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The Ca^{2+} Channel Blockade Changes the Behavioral and Biochemical Effects of Immobilization Stress

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We investigated how the effects of chronic immobilization stress in rats are modified by Ca^{2+} channel blockade preceding restraint sessions. The application of nifedipine (5 mg/kg) shortly before each of seven daily 2 h restraint sessions prevented the development of sensitized response to amphetamine as well as the stress-induced elevation of the densities of L-type Ca^{2+} channels in the hippocampus and significantly reduced the elevation of the densities of [^{3}H]nitrendipine binding sites in the cortex and D_1 dopamine receptors in the limbic forebrain. Neither stress, nor nifedipine affected the density of α_1-adrenoceptors and D_1 receptors in the cerebral cortex nor D_2 dopamine receptors in the striatum. A single restraint session caused an elevation of blood corticosterone level that remained unaffected by nifedipine pretreatment, but the reduction of this response during the eighth session was significantly less expressed in nifedipine-treated rats. We conclude that L-type calcium channel blockade prevents development of several stress-induced adaptive responses.
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KEY WORDS: *Immobilization stress; Ca^{2+} channel; Dopamine receptors; Corticosterone; Amphetamine sensitization; Nifedipine*

Repeated stress has several consequences for the response of an organism to environmental stimuli and to psychotropic drugs. One of those effects is sensitization of animals to the action of psychostimulants (Robinson et al. 1985). It was believed that stress and psychostimulants act similarly on the mesocortical dopamine system and that the mechanisms of development of sensitization by those treatments are similar (Antelman et al. 1980). Although recent studies have demonstrated differences between the action of stress and psychostimulants, particularly regarding the involvement of N-methyl-D-aspartate (NMDA) receptors (Tolliver et al. 1996), the relationship between stress and addictive stimulants is of interest, because the stress seems to potentiate and accelerate the development of addiction and reinstates the drug-seeking behavior after a prolonged withdrawal period (Ahmed and Koob 1997; Shaham et al. 1996). Repetitive unavoidable stress causes several neurochemical changes that may be regarded as adaptive changes, but on the other hand, may be causally related to the induction of sensitization to psychostimulants and potentiation of addictive properties of drugs.

We previously postulated that L-type Ca^{2+} channels play an important role in the development of adaptive changes and that their blockade may prevent adaptive processes at the neurochemical and behavioral levels (Antkiewicz-Michaluk et al. 1994a,b; 1995). This mechanism may explain prevention by Ca^{2+} channel blocking agents of morphine dependence, dopaminergic symp-

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toms after withdrawal from chronic neuroleptic treatment, or neurochemical and behavioral effects of LSD (Antkiewicz-Michaluk et al. 1997). In the present study, we investigated whether L-type Ca^{2+} channel blockade with nifedipine applied before every restraint session would affect the potentiating effect of immobilization stress on amphetamine hypermotility and antagonize the neurochemical consequences of repetitive immobilization stress.

MATERIALS AND METHODS

Animals

The experiment was carried out on male Wistar rats, 250 to 280 g. The animals were kept in groups of four or six (in 55 × 34 × 19 cm cages). The cages, made of opaque plastic and having sawdust bedding, were kept in a room at 21°C, under 12/12 h light/dark cycle. The animals had free access to food and water. The immobilization procedure and activity measurements were carried out in another room.

Drugs

The repetitive treatment was applied once daily for 7 consecutive days. Nifedipine (Polfa) was prepared as suspensions in 1% Tween 80 immediately before injection and was given in a dose of 5 mg/kg IP 15–20 min before immobilization of rats. Amphetamine sulphate (Sigma), 0.75 mg/kg SC, was dissolved in 0.9% NaCl and given after the period of adaptation of a rat in the actometer. The injections were made in a volume of 2 ml/kg.

Immobilization Stress

The animals were transferred to a room of lower temperature (18°C) and placed for 2 h in restraint cages of maximum dimensions 17.0 × 5.5 × 5.5 cm. The bottom and movable front and back were made of translucent plastic, the sides and top with metal rods whose position was adjustable, to assure complete restraint of the animals.

Locomotor Activity and Amphetamine Hypermotility

The motor activity was measured in Columbus, Ohio, infrared actometers (Autotrack) and expressed as the length of the path covered in centimeters during the recording period. The rats were placed in the actometers without injection for a 60 min adaptation period, and they were injected with saline. Sixty minutes later, amphetamine was administered, and the recording was continued for another 120 min. The tests were carried out 24 h after the last immobilization session.

Preparation of Tissue for Receptor Studies and General Procedure

The rats were guillotined 2 h after the end of the last immobilization, the brains were rapidly removed, and placed on an ice-cold glass plate, and the cerebral cortex, hippocampus, striatum, and limbic forebrain (consisting of limbic cortex, olfactory bulb, preoptic area, nucleus accumbens septi, and the amygdala) were dissected, and the tissues were stored at −70°C. On the day of assay, the tissues were homogenized (Polytron) at 0°C in 20 vol of 50 mm Tris-HCl buffer pH 7.6, if not stated otherwise. The homogenate was centrifuged at 1,000 *g* and 0°C for 10 min, and the supernatant was recentrifuged at 25,000 *g* for 30 min. The pellet was rehomogenized in the original volume of the buffer. The membrane preparation (fraction P_2 of Whittaker and Barker 1972) was adjusted with the Tris-HCl buffer to contain the appropriate concentration of protein (assayed according to Lowry et al. 1951). The radioligands were prepared in six concentrations. The incubation mixture contained 450 μl of homogenate, 50 μl of radioligand solution, and 50 μl of buffer or displacer, if not stated otherwise, and was incubated in a shaking water bath for 30 min. All incubations were carried out in duplicates. The incubation was terminated by rapid filtration through Whatman GF/C filters that were afterward rinsed twice with 5 ml of ice-cold buffer and placed in 3 ml of Aquascint (Biocare) solution and counted for radioactivity in a Beckman LS 3801 counter. The specific binding was defined as the difference between the total and unspecific binding and expressed in fmole/mg of protein. The B_{max} and K_D values were calculated by Scatchard analysis; the following procedures differed, depending upon the kind of receptor investigated.

The Assay of L-type Ca^{2+} Channels (Dihydropyridine Binding Sites) in the Cortex and Hippocampus

[^{3}H]Nitrendipine (NEN, s.a. 78.3 Ci/mmol) was used in final concentrations of 0.05 to 3 nmol/l, 10 μmol/l nifedipine served to assess the unspecific binding. Solutions of [^{3}H]nitrendipine were prepared in darkness. Cortices from a single animal or hippocampi pooled from two animals were used for an assay. The final concentration of membrane preparation was approx. 1.2 mg/ml of protein. The samples were incubated at 25°C.

The Assay of D_1 Dopamine Receptors ([^{3}H]SCH-23390 Binding Sites) in the Limbic Forebrain

[^{3}H]SCH-23390 (NEN, s.a. 85.5 Ci/mmol) was prepared in concentrations of 0.06 to 2.0 nmol/l, 5 μmol/l SCH-23390 served to assess the unspecific binding and 10 μm serotonin to block serotonin receptors. The tissue

was homogenized in 40 vol of 50 mm Tris-HCl buffer pH 7.4, the final homogenate of P_2 contained 0.3 to 0.4 mg/ml of protein. The incubation was carried out at 30°C.

The Assay of D_2 Dopamine Receptors [^{3}H]Spiperone Binding Sites) in the Striatum

[^{3}H]Spiperone (Amersham, s.a. 16.4 Ci/mmol) was prepared in concentrations of 0.06 to 2 nmol/l, and 10 μmol/l spiperone was used as the displacer. The striata were homogenized in 20 vol of Tris-HCl buffer pH 7.4, the final P_2 pellet was suspended in 50 mm Tris-HCl buffer pH 7.1 containing 120 mm NaCl, 5 mm KCl, 1 mm $CaCl_2$, 1 mm $MgCl_2$, 10 μm pargyline, and 0.1% ascorbic acid. The incubated sample (1 ml) contained 500 μl of membrane preparation 0.3 to 0.35 mg protein), 100 μl of spiperone solution, 200 μl of buffer with or without displacer, and 200 μl of 10 μm serotonin to block serotonin receptors. The samples were incubated at 37°C for 10 min, the incubation was terminated by filtering through Whatman GF/C filters subsequently rinsed twice with 5 ml of cold buffer. Other methodological details were the same as the [^{3}H]nitrendipine binding assay.

The Assay of α_1-Adrenoceptors ([^{3}H]Prazosin Binding Sites) in the Cerebral Cortex

[^{3}H]Prazosin (Amersham, s.a. 25 Ci/mmol) was prepared in six concentrations (0.06 to 2.0 nmol/l), 10 μmol/l phentolamine was used to assess the unspecific binding. The final homogenate of P_2 contained approximately 1.5 mg/ml of protein. The incubation was carried out at 25°C.

The Assay of Corticosterone in Blood Plasma

The rats tested for blood corticosterone after a single immobilization stress were for the previous 6 days handled and injected with saline, and immobilized for 1 h on the 7th day. The rats were killed by decapitation immediately after the session. The rats tested chronically were killed after the 7th immobilization session, also after 1 h of the stress. The trunk blood was collected on EDTA and centrifuged immediately. To a sample of 25 μl of plasma 75 μl of water, and 1,000 μl of absolute ethanol were added, and the mixture was shaken and centrifuged for 20 min at 1000 g at 4 to 8°C. A sample of 40 μl of the extract was dried under nitrogen stream at 37°C on the water bath and dissolved in 100 μl of 0.05 mm phosphate buffer pH 7.0 containing 0.9% NaCl and 0.1% gelatin (Sigma, G9382 type B). The incubation mixture consisted of 100 μl of the dissolved extract, 100 μl of solution of 1,2,6,7-[^{3}H]corticosterone (NEN, s.a. 71.7 Ci/mmol) in gelatine-containing phosphate buffer (20,000 dmp/sample), and 100 ml of solution of anticorticosterone antibody A906RIT Ab, Bioproducts in gelatine-containing buffer in the amount resulting in approximately 50% [^{3}H]corticosterone binding in the sample without the standard. The samples were incubated overnight (12–16 h) at 4 to 6°C. Free and bound corticosterone were separated using dextran-coated charcoal: 0.0625% dextran (Dextran T 70, Pharmacia) and 0.625% charcoal (activated, Sigma) in gelatine-containing buffer. The samples were incubated for 10 min and centrifuged at 1,000 g for 20 min. Samples of 200 μl of supernatant were taken to scintillator for radioactivity assay. Corticosterone content was calculated using log–logit transformation.

Statistics

The data were analyzed with one-way analysis of variance (ANOVA) followed by Fisher's LSD test, using the "Solo" statistical program.

RESULTS

Amphetamine Hyperactivity

The basic activity was low and was not significantly affected by stress or by nifedipine. Amphetamine hyperactivity was significantly augmented in rats subjected to chronic restraint stress for the 7 successive days 1 day after the end of stressing. Chronically administered nifedipine did not change amphetamine hyperactivity in nonstressed rats, but nifedipine injections preceding successive restraint sessions completely inhibited the stress-induced augmentation of amphetamine effect (Figure 1).

Ca^{2+} Channels in the Hippocampus and Cerebral Cortex

The restraint stress caused a significant elevation of [^{3}H]nitrendipine binding sites in the hippocampus (by approximately 25%) and the cortex (by approximately 35%) without changes in their affinity. Administration of nifedipine before each restraint session completely prevented the rise in the [^{3}H]nitrendipine binding sites in the hippocampus and significantly reduced it in the cerebral cortex. Nifedipine administered repeatedly to nonstressed animals did not affect the parameters of [^{3}H]nitrendipine binding sites (Table 1).

Dopamine D_1 Receptors in the Limbic Forebrain and Cerebral Cortex

The restraint stress induced a significant elevation of the density of [^{3}H]SCH 23390 binding sites in the limbic

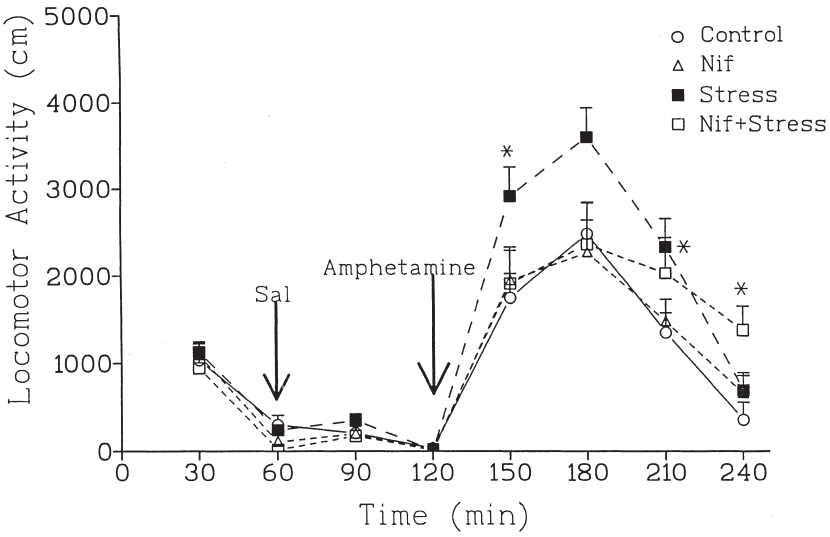

Figure 1. Mean locomotor activities ± SEM of rats placed in autotrack, recorded every 30 min (in cm). Saline (Sal) was injected after 60 min, and amphetamine, 0.75 mg/kg SC—after the following 60 min. In chronically stressed rats, 24 h after the last restraint session amphetamine produced significantly higher hypermotility (*$p < .05$) than in the controls. Nifedipine (Nif), 5 mg/kg IP, administered before every restraint session abolished the facilitatory effect of the stress.

forebrain (by 36%). Nifedipine administration before the stress partially prevented the B_{max} increase, and in nonstressed rats, nifedipine administration produces no changes in the [^{3}H]SCH 23-390 binding parameters. The density of [^{3}H]SCH 23-390 binding sites in the cerebral cortex was at the control level in all groups (Table 2).

Dopamine D_2 Receptors in the Striatum

The restraint stress did not significantly affect the binding of [^{3}H]spiperone to striatal membranes, although a tendency to decrease of the B_{max} value (14%) that did not reach the level of significance, was observed in this group. In the nifedipine-pretreated stressed group no such tendency was observed (Table 3).

Adrenergic α_1-Receptors in the Cerebral Cortex

The decrease (20%) in the density of [^{3}H]prazosin binding sites after restraint stress did not reach the level of statistical significance ($0.1 > p > .05$). No such tendency was observed in the stressed groups pretreated with nifedipine (Table 4).

Plasma Corticosterone Level

Neither acute nor chronic nifedipine administration affected the plasma corticosterone level. A single restrained stress produced approximately 30-fold elevation of plasma corticosterone that was not inhibited by previous administration of nifedipine. After chronic stress the increase in corticosterone level was much

Table 1. The Effect of Prestress Nifedipine Administration on [^{3}H]Nitrendipine Binding Sites in Brain Areas of Rats Repeatedly Exposed to Immobilization Stress

Treatment	B_{max} (fmol/mg prot)	% Contr.	K_D (nm)	% Contr.
Hippocampus				
Control	125 ± 9	100	0.93 ± 0.02	100
Nifedipine	117 ± 3	94	1.00 ± 0.05	107
Stress	155 ± 9*	124	0.94 ± 0.06	101
Nifedipine + stress	119 ± 7†	95	1.00 ± 0.07	107
Cerebral cortex				
Control	148 ± 12	100	0.90 ± 0.11	100
Nifedipine	151 ± 11	102	0.99 ± 0.09	110
Stress	200 ± 20*	135	0.98 ± 0.12	108
Nifedipine + stress	170 ± 11†	114	1.10 ± 0.07	121

The data are means ± SEM. The data were obtained from four (hippocampus) or five (cerebral cortex) individual Scatchard analyses.

*$p < .05$ (difference from the control), †$p < .05$ (difference between stressed groups with and without nifedipine).

Table 2. The Effect of Prestress Nifedipine Administration on [^{3}H]SCH23390 Binding Sites in Brain Areas of Rats Repeatedly Exposed to Immobilization Stress

Treatment	B_{max} (fmol/mg prot)	% Contr.	K_D (nm)	% Contr.
Limbic forebrain				
Control	125 ± 4	100	0.85 ± 0.04	100
Nifedipine	143 ± 16	114	0.86 ± 0.07	101
Stress	170 ± 11*	136	0.86 ± 0.05	101
Nifedipine + stress	152 ± 10	121	0.87 ± 0.06	102
Cerebral cortex				
Control	163 ± 14	100	1.40 ± 0.40	100
Nifedipine	155 ± 12	95	1.10 ± 0.10	79
Stress	172 ± 10	105	0.90 ± 0.01	64
Nifedipine + stress	178 ± 19	109	1.00 ± 0.01	71

The data are means ± SEM. The data were obtained from five (limbic forebrain) or six (cerebral cortex) individual Scatchard analyses.
*$p < .05$ (difference from the control).

smaller than after a single one, and the reduction of the corticosterone response was stronger in the group restrained without nifedipine premedication (Fig. 2).

DISCUSSION

The present results confirmed that the repetitive immobilization stress potentiates the psychomotor action of amphetamine (Robinson et al. 1985; Tolliver et al. 1996) and demonstrated for the first time that it induces an elevation of Ca^{2+} channel density in the hippocampus and cerebral cortex, and dopamine D_1 receptor density in the limbic forebrain. Previous studies have demonstrated that the increase in L-type Ca^{2+} channel density is observed in a variety of conditions that produce an increase in responsiveness of rats to dopaminergic stimuli, such as repeated electroconvulsive shock (Antkiewicz-Michaluk et al. 1990, 1994b), morphine abstinence (Antkiewicz-Michaluk et al., 1993, 1994a) or neuroleptic withdrawal (Mamczarz et al. 1994, Antkiewicz-Michaluk et al. 1995). Co-administration of nifedipine with those treatments inhibits their propensity to produce of various changes, believed to be of adaptive character. The role of the dopamine D_1 receptor in the ventral tegmental area was postulated to be critical for the development of sensitization to stimulants Kalivas and Stewart 1991), but its role in the immobilization stress is less clear. Thus, Diaz-Otanez et al. (1997) reported that the D_1 receptor blockade inhibited the sensitized response to amphetamine induced in rats by restraint stress, and Puglisi-Allegra et al. (1991) have not observed changes in the D_1 receptor density in the nucleus accumbens of repeatedly immobilized mice. Our present results indicate that the D_1 receptors in the limbic forebrain undergo adaptive changes during the restraint stress, but that effect is limited to some brain areas, because it does not appear in the cerebral cortex.

It was also confirmed that a single restraint stress greatly elevated the plasma corticosterone level and that this response diminishes when the stress is repeated for a prolonged period (Hauger et al. 1990). Although immobilization stress was reported to affect catecholamine and serotonin metabolism (Dunn 1988; Nakane et al. 1994), we observed no changes in the characteristics of striatal D_2 receptors, nor cortical α_1-adrenoceptors. Our results concerning the striatum are similar to those reported by mice by Puglisi-Allegra et al. (1991), who also found only small (11%) decrease in the density of D_2 receptors in the caudate-putamen, although they observed much more prominent decrease (64%) in the nucleus accumbens.

The changes induced by immobilization stress may be prevented by various treatments applied before the

Table 3. The Effect of Prestress Nifedipine Administration on [^{3}H]Spiperone Binding Sites in the Striatum of Rats Repeatedly Exposed to Immobilization Stress

Treatment	B_{max} (fmol/mg prot)	% Contr.	K_D (nm)	% Contr.
Control	286 ± 26	100	0.80 ± 0.06	100
Nifedipine	256 ± 12	90	0.80 ± 0.07	100
Stress	248 ± 11	86	0.75 ± 0.08	93
Nifedipine + stress	298 ± 36	104	0.82 ± 0.09	103

The data are means ± SEM. The data were obtained from three individual Scatchard analyses.

Table 4. The Effect of Prestress Nifedipine Administration on [^{3}H]Prazosine Binding Sites in the Cerebral Cortex of Rats Repeatedly Exposed to Immobilization Stress

Treatment	B_{max} (fmol/mg prot)	% Contr.	K_D (nm)	% Contr.
Control	146 ± 17	100	0.15 ± 0.04	100
Nifedipine	137 ± 16	93	0.16 ± 0.02	106
Stress	117 ± 15	80	0.13 ± 0.02	86
Nifedipine + stress	140 ± 8	95	0.14 ± 0.01	93

The data are means ± SEM. The data were obtained from five individual Scatchard analyses.

restraint sessions. Sensitization to amphetamine was reduced or abolished by dopamine D_1 and D_2 receptor blockers or opiate receptor antagonist naltrexone (Diaz-Otanez et al. 1997). The agents that block Ca^{2+} entry may also antagonize several effects of the restraint stress, such as; for example, gastric ulcer formation (Glavin 1988; Yegen et al. 1992) or activation of renin and aldosterone (Ceremuzynski et al. 1991). Here we found that application of L-type Ca^{2+} channel blockade before each restraint session abolished the propensity of the stress to induce sensitization to amphetamine and to elevate the densities of Ca^{2+} channels and D_1 receptors. The pretreatment with nifedipine also prevented the otherwise insignificant tendency of decrease in the densities of dopamine D_2 and adrenergic α_1 receptors in the stressed rats.

Our results demonstrate that blocking of Ca^{2+} influx reduces the stress-induced amphetamine facilitation. Because the latter is regarded as at least a partial model for drug addiction (Roberts et al. 1995), the present data suggest that L-type Ca^{2+} channel blocking agents may be useful in the treatment of drug dependence. This, in fact, corroborates our previous studies demonstrating that morphine administration in the presence of nifedipine and other L-type Ca^{2+} blockers prevents the ability of naloxone to induce withdrawal syndrome in rats chronically injected with morphine (Antkiewicz-Michaluk et al. 1990, 1993; Michaluk et al. 1998).

In light of our hypothesis that functional L-type Ca^{2+} channels are necessary to develop of adaptive changes (Antkiewicz-Michaluk et al. 1995) the present data indicate that the increases in the density of Ca^{2+} channels and D_1 receptors caused by immobilization stress are the adaptive responses, as Ca^{2+} channel blockade prevents their development. It has been suggested that the stress-induced hypersensitivity to amphetamine is caused by alteration of dopaminergic systems and that dopamine neurotransmission seems crucial for the expression of sensitized behaviors (cf., Roberts et al. 1995). However, the role of Ca^{2+} channels in this phenomenon cannot be neglected.

It is generally agreed that sensitization to locomotor effects of amphetamine by immobilization stress also depends upon stress-related corticosterone release (Deroche et al. 1992, Roberts et al. 1995), although the sensitization to stress-induced feeding may be independent of corticosterone (Badiani et al. 1996). We have confirmed the findings that single immobilization stress increases the plasma level of corticosterone and that the response declines after repeated immobilization (Hauger et al. 1990). Interestingly, this adaptive decline in corticosterone depression was significantly smaller in the nife-

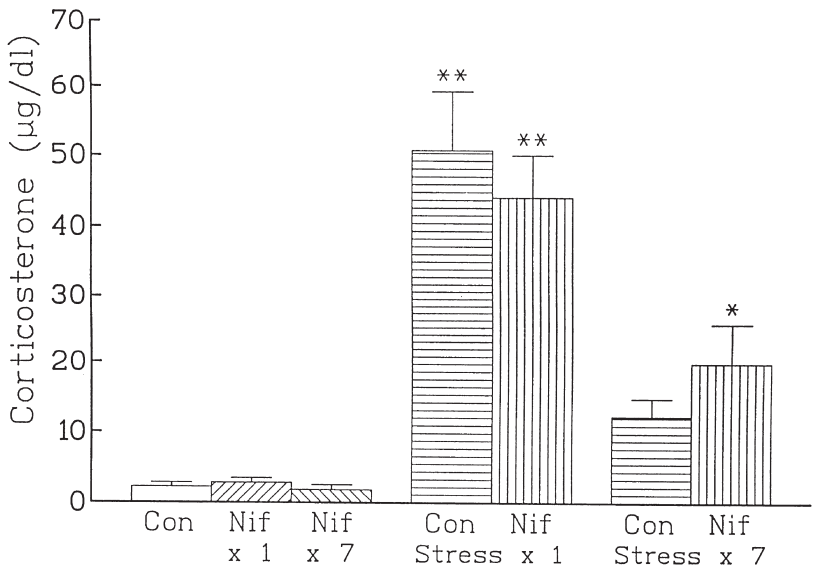

Figure 2. Mean corticosterone blood plasma concentrations ± SEM (in μg/dl) of rats 60 min after a single (×1) or multiple (×7) restraint stress. A single stress significantly elevated the corticosterone level (**$p < .01$); whereas, after multiple restraint, the elevation corticosterone was not longer significant. Nifedipine (Nif), 5 mg/kg IP, administered before every restraint session did not affect significantly the corticosterone elevation after the single stress, but partially prevented the decline of corticosterone level after the multiple stress (*$p < .05$, difference from control).

dipine-pretreated group, thus suggesting that Ca^{2+} channels are involved in several types of adaptive responses.

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