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GABAergic Mechanisms in the Nucleus Accumbens Septi Regulating Rat Motor Activity: The Effect of Chronic Treatment With Desipramine

A. PŁAŻNIK, R. STEFAŃSKI AND W. KOSTOWSKI

Department of Pharmacology and Physiology of the Nervous System
Institute of Psychiatry and Neurology, 02-957 Warsaw
Al. Sobieskiego 1/9, Poland

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PŁAŻNIK, A., R. STEFAŃSKI AND W. KOSTOWSKI. *GABAergic mechanisms in the nucleus accumbens septi regulating rat motor activity: The effect of chronic treatment with desipramine.* PHARMACOL BIOCHEM BEHAV **36**(3) 501–506, 1990.—The influence of chronic treatment with desipramine upon GABAergic mechanisms within the nucleus accumbens septi (NAS) affecting rat motor behavior was studied in the automatic open fields. It was shown that intra-accumbens injections of picrotoxin on one hand, and muscimol and baclofen on the other, produced dose-dependent increase or decrease in rat motility, respectively. Locomotor stimulation usually observed after picrotoxin did not occur in rats given local injections of a solution containing both picrotoxin and GABA A receptor agonist muscimol. Muscimol (130 ng as a pure compound) blocked also hypermotility produced by intra-accumbens administration of dopamine releasing drug d-amphetamine (10 μg). This part of the experiment was summarized as indicating that both GABA A and GABA B receptor-related mechanisms, which are under negative control of dopaminergic neurons in the NAS, play an important role in regulating behavior in the rat. In the second part of the experiment it was observed that chronic treatment of rats with desipramine (DMI) (10 mg/kg, PO, twice daily for 21 days, rats were tested 24 hr after the last dose of the drug) significantly attenuated or blocked the inhibitory effect on locomotion of both baclofen and muscimol. The stimulatory influence of picrotoxin seemed also to be diminished, but it still attained the level of accepted statistical significance. On the basis of these and other data it is concluded that observed changes in the effects of GABAergic agonists in DMI-treated rats are probably due to an enhancement of local dopaminergic mechanisms, thus leading to the potentiation of a negative interaction between dopaminergic and GABAergic mechanisms within the NAS. It is also suggested that described phenomenon may be of importance in understanding the mechanisms of therapeutic effect of DMI on psychomotor retardation in depressed patients.

Nucleus accumbens GABAergic mechanisms Microinjections Muscimol Baclofen Picrotoxin
Chronic desipramine Locomotor activity Rat

IT was recently observed that chronic treatment of rats with desipramine attenuated locomotor stimulation produced by intra-hippocampal injections of GABA antagonist, picrotoxin (22). The data were interpreted as indicating an enhancement of local GABA A receptor-related mechanisms in the course of chronic administration of the tricyclic antidepressant. This finding may be of some interest in discussing the role of GABA system in affective disorders [cf. (1)], and in the interpretation of therapeutic efficacy of GABA agonists in depression (10). Nucleus accumbens septi (NAS) was also found to have dense GABAergic innervation (4), with dopaminergic terminals making synaptic contact with local GABAergic cell bodies (18). Moreover, the nucleus appears to form, along with the hippocampus, an important relay station in transforming and transmitting sensory output from associative cortical areas to brainstem centers regulating animals' motor activity (31). It is also suggested that GABAergic inhibitory neurons projecting from the NAS to the globus pallidus and downstream to the pedunculopontine nucleus are influenced by inhibitory dopaminergic synapse of the mesolimbic neurons (2, 7, 8, 15, 27, 31). Furthermore, accumbens dopaminergic transmission appears to be strongly affected by chronic treatment with desipramine (21,30). It seemed, therefore, conceivable that repeatedly administered desipramine (DMI) may influence animal activity due to drug-induced changes in the balance of dopaminergic versus GABAergic mechanisms within the NAS. The involvement of GABA A and GABA B receptor-related mechanisms in the NAS in the regulation of animal motility was studied in naive rats as well as in animals pretreated chronically with DMI. Thus, we have tried to observe some adaptive changes occurring in the accumbens GABA innervation in response to prolonged exposure of rats to the potent tricyclic antidepressant.

METHOD

Animals

Male Wistar rats (220 ± 20 g), bought from a licensed breeder, were used in the study. The animals were kept individually in wire mesh cages after surgery (30 × 30 × 20 cm) to avoid damage to the implanted sockets. Animals were kept in standard laboratory conditions with food and water ad lib. The experiment was performed during several months from February 1989 to January 1990.

Surgery

Rats were operated upon under light ethyl ether anesthesia. A socket with two metal guide cannulas was implanted stereotaxically (20) 2 mm above the central part of the NAS, A 9.5 mm; L 1.0 mm; V 5.5 mm below the dura, and then fixed to the skull cap with three jewelry screws and dental acrylic cement. Seven days later rats were subjected to behavioral testing.

Procedure

Microinjections were given bilaterally with two Hamilton microsyringes connected via polyethylene tubings to injection needles (0.3 mm external diameter), inserted 2 mm below the tip of the guide cannula, i. e., at the level of commissura anterior in the NAS. All drugs used for microinjections were dissolved in bidistilled water immediately before administration. Control rats were treated with bidistilled water only. Each animal was injected twice at the most, with an interval of at least 5–7 days prior to subsequent treatment (chronic desipramine-treated groups; picrotoxin alone and picrotoxin plus muscimol-administered rats; muscimol alone and baclofen alone-injected animals). Solutions (0.5 μl) were administered bilaterally over 30 sec. The injection needles remained in place for an additional 30 sec before it was removed and the stylet replaced. Behavioral testing started immediately after injection, and lasted for 30 min. In some experiments when stimulatory effect was expected (picrotoxin) microinjections were given after a 15-min habituation and behavioral reaction was scored during the next 15-min period only. The results obtained in these groups of animals are characterized by lower baseline levels of activity of control rats. This was done purposely to enhance and equalize the stimulatory effect of the compound.

Drugs

Picrotoxin (Serva), metoclopramide hydrochloride (Polfa), baclofen (Polfa), muscimol hydrobromide (Serva), d-amphetamine hydrochloride (Astra), were freshly prepared in bidistilled water. In some experiments two drugs were applied simultaneously in one solution. Desipramine hydrochloride (Ciba-Geigy) was administered in a dose of 10 mg/kg twice daily, and dissolved in water (5 ml/kg), per os, for 21 days. Twenty-four hr after the first (acute treatment) and 21st (chronic treatment) dose, the animals were given intracerebral injections and subjected to behavioral testing. Control groups received twice daily per os injections of water only.

Open Field

The open field test was performed for 30 min in 3 automated boxes (80 cm diameter round arena with 30 cm high walls) equipped with 3 horizontally placed photocells, in a soundproof chamber, under dim light and white noise conditions. The number of photobeam interruptions was recorded every 5 min in an adjacent room and used as an index of locomotor activity.

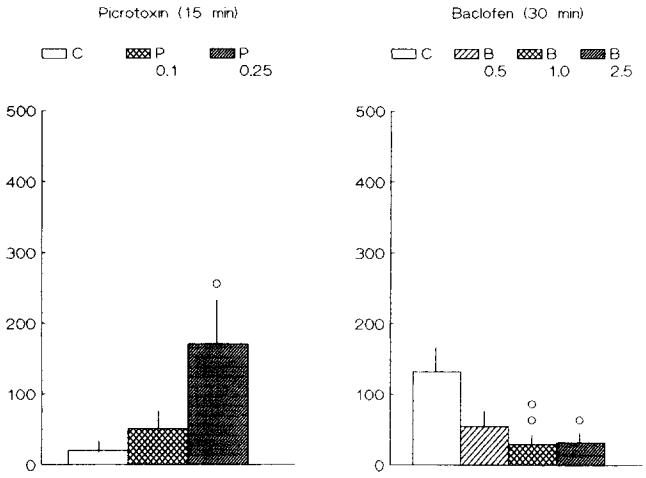

FIG. 1. The effect of intra-accumbens injections of picrotoxin and baclofen upon rat locomotor activity. The injection of picrotoxin was given after a 15-min habituation, and observation was continued for the next 15 min. In the part of the experiment with baclofen, the drug was administered immediately prior to a 30-min test session. Ordinate: number of photobeam interruptions during a 15-min (picrotoxin) or 30-min (baclofen) observation period; C: control; P: picrotoxin; B: baclofen. Number of rats in the part of the experiment with picrotoxin: C = 6, P 0.1 = 9: P 0.25 = 9; number of rats in the part of the experiment with baclofen: C = 6, B 0.5 = 7, B 1.0 = 7, B 2.5 = 7; doses of picrotoxin and baclofen are shown in the legend (e.g., P 0.1 picrotoxin in a dose of 0.1 μg); ○: differs from control. ○ = $p<0.05$; ○○ = $p<0.01$.

Histological Analysis

All animals were sacrificed after the final testing day, their brains were removed and stored in 5% formalin, and then checked histologically. The frozen tissue was dissected out into slices and the place of injections inspected with Meoflex (×40). This apparatus is comprised of a magnifying glass and a slide projector.

Statistical Analysis

All data are expressed as mean ± S.E.M. The data were analysed by the one-way ANOVA followed by the Student's *t*-test.

RESULTS

Histological analysis showed that the site of injection was essentially the same as observed in our previous experiment (21), i.e., in the area of commissura anterior within the NAS. Taking into account other histological and isotopic data showing the 0.6 mm radius of a 0.5 μl solution diffusion after intrastructural injection (17, 19, 24), the present behavioral data may be related to changes in the functioning of this particular brain region (antero-medial part of the NAS). About 10% of rats were rejected due to incorrect site of injections.

Intra-accumbens injections of picrotoxin stimulated dose-dependent rat motor activity. Figure 1 (left part) shows that there was an overall significant effect of picrotoxin on number of photobeam interruptions across all drug conditions, $F(2,21) = 6.35$, $p<0.01$. Post hoc comparison indicates that the dose of 0.25 μg picrotoxin significantly stimulated rat locomotion ($t = 2.3$, $p<0.05$). On the other hand, administration of baclofen and muscimol very potently

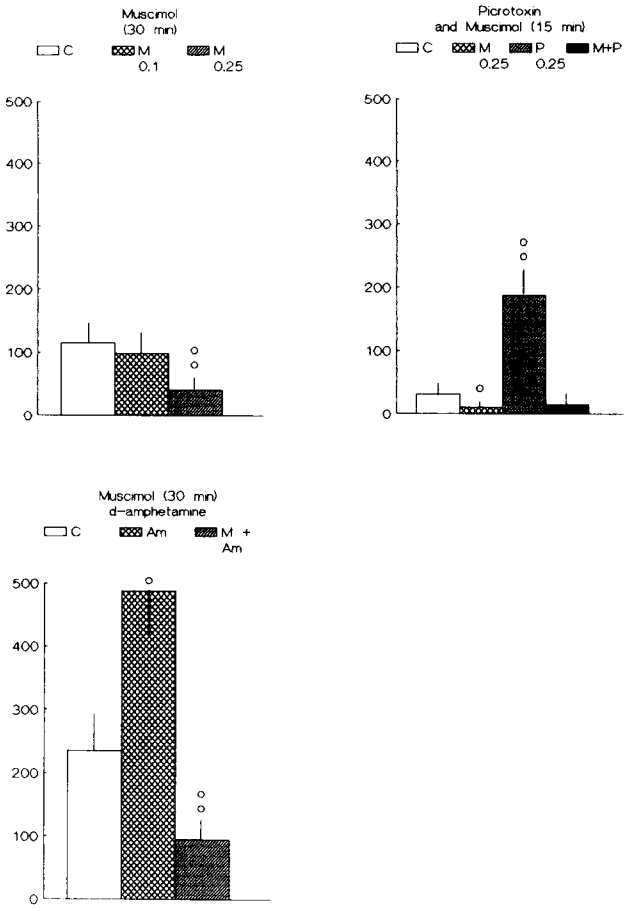

FIG. 2. The effect of intra-accumbens injections of muscimol, picrotoxin and muscimol, and muscimol plus d-amphetamine upon rat locomotor activity. M: muscimol. Behavioral scoring was started immediately after injections and was continued for the next 30 min. Number of rats: C = 5, M 0.1 = 7, M 0.25 = 5. In the part of the experiment with picrotoxin (0.25 μg), muscimol was given in a dose of (0.25 μg), and the data show animals' activity during a 15-min postinjection period, following a 15-min preinjection habituation session (not shown); number of rats: C = 6, M = 5, P = 5, M+P = 6. In the part of the experiment with d-amphetamine (10 μg) muscimol was given in a dose of (0.25 μg), and the data show animals' activity during a 30-min postinjection period. Number of rats: C = 5, A = 9, M+A = 8. Other explanations as in Fig. 1.

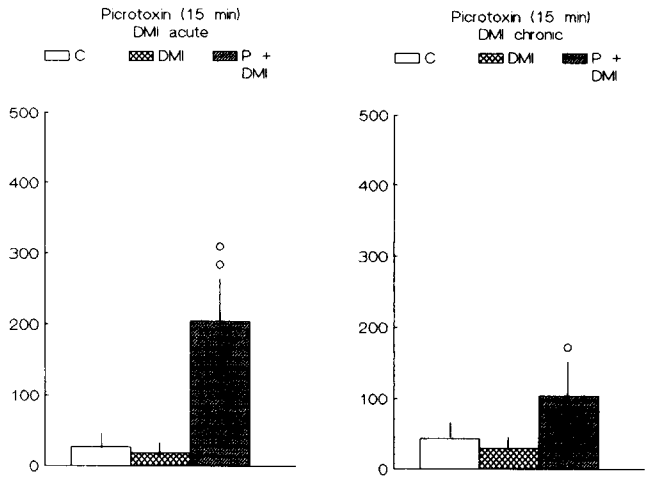

FIG. 3. The effect of acute and chronic administration of desipramine upon locomotor effect of intra-accumbens injections of picrotoxin (0.25 μg). Rat behavior was scored for 15 min after picrotoxin injection preceded by a 15-min preinjection habituation session (data not shown). The test was performed 24 hr after the first (acute treatment) or 21st day (chronic treatment) of antidepressant administration (10 mg/kg, PO, twice daily). Number of rats: acute treatment C = 6, DMI = 6, P+DMI = 7, chronic treatment C = 8, DMI = 6, P+DMI = 7. Other explanations as in Fig. 1.

inhibited animals' activity. Figures 1 (right part) and 2 show that there was an overall significant effect of baclofen, $F(3,22) = 7.13$, $p<0.01$, and of muscimol, $F(2,14) = 3.89$, $p<0.05$, on number of photobeam interruptions across all drug conditions. Post hoc comparisons indicate that baclofen in doses 0.5 μg ($t = 2.25$, $p<0.05$), 1.0 μg ($t = 2.87$, $p<0.01$) and 2.5 μg ($t = 2.57$, $p<0.05$) inhibited rats' motility. Likewise, muscimol caused significant behavioral depression in a dose of 0.25 μg ($t = 3.14$, $p<0.01$). Significant effects on locomotion appeared also after local injections of solution containing both picrotoxin and muscimol, $F(3,18) = 60.4$, $p<0.01$) (Fig. 2). The effect of picrotoxin (0.25 μg) was blocked by muscimol in a dose of 0.25 μg ($t = 7.03$, $p<0.01$). Similar changes were observed after microinjection of solution containing d-amphetamine and muscimol, $F(2,18) = 9.18$, $p<0.01$ (Fig. 2). Muscimol given in a dose of 0.25 μg together with d-amphetamine antagonized behavioral stimulation observed after d-amphetamine (10 μg) ($t = 3.9$, $p<0.01$). The effect of picrotoxin appeared to be less pronounced in the chronic DMI-treated rats [acute treatment, $F(2,16) = 14.9$, $p<0.01$; chronic treatment, $F(2,18) = 3.19$, $p<0.1$], however, it still reached the level of statistical significance in post hoc comparison (picrotoxin plus desipramine versus control group, $t = 1.85$, $p<0.05$) (Fig. 3). On the other hand, chronic but not single administration of desipramine antagonized the inhibitory effect on locomotion of intra-accumbens injection of baclofen (2.5 μg); acute treatment, $F(2,21) = 3.82$, $p<0.05$, chronic treatment, $F(2,15) = 0.34$, n.s. (Fig. 4). Similar changes in the effects of locally injected muscimol were observed after chronic administration of desipramine; acute treatment, $F(2,19) = 4.98$, $p<0.01$, chronic treatment, $F(2,16) = 0.36$, n.s. (Fig. 4). The effect of desipramine appeared to be specific since chronic treatment of rats with water only did not modify behavioral effects of muscimol and baclofen [$F(2,21) = 26.9$, $p<0.01$; muscimol, $t = 4.84$, $p<0.01$; baclofen, $t = 5.58$, $p<0.01$], as well as of picrotoxin ($t = 2.91$, $p<0.05$) (Fig. 5).

DISCUSSION

In agreement with previous reports intra-accumbens injections of picrotoxin (a selective blocker of GABA A receptor-gated chloride channel) were found to produce dose-dependent increase in rat motor activity (7,16). This effect seems to be due to attenuation by picrotoxin of local GABAergic mechanisms, which have an inhibitory influence on processes of motor activity regulation. It was also observed that local injections of GABA A and GABA B receptor agonists, muscimol and baclofen, decreased rats' motility in a dose-dependent manner. The inhibitory effect on locomotion appeared also after intra-accumbens injections of GABA in a dose of 33 μg (7). These data indicate, therefore, that both GABA A and GABA B receptors in the NAS are involved in the control of animal behavior. The involvement of GABA A receptor-Cl^- ionophore complex is confirmed by an antagonism of picrotoxin effect by simultaneous injection of muscimol. The characteristic feature of the present experiment was the relatively high variability of control groups activity (the

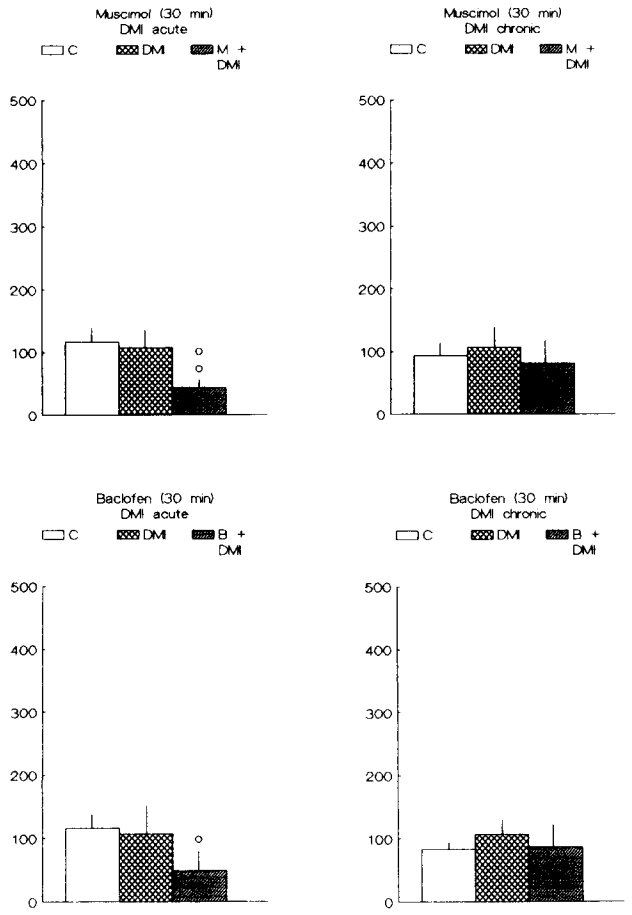

FIG. 4. The effect of acute and chronic administration of desipramine upon locomotor effect of intra-accumbens injections of muscimol (0.25 μg) and baclofen (2.5 μg). Rat behavior was scored for 30 min after microinjection and 24 hr after the first (acute treatment) and 21st day (chronic treatment) of antidepressant administration (10 mg/kg, PO, twice daily). Number of rats in the part of the experiment with muscimol; acute treatment C = 9, DMI = 6, M+DMI = 7, chronic treatment C = 8, DMI = 6, M+DMI = 5. Number of rats in the part of the experiment with baclofen; acute treatment C = 9, DMI = 6, B + DMI = 9, chronic treatment C = 6, DMI = 6, B + DMI = 6. Other explanations as in Fig. 1.

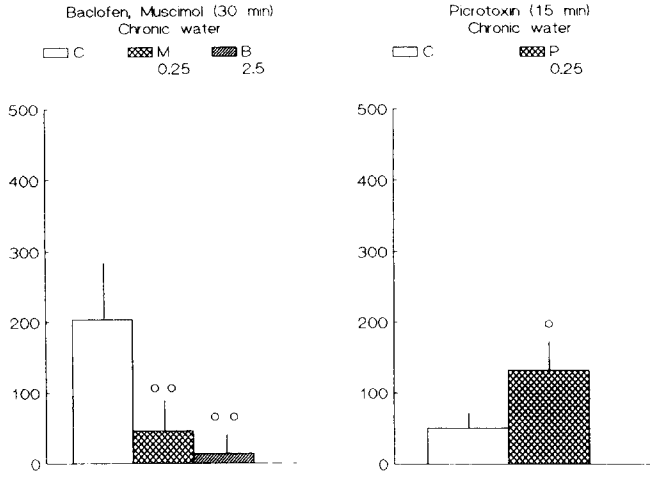

FIG. 5. The effect of chronic administration of water upon locomotor effect of intra-accumbens injections of muscimol (M, 0.25 μg), baclofen (B, 2.5 μg) and picrotoxin (P, 0.25 μg). Rat behavior was measured for 30 min after muscimol and baclofen without preceding habituation session, and for 15 min after picrotoxin injection, preceded by a 15-min preinjection habituation session (data not shown). The tests were performed 24 hr after the 21st day of chronic water administration. The number of rats in the part of the experiment with muscimol and baclofen: C = 8, M = 8, B = 8, and in the part with picrotoxin: C = 5, P = 6. Other explanations as in Fig. 1.

highest variability factor was 2.3; from around 100 photocell breaks in 30 min for baclofen and muscimol dose-response study to 230 for the amphetamine and muscimol study). This may be due to the seasonal variability of rat motor behavior in the course of the experiment performed during several months.

Based on these and other data the question can be posed as to what extent motor effects of locally administered GABAergic drugs are related to changes in the functioning of mesolimbic DA system. As it was pointed out in the Introduction the NAS is predominantly a dopaminergic structure, with dopaminergic terminals making synaptic contact with local GABAergic cell bodies (18). Moreover, it was repeatedly suggested that GABAergic neurons form main output system of the NAS, influenced by inhibitory dopaminergic synapse (31). Thus, it was conceivable that described by us effects of GABAergic drugs can be secondary to the changes in the balance of GABA versus dopamine neuron activity. Previous reports described an antagonism of locomotor effects of intra-accumbens dopamine injections by administration of GABA into the NAS, globus pallidus, lateral preoptic area or substantia innominata, i.e., terminal fields descending from the NAS (2, 7, 8, 15, 27). Accordingly, it was found in the present paper that the dose of 130 ng of GABA A receptor agonist muscimol reversed the simulatory effect on motor behavior of locally injected d-amphetamine (10 μg), a dopamine releaser. Since the efect of d-amphetamine in the NAS is recognized to be dopaminergic in nature (28), these data further point at the existence within the NAS of a negative interaction between GABA and dopaminergic mechanisms controlling rat motor behavior. Another possibility is that stimulation of GABA receptors located on accumbens dopaminergic terminals may control dopamine release. Accordingly, it was found that agonists of GABA receptors reduce both synthesis and release of striatal and accumbens dopamine (25). It is possible, therefore, that this neurochemical finding reflects neural processes involved in a decrease of animal motility after local injections of muscimol and baclofen.

The influence of chronic desipramine (DMI) treatment appeared to be of interest in the context of this discussion. It was found that rather intensive exposure of rats to the tricyclic antidepressant (10 mg/kg twice daily for 21 days) completely abolished the inhibitory effect on locomotion of baclofen and muscimol, while there was only tendency for the stimulatory influence of picrotoxin to be attenuated. Recently, it was reported that chronic administration of DMI (10 mg/kg daily for 21 days) very potently enhanced the activity of dopaminergic mechanisms within the NAS (21). For example, such a treatment revealed or enhanced the stimulatory potency of locally injected to the NAS small doses of dopaminergic agonists on rat motor behavior in the open field and Porsolt tests (21). Antidepressants including desipramine and citalopram, as well as electroconvulsive shocks, were found to increase self-stimulation and the stimulatory effect of apomorphine and amphetamine on rat motility, thus pointing at the brain mesolimbic system as a target area for antidepressive treatment (3, 12, 29). More directly, Heal and Green (5) observed a potentiation of the dopamine- and dibutyryl cyclic AMP-induced locomotion when the drugs were injected into the NAS after chronic electroconvulsive treatment. The most often cited facts in

favor of the concept that chronic antidepressive treatment (including desipramine) enhances responsiveness of the mesolimbic dopaminergic system were recently summarized by Willner (30). Consequently, it can be assumed that the described adaptive processes occurring in accumbens dopaminergic system after DMI could contribute to the drug-induced changes in the effects of baclofen and muscimol. An enhancement of local dopaminergic mechanisms after DMI might intensify the above discussed negative interaction between dopamine and GABAergic mechanisms within the NAS, thus, finally leading to the attenuation of behavioral effects of GABA agonists. Such conclusion can be based, however, on functional data only (behavioral and electrophysiological) (7, 8, 15, 31), since no direct information on the intrinsic mechanisms of dopamine- versus GABA-neuronal systems interaction within the NAS is yet available.

Another possibility is that chronic DMI treatment releases accumbens DA system from inhibitory control of local GABA interneurons. It was reported that in naive animals GABAergic agonists reduce synthesis and release of striatal and accumbens dopamine (25). Furthermore, it was found that DMI enhances GABA release and that chronic exposure of cultured neurons from embryonic brain to GABA or muscimol down regulates the GABA-chloride receptor complex, as shown by a decrease in the specific binding of ^{3}H-muscimol (9,14). Chronic treatment of rats with imipramine produced also a decrease in B_{max} of both (^{3}H)dihydroalprenolol and (^{3}H)GABA binding in the cerebral cortex and hippocampus (26). This finding indicates a possible relationship between both phenomenons, however, the exact nature of this interaction is not yet known. There is no available univocal information on the influence of reduced B_{max} for (^{3}H)dihydroalprenolol binding after chronic antidepressant treatment upon functioning of the GABA neuronal system (11). However, there are some preliminary observations that β-adrenergic and GABA B receptors are linked in an integrated control of cyclic AMP production (6). This problem apparently awaits further research. Since GABA is a ligand for both GABA A and GABA B receptors, the decrease in (^{3}H)GABA binding after chronic imipramine may explain also the decreased effect of selective GABA receptor agonists in a functional model applied in the present experiment. In other words, such mechanism might attenuate the discussed above (25) depressive influence of GABA agonists on accumbens dopamine synthesis and release, thus enhancing dopamine-related central processes. However, the lack of uniform data on antidepressant-induced changes in GABA A receptor subgroup remains this possibility unsolved (10, 11, 25, 26).

Irrespective of the mechanism, however, it is noteworthy that such disinhibitory influence of DMI appeared after chronic treatment only. This indicates that the described phenomena may be of some importance in discussing the mechanisms of therapeutic effect of DMI on psychomotor retardation observed in depressive patients. Finally, we cannot offer any credible explanation for the weak effect of chronic DMI on picrotoxin-induced hyperlocomotion. It is possible that behavioral stimulation after the dose of 0.25 μg of picrotoxin was too strong to observe strong modulatory effect of repeatedly administered antidepressant (ceiling effect). It is also possible that the less potent statistical difference between control and picrotoxin plus DMI-treated groups was due to higher baseline level of motor activity of the control animals. The lack of clear-cut effects of desipramine on picrotoxin-induced motility seems to be unexpected in the light of the above discussed hypothetical mechanisms of GABA versus dopamine interaction, as well as new findings of an inhibition by antidepressants of the GABA-receptor chloride uptake (13). Since picrotoxin is believed to selectively block the function of GABA A receptor-linked chloride channel, one might expect a strong synergistic interaction between desipramine and picrotoxin treatment (23). However, in contrast to many other antidepressants, desipramine appeared to not alter GABA-stimulated chloride uptake at any concentration tested (13). This finding, along with the fact that picrotoxin is not directly linked with the function of the GABA receptor complex (23), might help to understand the weak, if any, effect of desipramine on intra-NAS picrotoxin-induced hypermotility. In other words, picrotoxin action on the output system of the GABA A receptor-related complex, might not be sensitive to desipramine-induced changes in GABA receptors and/or GABA versus dopamine interactive mechanisms.

In summary, the present data show that both GABA A and GABA B receptor-related mechanisms in the NAS, which are negatively coupled with local dopaminergic neurons, regulate rats' motor behavior. Both neurotransmitter systems appeared to be affected by chronic administration of DMI, and the behavioral outcome of the treatment is proposed to be the result of the changes occurring primarily in the dopaminergic neurons. However, any generalization of this conclusion as well as its applicability for the construction of a hypothesis of clinical effects of antidepressive therapy, apparently needs more research with different drugs and antidepressive treatments involved. Moreover, a trial to correlate the above discussed data with the effects of antidepressants on GABA-stimulated ^{36}Cl-uptake by rat cerebral tissues from mesolimbic nuclei should answer the question on the biochemical substrate of the observed behavioral phenomena.

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