice daily for 4 days. Each group consisted of 8–9 rats.

The exploratory activity in rats was measured in the open field by a slightly modified method of Janssen *et al.* (10), using an open arena without walls. Its diameter was 100 cm, its height 50 cm. The only source of light in the room was a 70-W bulb, attached directly above the arena and illuminating its centre. Each group consisted of 8 rats. Individual control or drug-injected animals were placed gently in the centre of the arena and allowed to explore freely. Ambulation (the number of episodes of crossing the arena diameters), total time of walking, rearing (the number of times an animal stood on its hind legs) and peeping (the number of times an animal peeped down from the edge of the arena) were recorded for 3 min. Rearing and peeping reactions were pooled together, as they were thought to represent the same kind of exploratory behavior. Groups of rats were treated repeatedly with calcium channel antagonists, 10 mg/kg PO, twice daily for 4 days (8 times). Control groups of rats received the vehicle. The vehicle or the respective agonists phenylephrine (PHE), 25 μg/10 μl intracerebroventricularly (ICV) according to Herman (9), and clonidine (CLO), 0.2 mg/kg IP, were administered 24 hr after the last injection of vehicle or calcium channel antagonists, and 30 min before the beginning of the test.

Phenylephrine (hydrochloride) was dissolved in distilled water, clonidine (hydrochloride) was dissolved in saline. The statistical analysis of the differences between means was estimated by the analysis of variance (ANOVA), followed—if appropriate—by individual comparisons with the Dunnett's test.

RESULTS

None of the investigated calcium channel antagonists given in a single dose influenced the duration of immobility of rats in FST (Table 1). NIF and NIM, administered twice, reduced significantly—by about 30%—the duration of immobility; DIL showed tendency to reduce the duration of immobility, but its effect did not reach statistical significance (Table 1). When administered 8 times, all the three compounds reduced significantly—by about 50%—the time of immobility (Table 1).

NIF and NIM given repeatedly (8 times) significantly reduced the locomotor activity of rats measured in actometers; DIL was without effect on that behavior (Table 2). None of the investigated compounds influenced the exploratory behavior in the open field test (Table 3).

The effects of NIF and NIM and DIL, given repeatedly (8 times), on the exploratory behavior of PHE-treated rats in the open field test are shown in Table 4. PHE (25 μg/10 μl) markedly enhanced exploratory behavior of rats. Pretreatment with NIF, NIM and DIL did not change the action of PHE in the open field test.

The effects of NIF, NIM and DIL, given repeatedly (8 times), on the CLO-induced behavioral hypoactivity in the open field test are shown in Table 5. CLO (0.2 mg/kg IP) markedly reduced the exploratory behavior of rats, that effect having manifested itself by the reduction of the time of walking, ambulation and rearing + peeping. NIF administration significantly attenuated the CLO-induced reduction of the time of walking, but not of ambulatory activity and rearing + peeping. Pretreatment with NIM markedly diminished the CLO-induced reduction of the time of walking, ambulation and rearing + peeping. DIL did not influence the action of CLO.

TABLE 1

EFFECT OF CALCIUM CHANNEL ANTAGONISTS (10 mg/kg PO) ON THE TOTAL DURATION OF IMMOBILITY OF RATS IN FST

Treatment	Times of Administration	Duration of Immobility (sec) Mean ± SEM	%
Vehicle	1	170.0 ± 23.1	100
Nifedipine		194.0 ± 13.2	114
Nimodipine		181.1 ± 21.0	106
Diltiazem		174.0 ± 22.8	102
Vehicle	2	192.7 ± 8.6	100
Nifedipine		132.1 ± 11.0*	69
Nimodipine		135.3 ± 16.4*	70
Diltiazem		148.0 ± 18.5	77
Vehicle	8	192.4 ± 10.5	100
Nifedipine		86.2 ± 13.7†	45
Nimodipine		95.7 ± 16.0†	50
Diltiazem		85.9 ± 11.7†	45

Each group consisted of 10 rats.

Differences from control were assessed statistically using the Dunnett's test after ANOVA.

*$p<0.05$; †$p<0.001$.

DISCUSSION

Our previous data showed that calcium channel antagonists (of the DHP type) given in the single dose inhibited dose-dependently the duration of immobility in mice (17). It has been demonstrated in this paper that calcium channel antagonists inhibit the immobility also of rats in the FST, yet such effects are observed after 2 and 8 doses (repeated administration) of both the DHP antagonists. Inhibition of the immobility duration does not result from locomotor activity stimulating properties, since calcium channel antagonists given repeatedly either inhibit (NIF and NIM) the locomotor activity of rats or do not influence it (DIL). Thus, our results resemble those obtained for ADs: the immobility reducing effects of ADs are more pronounced when either 2 or more injections are made (11, 23, 24). Moreover, there is an analogy between the action of NIF and NIM in the FST and the action of

TABLE 2

EFFECT OF CALCIUM CHANNEL ANTAGONISTS (10 mg/kg PO) GIVEN REPEATEDLY (8 TIMES) ON THE LOCOMOTOR ACTIVITY OF RATS

Treatment	Number of Movements Mean ± SEM
Vehicle	227.4 ± 18.1
Nifedipine	122.6 ± 27.7*
Nimodipine	119.1 ± 26.1*
Diltiazem	205.1 ± 29.6

Each group consisted of 8–9 rats.

*$p<0.01$ vs. vehicle.

Differences from the vehicle were assessed statistically using the Dunnett's test after ANOVA.

TABLE 3

EFFECT OF CALCIUM CHANNEL ANTAGONISTS (10 mg/kg PO) GIVEN REPEATEDLY (8 TIMES) ON THE EXPLORATORY BEHAVIOR OF RATS (OPEN FIELD TEST)

Treatment	Mean ± SEM Time of Walking (sec)	Ambulatory Activity	Rearing and Peeping
Vehicle	75.0 ± 9.5	18.9 ± 2.6	15.3 ± 2.5
Nifedipine	61.5 ± 9.0	17.6 ± 3.5	13.9 ± 3.5
Nimodipine	63.0 ± 15.3	19.2 ± 5.5	12.5 ± 3.1
Diltiazem	72.1 ± 4.7	21.6 ± 2.6	14.7 ± 1.9

Each group consisted of 8 rats.

The statistical analysis of differences between the means estimated by ANOVA did not show any significance.

these drugs in another model used for evaluation of antidepressant activity of substances, i.e., in the learned helplessness test in rats (7,15).

In both these models the compounds used were effective when they were administered subchronically, and when rats were subjected to an aversive situation (a pretest forced swimming and an inescapable shock, which induced an escape response deficit). It cannot be excluded that those pretest sessions which are stressful to the animals, are necessary to make nervous system more sensitive to calcium channel antagonists. Under stress condition increased number of depolarizations occur, at least in the locus coeruleus region (27). On the other hand, depolarization of cell membrane greatly enhances the activity of calcium channel antagonists and often represents a prerequisite for their effectiveness.

Central DHP binding sites may play some role in the FST, since BAY K 8644, a DHP calcium channel agonist, enhances the immobility of mice, this effect being blocked by NIF (18). However, these sites do not seem to undergo adaptive changes after repeated treatment of rats with imipramine and NIF, as the K_D and B_{max} values of the cortical DHP-binding sites labelled with ^{3}H-nitrendipine are not modified (7). Although the distribution of binding sites for dihydropyridines in the brain of rats is not correlated with the distribution of any single known neurotransmitter, possible association of DHP binding sites with multiple neurotransmitters is not excluded (2). The DHP derivatives, both calcium channel agonists or antagonists, have been shown to

TABLE 4

EFFECT OF CALCIUM CHANNEL ANTAGONISTS (10 mg/kg PO) GIVEN REPEATEDLY (8 TIMES) ON THE EXPLORATORY BEHAVIOR (OPEN FIELD TEST) OF RATS TREATED WITH PHENYLEPHRINE (25 μg/10 μl, ICV)

Treatment	Mean ± SEM Time of Walking (sec)	Ambulatory Activity	Rearing and Peeping
Vehicle	74.5 ± 7.2	23.1 ± 2.5	17.8 ± 2.2
Phenylephrine (PHE)	124.5 ± 6.5‡	32.9 ± 2.3*	18.9 ± 1.9
Nifedipine + PHE	113.9 ± 4.9‡	31.4 ± 2.4	21.9 ± 1.5
Nimodipine + PHE	116.9 ± 5.9‡	30.3 ± 2.8	19.5 ± 2.2
Diltiazem + PHE	130.3 ± 5.1‡	33.7 ± 2.3†	13.6 ± 1.5

Each group consisted of 14 rats.

*$p<0.05$, †$p<0.01$, ‡$p<0.001$ vs. vehicle.

The results were statistically insignificant vs. the PHE group.

Differences from the vehicle were assessed statistically using the Dunnett's test after ANOVA.

TABLE 5

EFFECT OF CALCIUM CHANNEL ANTAGONISTS (10 mg/kg PO) GIVEN REPEATEDLY (8 TIMES) ON THE EXPLORATORY BEHAVIOR (OPEN FIELD TEST) OF RATS TREATED WITH CLONIDINE (0.2 mg/kg IP)

Treatment	Mean ± SEM Time of Walking (sec)	Ambulatory Activity	Rearing and Peeping
Vehicle	75.4 ± 6.4	19.2 ± 2.0	14.1 ± 2.4
Clonidine (CLO)	34.5 ± 2.7†	12.2 ± 0.9*	7.8 ± 0.8*
Nifedipine + CLO	52.6 ± 2.4†‡	12.7 ± 0.9*	7.6 ± 1.0*
Nimodipine + CLO	83.9 ± 6.9‡	17.6 ± 1.6‡	10.6 ± 0.9‡
Diltiazem + CLO	48.0 ± 6.9†	13.6 ± 2.4	6.7 ± 1.4*

Each group consisted of 8 rats.

*$p<0.05$; †$p<0.001$ vs. vehicle control.

‡$p<0.05$ at least vs. CLO control.

Differences from the vehicle (*,†) or CLO (‡) were assessed statistically using the Dunnett's test after ANOVA.

modulate the stimulated release from brain tissue of neurotransmitters involved in the central control of behavior, such as noradrenaline, serotonin (16), and dopamine (28). Moreover, the effects of dihydropyridines on the release of transmitters were correlated with changes in the voltage-dependent entry of calcium into synaptosomes. In addition, BAY K 8644 increases and nimodipine decreases the catecholamine synthesis; both compounds reduce the synthesis of 5-hydroxytryptophan in the mouse brain (21). Therefore, it is likely that the antidepressant-like effect of calcium channel antagonists in the FST is mediated by an effect on central DHP binding sites involved in neuromodulation.

Interestingly, DIL, a calcium channel antagonist of the benzothiazepine group, acted like NIF and NIM in the FST in rats. However, unlike the DHP type compounds, DIL did not influence the immobility of mice (17). It should be added that in the quoted study (17) only single administration of calcium channel antagonists was tested (and dihydropyridines were effective already in a single dose). Possibly DIL should be administered more than once in both animal species to show positive effects.

As has already been mentioned in the introduction, a number of antidepressants administered repeatedly evoke adaptive changes in α_1-adrenoceptors, which manifest themselves by increased responsiveness to PHE in the open field test (19). After 4 days of administration (twice daily) calcium channel antagonists show clear antidepressant activity in the FST. Therefore, we tried to determine whether calcium channel antagonists under conditions of their antidepressant activity in the FST modify the behavioral response to PHE. In the open field test none of the compounds changed the behavior of normal rats or the behavioral responses to PHE; this finding points to the lack of functional changes in the sensitivity of α_1-adrenoceptors to their agonists, at least after 4 days treatment. Hence, adaptive changes of α_1-adrenergic receptors cannot be the cause of the considerable effect of calcium channel antagonists in the FST. Our preliminary data from binding studies supports this conclusion. Specific binding of ^{3}H-prazosin to the rat cerebral cortical membranes is not changed (Vehicle: $K_D = 0.1 \pm 0.02$ nM, $B_{max} = 13.0 \pm 0.58$ pmol/g weight; NIF: $K_D = 0.1 \pm 0.02$ nM, $B_{max} = 13.1 \pm 0.12$ pmol/g weight) after repeated treatment with nifedipine (10 mg/kg PO, twice daily for 7 days). Therefore, there is a difference between calcium channel antagonists and antidepressant drugs in this respect.

NIM administered repeatedly (4 days) inhibited the action of CLO in the open field, which may indicate a diminished responsiveness of α_2-adrenoceptors to their agonist. However, since of

all the tested compounds only NIM inhibited the action of CLO (NIF reduced the inhibitory action of CLO on the time of walking only; DIL affected no parameter), it may be excluded that calcium channel antagonists are capable of inducing adaptive changes within α_2-adrenoceptors. The CLO-induced sedation is also slightly reduced by NIF, NIM and DIL given in the single dose (3). The latter effect may indicate a possible blockade of α_2-adrenoreceptors by the calcium channel antagonists used. Actually, these compounds seem to have α_2-adrenoceptor blocking properties, at least in the periphery (8).

It is noteworthy that NIM improves motor performance. Recently, Schuurman *et al.* (25) showed that repeated oral administration of NIM results in an improved motor coordination and walking of aged rats. CLO hinders motor performance, hence, the effect of NIM on CLO-induced hypoactivity in the open field may also point to its effect on motor function. This phenomenon requires further investigation.

It is not likely, either, that β-adrenoceptors are involved, since, as indicated by our preliminary data, NIF administered repeatedly (twice daily for 7 days) does not affect cortical β-adrenoceptors in rats, as measured by ^{3}H-dihydroalprenolol (^{3}H-DHA) binding (^{3}H-DHA specific binding; vehicle: $K_D = 0.4 \pm 0.04$ nM, $B_{max} = 5.3 \pm 0.3$ pmol/g weight; NIF: $K_D = 0.4 \pm 0.04$ nM, $B_{max} = 5.3 \pm 0.4$ pmol/g weight).

On the basis of our earlier findings which showed that DHP calcium channel antagonists were active in various pharmacological tests used to evaluate antidepressant drugs, a hypothesis has been put forward that these compounds may have antidepressant activity (3, 7, 17). The present data, which show that calcium channel antagonists administered repeatedly are active in the FST in rats, supports this hypothesis. However, the mechanism underlying the "antidepressant" action of calcium channel antagonists in the FST requires further investigation.

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