Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 2, pp. 315-325, 1994

0091-3057/94 $6.00 + .00

0091-3057(93)E0028-3

Antidepressant Treatment and Limbic Serotonergic Mechanisms Regulating Rat Locomotor Activity

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Received 20 July 1993

PLAZNIK, A., R. STEFANSKI, W. PALEJKO, A. BIDZINSKI, W. KOSTOWSKI, M. JESSA AND M. NAZAR. *Antidepressant treatment and limbic serotonergic mechanisms regulating rat locomotor activity.* PHARMACOL BIOCHEM BEHAV **48**(2) 315-325, 1994. — The effects of chronic administration of desipramine, citalopram, and electroconvulsive shocks (ECS) on changes in rat motility after intraaccumbens (NAS) injections of selective serotonergic drugs were studied in intact and 5.7-DHT lesioned animals. It was shown that local injections of 8-OHDPAT and DOI-HCl depressed rat locomotor activity. Their effects appeared to be mediated postsynaptically, and could be antagonized by NAN-190 and ritanserin, respectively. Chronic but not acute pretreatment of rats with antidepressants (21 days long; the experiment was performed 24 h after the last dose) as well as repeated ECS (shocks were applied five times every second day), antagonized behavioral depression after 8-OHDPAT and DOI-HCl. The influence of antidepressant treatment was prevented by serotonergic lesions. Chronic administration of antidepressants and ECS did not equivocally affect the levels or metabolism of 5-HT, dopamine, and noradrenaline in the rat limbic forebrain. It is concluded that the present data indicate diminished activity of 5-HT systems related to the 5-HT1A and 5-HT2 receptors in the limbic nucleus, after chronic antidepressant treatment. This effect of drugs and ECS concerns nervous processes linked with the function of postsynaptically localized 5-HT receptor subtypes, and it probably depends on intact presynaptic 5-HT innervation.

8-OHDPAT Buspirone DOI-HCl Alpha-Methyl-5-HT Ritanserin Citalopram Desipramine
ECS 5,7-DHT Nucleus accumbens Microinjections Open field Rats

ALTHOUGH serotonergic neuronal systems have been implicated in the therapeutic effects of antidepressant treatment for a number of years (6), evidence in favor of this role is still controversial. Electroconvulsive shocks (ECS) and antidepressant drugs (AD) oppositely influence the number of 5-HT_2 receptors in the frontal cortex of the rat [cf. (29,37)]. The concentration of postsynaptic 5-HT_{1A} receptors has been reported to be increased, decreased, or not changed by chronic antidepressant treatment (24-27,36). These experimental facts as well as the lack of concordance between the results of receptor binding and second messenger experiments (25) suggest a postreceptor effect of the antidepressant treatments on brain 5-HT system. Such mechanism may account for the multiple effects of drugs and ECS observed at the functional level, e.g., on the 5-HT-related behaviors. Recently, we have reported that chronic treatment of rats with desipramine significantly attenuated behavioral depression (locomotor inhibition) after 5-HT and quipazine microinjections into the nucleus accumbens (30). This finding, along with many others conducted in our laboratory over the last decade, provide evidence for the existence of limbic neurotransmitter modulatory mechanism of action of AD and ECS. It is suggested that antidepressant treatment, on the one hand, reduces inhibitory signals mediated through 5-HT, GABA, and alpha-2 adreno-

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ceptors, while on the other hand, it enhances excitatory central processes mediated via the dopaminergic and adrenergic alpha-1 receptors (31). This may explain the energizing influence of antidepressant treatment on psychomotor retardation, a part of endogenous depression in human beings. However, in the electrophysiological studies (single unit recordings and microiontophoretic techniques) 5-HT was found in some brain nuclei (e.g., in the facial nucleus) to mediate excitatory responses; the phenomenon being enhanced after daily injections of several clinically effective tricylics for 14–20 days (19). This finding indicates that the character of interaction between antidepressant treatment and brain serotonin system depends on the level of organization of the central nervous system function. Apparently, behavioral analysis help to reveal the final output of the central nervous system activity. The aim of the present study was threefold: a) to extend previous findings by studying the effects of other antidepressant drugs and ECS; b) to conduct more detailed analysis of contribution of the 5-HT_2 and 5-HT_{1A} receptors in the described phenomenon; and c) to establish the role of pre- vs. postsynaptic 5-HT mechanisms in the development of antidepressant treatment-induced adaptive processes in limbic 5-HT receptor subpopulations. For those purposes, as a model we have used changes in rats' motility after stimulation with selective serotonergic drugs, 8-OH-DPAT and DOI-HCl, of local 5-HT mechanisms within the limbic nucleus accumbens (NAS). This brain area has a considerable amount of 5-HT and moderate concentrations of 5-HT_2 and 5-HT_{1A} receptors (33,35). The integrative role of neurotransmitter systems of the NAS in transmitting signals from the hippocampus to the ventral pallidal areas and the brain stem mesencephalic locomotor region has been suggested by some authors (38). The NAS is considered the place where "motivation gets translated into action" (21), as reflected by changes in animals motor behavior (16,30).

METHOD

Animals and Housing

Male Wistar rats (200 ± 20 g), bought from a licensed breeder, were used in the study. After the operation, the animals were housed individually to a cage (30 × 30 × 20 cm) under a 12 L : 12 D cycle (lights on at 0600 h), and at constant temperature, with free access to food and tap water.

Surgery

The rats were operated upon under ketamine anesthesia. The sockets with two stainless steel guide cannulae (0.7 mm external diameter, 0.5 mm internal diameter, 15.0 mm long) were implanted stereotaxically 1.5 mm above the nucleus accumbens septi (A 9.5 mm, V 5.5 mm, L 1.5 mm, incisor bar 5.0 mm above the i.a.l.) according to Pellegrino et al. (28), and fixed to the skull with jewelry screws and dental acrylic cement. Seven to 10 days later the rats were subjected to behavioral testing.

Microinjections

Intracerebral injections of drugs were given using Hamilton microsyringes connected via polyethylene tubings with two metal needles (0.3 mm external diameters). The injection needles were lowered 1.5 mm below the tip of the guide cannula. Solutions were administered bilaterally over 60 s. The injection needle remained in place for the additional 30–60 s before it was removed and the stylet replaced. Behavioral tests were started 5 min after drug injection.

Drugs and Treatments

The following drugs were used in the experiment: 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT, Research Biochemicals, Natick, MA), buspirone (Bristol Myers, England), (±)DOI-hydrochloride (DOI, Research Biochemical Natick, MA), alpha-methyl-5-hydroxytryptamine maleate (alpha-m-5-HT, Research Biochemical, Natick, MA), ritanserin (Research Biochemical, Natick, MA), NAN-190 hydrobromide (Research Biochemical, Natick, MA), desipramine hydrochloride (Ciba-Geigy, Switzerland), citalopram hydrochloride (H. Lundbeck A/S, Denmark). For microinjections, all drugs were dissolved in sterile water immediately before administration, and injected in a volume of 0.5 μl/site. Control rats received 0.5 μl of bidistilled water. Each animal was injected only twice, at the commencement and termination of the experiment. Desipramine and citalopram were given per os as a water solution in a dose of 10 mg/kg daily, two times at 0800 h and 1500 h, for 21 days. The rats were examined (local drug application and open field test) 24 h after the first day of antidepressant administration (acute treatment) and 24 h after the last dose (chronic treatment). In a separate experiment NAN-190 and ritanserin were given intra-NAS 5 min prior to local injections of appropriate 5-HT receptor agonists, and 10 min before behavioral testing.

Electroconvulsive Shocks

ECS (200 mA, 0.3 s, 50 Hz) were applied every second day without anaesthesia, through ear electrodes. Control rats were subjected to the identical procedure except that no electric current was delivered. Twenty-four hours after the first (acute) and fifth (chronic) ECS application the rats were subjected to the microinjections and behavioral testing.

5,7-DHT Lesions

Each animal was pretreated with an intraperitoneal injection of desipramine (Sigma, St. Louis, MO) at the dose of 25 mg/kg 60 min before intracerebroventricular injection of 5,7-dihydroxytryptamine creatinine sulfate (Sigma) to prevent uptake of 5,7-DHT into the noradrenergic terminals. Rats were anesthetized with ketamine and placed in a stereotaxic apparatus. Lesioned animals received unilateral intraventricular infusion of 5,7-DHT (250 μg of the free base in 10 μl 0.9% NaCl solution containing 0.2% ascorbic acid) through a Hamilton syringe (coordinates: A −1.2 mm to bregma, V 3.5 mm, L 1.5 mm; according to the atlas of Pellegrino et al. (28). Control animals received an equivalent infusion of vehicle. Each infusion took place over a 2 min period. Immediately afterwards, the rats were moved to another stereotaxic apparatus and they were implanted with two metal guide cannulae into the NAS, as described in the Method section.

Open-Field Test

The apparatus designed by COTM Bialystok consisted of four white square arenas (40 × 40 cm) bound by a 30 cm high Plexiglas wall and equipped with 16 parallel infrared photocell beams on the × and 16 on the Y axis, 2 cm above the floor. The photocell beams divided floor arena into 16 equal squares; 12 peripheral and 4 central. Information from the arena was stored every 0.2 s and analyzed by a computer program after 10 min-long session. The behavioral pattern

recorded was the distance covered by a rat during experimental session. The test was carried out in a dimly lit room between 0900 and 1100 h under white noise conditions (75 dB).

Biochemical Analysis

Immediately following the conflict experiment rats were sacrificed by decapitation and the brains were dissected according to Glowinski and Iversen (10) into the hippocampus and limbic forebrain (including the NAS, olfactory tubercles, the amygdala, septum). The HPLC system consisted of a Shimadzu LC-9A pump, with programmable flow rate, equipped with a 20 μl injection loop (Rheodyne, CA). Separation of monoamines and their metabolites was obtained on a Nucleosil 7 C-18 column (Machery-Nagel, Germany) thermostated at 32°C in Shimadzu CTO-6A column oven. Electrochemical detector (Shimadzu L-ECD-6A) was set at +0.8 V potential vs. calomel reference electrode. The mobile phase was: citric

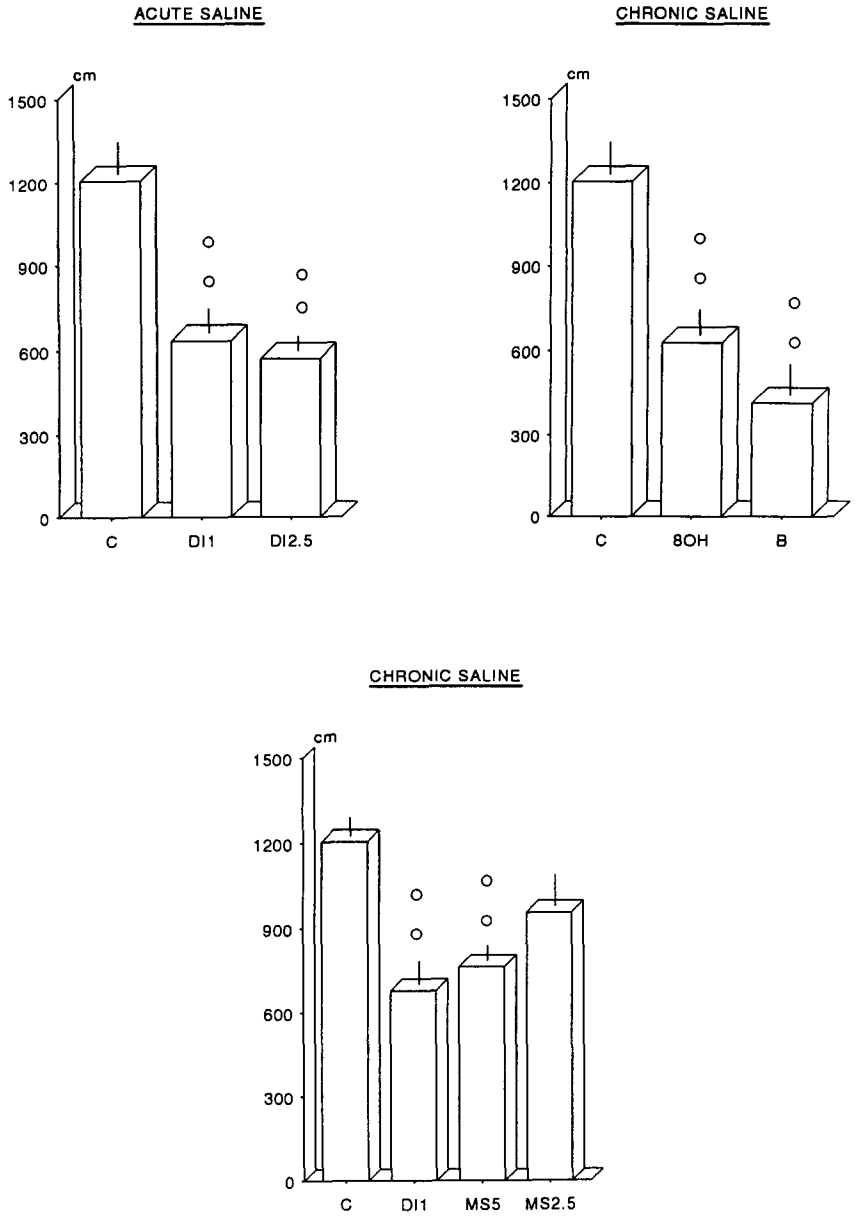

FIG. 1. The effect of intra-NAS injections of serotonergic agonists on motor behavior of rats subjected to acute and chronic administration of saline. The data are shown in cm as mean values ± SE. The number of rats in groups varied between 7-9. C—control, vehicle microinjected rats; DI—DOI-HCl (1 and 2.5 μg), 8OH—8-OHDPAT (10 μg); B—buspirone (5 μg); MS—alpha-methyl-5-HT (2.5 and 5 μg). Acute saline—rats given saline orally only once and examined 24 h later. Chronic saline—rats treated chronically with saline per os for 21 days and microinjected 24 h after. ○—differs from control. ○○—$p < 0.01$.

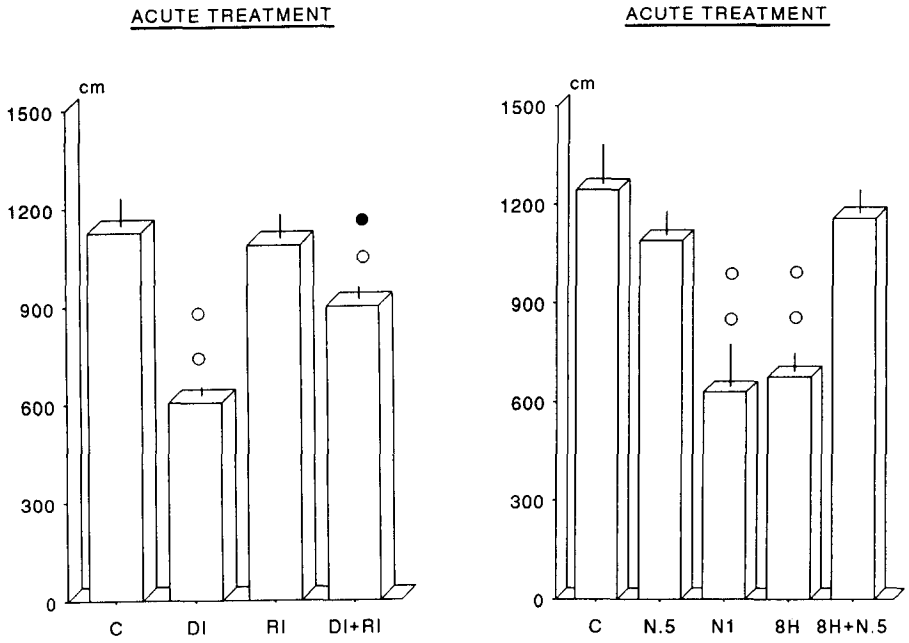

FIG. 2. The influence of serotonergic receptor antagonists on the effects of 8-OHDPAT and DOI in the open field, after intra-NAS drug injections. The number of rats in groups varied from 7 to 11. C—control; DI—DOI-HCl (1 μg); RI—ritanserin (2.5 μg); N—NAN-190 (0.5 and 1 μg); 8H—8-OHDPAT (10 μg). ●—differs from DI group. ○,●—$p < 0.05$. For other explanations see Fig. 1.

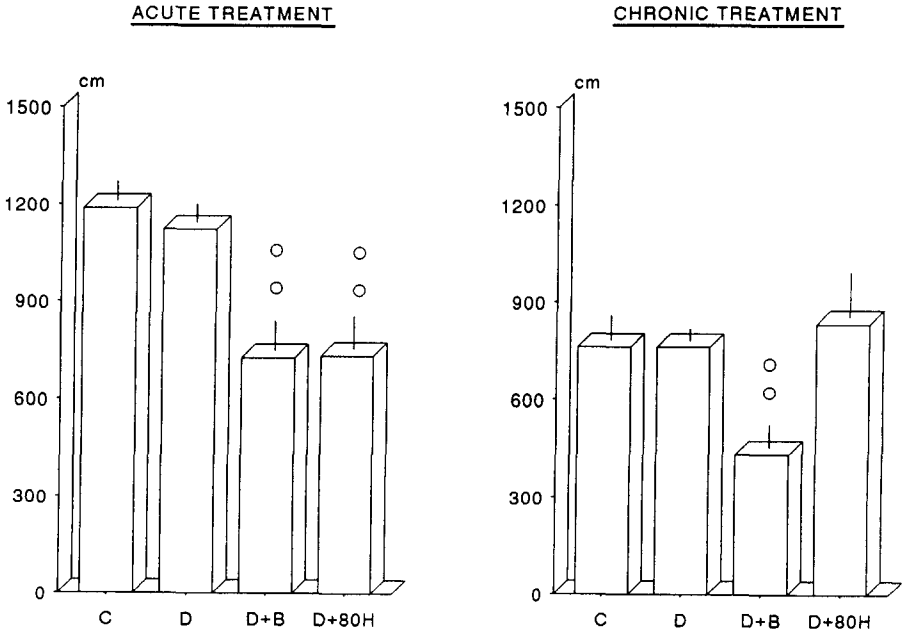

FIG. 3. The effect of acute and chronic treatment of rats with desipramine (D) on the locomotor effects of intra-NAS injected buspirone and 8-OHDPAT. The number of rats in groups varied from 7 to 10. B—buspirone (5 μg); 8OH—8-OHDPAT (10 μg). For other explanations see Fig. 1.

acid (7.5 g/l); $Na_2HPO_42H_2O$ (5 g/l); $EDTANa_22H_2O$ (10 mg/l); octane sulphonic acid (180 mg/l); methanol (12.5% v/v). The flow was programmed from 1.0 to 1.2 ml/min over 18 min for each analytical run. The mobile phase was continuously degassed with helium. Integration of the chromatograms was performed with Shimadzu C-R4AX Chromatopac computing integrator. Dihydroxybenzylamine (DHBA) was used as an internal standard. Sample preparation: tissue sections were immediately frozen and kept at −80°C until used. Frozen tissue sections were homogenized in 15 vol of ice-cold 0.05 M perchloric acid with internal standard added. Homogenates were centrifuged at 15000 × *g* and filtered through 0.22 μ membranes (Millipore, USA).

Histological Analysis

All animals, with exception of those used in biochemical analysis, were sacrificed after the final testing day, their brains were removed, and stored in 5% formalin solution. The frozen tissue was dissected into slices and the place of injection inspected with Meoflex (×40). This apparatus is comprised of a magnifying glass and a slide projector.

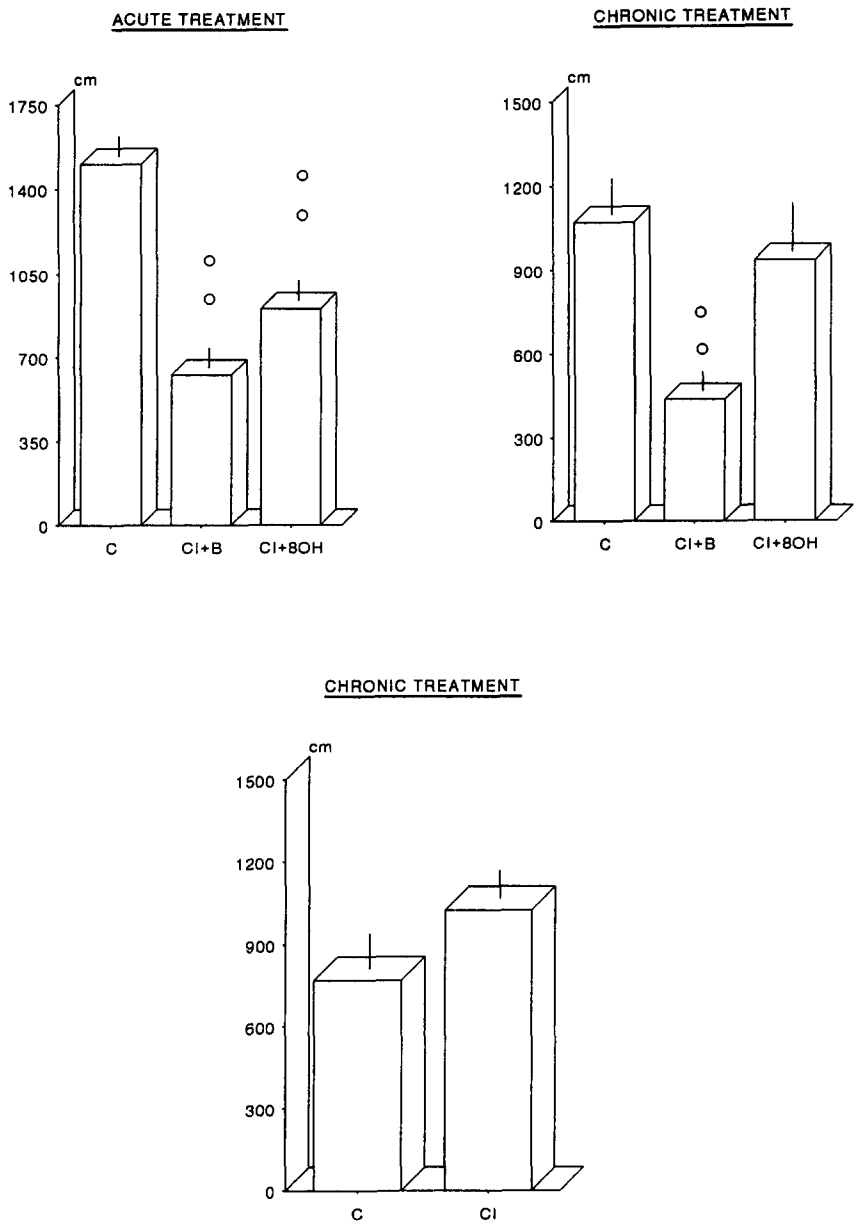

FIG. 4. The effect of acute and chronic treatment of rats with citalopram (CI) on the locomotor effects of intra-NAS injected buspirone and 8-OHDPAT. The number of rats in groups varied from 8 to 10. B—buspirone (5 μg); 8OH—8-OHDPAT (10 μg). For other explanations see Fig. 1.

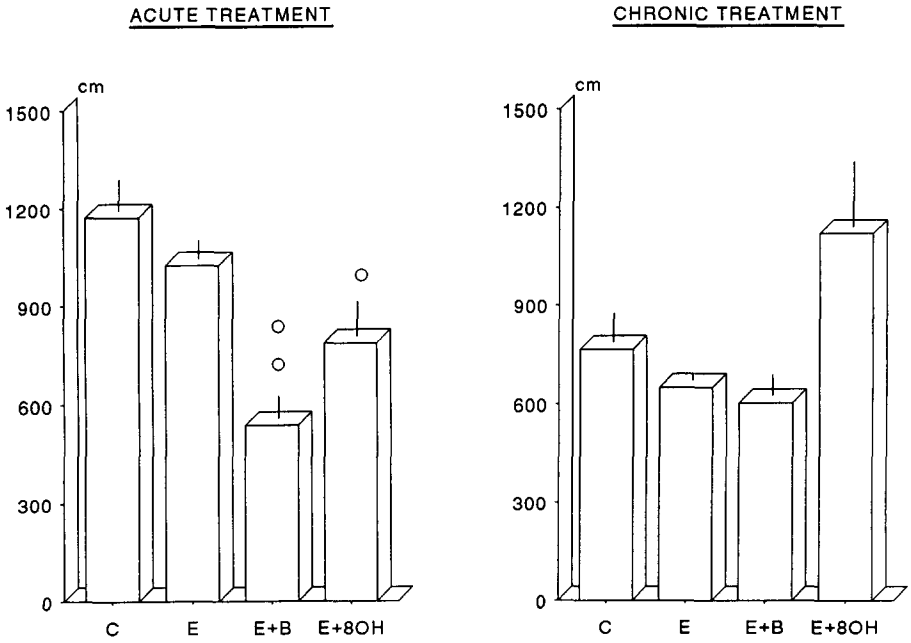

FIG. 5. The effect of acute and chronic administration of ECS (E) on the locomotor effects of intra-NAS injected buspirone and 8-OHDPAT. The number of rats in groups varied from 6 to 9. B—buspirone (5 μg); 8OH—8-OHDPAT (10 μg). For other explanations see Fig. 1.

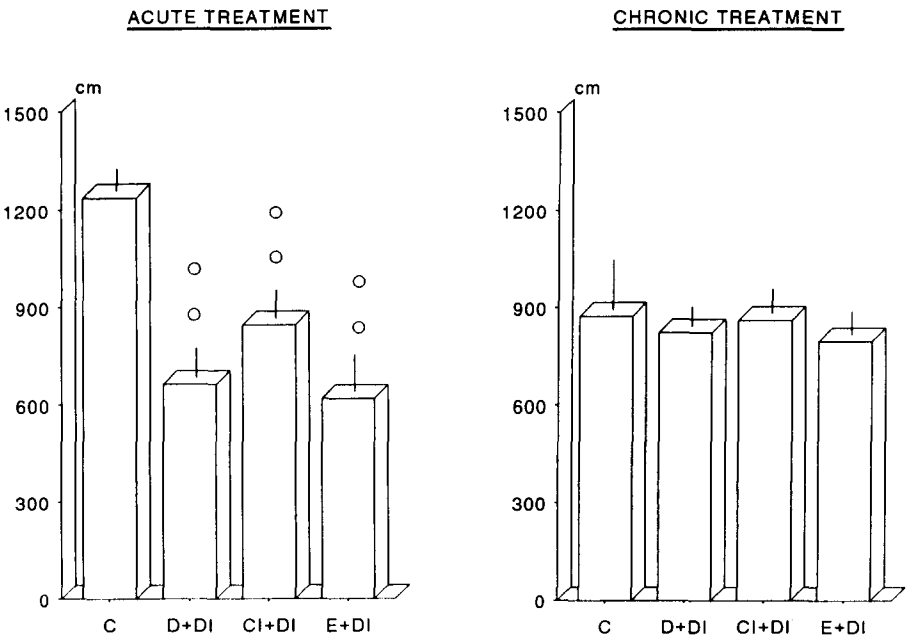

FIG. 6. The effect of acute and chronic treatment of rats with desipramine (D), citalopram (CI), and ECS (E) on the locomotor effects of intra-NAS injected DOI-HCl. The number of rats in groups varied from 8 to 11. DI—DOI-HCl (1 μg). For other explanations see Fig. 1.

TABLE 1

THE EFFECT OF CHRONIC TREATMENT OF RATS WITH CITALOPRAM (Cl), DESIPRAMINE (D) AND ELECTROCONVULSIVE SHOCKS (E) ON THE CONCENTRATION OF MONOAMINES, 5-HIAA AND HVA IN THE RAT LIMBIC FOREBRAIN

	NA	DA	5-HIAA	HVA	5-HT
C (n = 10)	367.3 ± 19.1	414.7 ± 25.6	333.8 ± 14.6	59.8 ± 2.1	528.3 ± 24.1
Cl (n = 9)	381.5 ± 20.3	393.5 ± 11.0	399.8 ± 16.2*	64.5 ± 5.7	525.7 ± 19.3
D (n = 9)	368.6 ± 12.5	407.2 ± 21.3	355.0 ± 12.6	62.5 ± 5.3	536.1 ± 18.2
E (n = 8)	352.2 ± 17.1	462.2 ± 35.4	373.8 ± 15.3	65.1 ± 7.5	512.6 ± 18.5

The data are shown in ng/g tissue as mean values ± SE. The number of rats is shown in the brackets.
*Differs from C (control group); *$p < 0.05$.

Statistical Analysis

The data are shown as mean ± SEM. Statistical analysis was made with the one-way ANOVA followed by Student's t-test.

RESULTS

Histological analysis confirmed the injection sites within the NAS, in its anterio-medial part close to the commissurae anterior. The site of injection and extent of tissue damage was essentially the same as observed in our previous experiments [cf. (30)]. Only animals with their injection sites within the limits of the nucleus accumbens (about 85%) were used in the statistical analysis.

Control experiments showed that 8-OHDPAT, buspirone, alpha-m-5-HT, and DOI administered locally to the NAS, significantly inhibited rat motor behavior in the open field test (Figs. 1, 2). Chronic treatment of rats with saline (3 weeks) did not affect ability of the aforementioned drugs to interfere with motor activity regulation (Fig. 1). The effect of DOI and 8-OHDPAT could be attenuated or antagonized by appropriate receptor antagonists ritanserin and NAN-190, respectively (Fig. 2). NAN-190, in a higher dose of 1 μg, significantly inhibited rat behavior on its own (Fig. 2). Chronically administered antidepressant drugs and repeated ECS antagonized suppression of rats motility after local injection of 8-OHDPAT (Figs. 3, 4, and 5). The drugs and ECS were ineffective in this respect when given on a acute basis. The buspirone motor effect was blocked by repeated ECS only (Fig. 5). Antidepressant treatment did not change rat behavior on its own. As in the part of the experiment with 8-OHDPAT, antidepressants and ECS attenuated the DOI-induced hypolocomotion, after chronic administration only (Fig. 6). Prolonged treatment of rats with desipramine, citalopram, and ECS did not affect the concentrations of monoamines and their metabolites in the limbic areas examined 24 h after the last dose (Table 1). The only exception was a small but significant increase of 5-HIAA level after citalopram. Neurotoxin-induced lesions depleted almost totally forebrain concentrations of 5-HT and 5-HIAA, leaving NA and DA intact (Table 2). In these rats, the locomotor effects of intra-NAS administered 8-OHDPAT and DOI were not changed (Fig. 7). However, serotonergic lesions abolished the attenuating effect of chronic desipramine treatment on locomotor inhibition following 8-OHDPAT and DOI injections into the NAS (Fig. 8 and 9).

DISCUSSION

In agreement with our previous studies, it has been shown that both postsynaptic 5-HT_{1A} and 5-HT_2 receptors contribute to changes in rats' motility observed following intra-NAS microinjections of 5-HT (30). The NAS may also be considered a neuroanatomical substrate for motor effects of peripherally administered 8-OHDPAT and DOI (9,14,32). Probably, local 5-HT innervation interacts with dopaminergic neurons in regulating rat motor activity, because intra-NAS injection of 5-HT was found to antagonize d-amphetamine-induced locomotion (16). It is possible that accumbens postsynaptic 5-HT_{1C} receptors contribute to motor regulation as well. All drugs used in this part of the study—DOI, alpha-m-5-HT, and ritanserin—are mixed 5-HT_2 and 5-HT_{1C} receptor agonists and antagonist, respectively (15). Actually, other 5-HT_{1C} receptor agonists, MCPP and TFMPP, have been shown to inhibit locomotor activity in rats (17). The behavioral effects of 8-OHDPAT and DOI are apparently postsynaptic in nature, because they were not affected by potent depletion of 5-HT in the limbic forebrain after 5,7-DHT. Similarly, it was recently reported that intracerebroventricular injection of 5,7-DHT or

TABLE 2

THE EFFECT OF 5,7-DHT LESIONS ON CONCENTRATIONS OF MONOAMINES AND 5-HIAA IN THE RAT LIMBIC FOREBRAIN

	NA	DA	5-HIAA	5-HT
S (n = 10)	351.9 ± 13.3	482.6 ± 28.8	258.8 ± 4.0	386.4 ± 14.8
L (n = 9)	392.9 ± 4.9	511.4 ± 14.3	28.2 ± 3.5*	8.6 ± 2.9*

The data are shown in ng/g tissue as mean values ± SE.
S—sham rats; L—neurotoxin lesioned rats. The number of rats is shown in the brackets.
*Differs from S (control group); *$p < 0.001$.

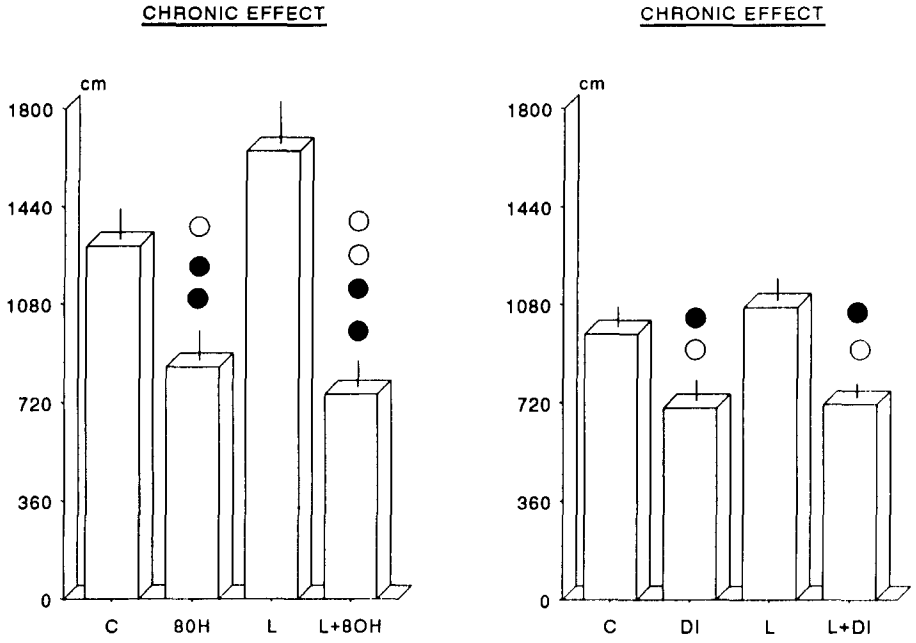

FIG. 7. The influence of 5,7-DHT-lesions (L) and chronic administration of saline on the effects of 8-OHDPAT (80H, 10 μg) and DOI-HCl (DI, 1 μg) on rat motor behavior, after intra-NAS drug application. The number of rats in groups varied between 8 to 10. ○—differs from control group; ●—differs from L group. ○,●—$p < 0.05$; ○○, ●●—$p < 0.01$. For other explanations see Fig.1.

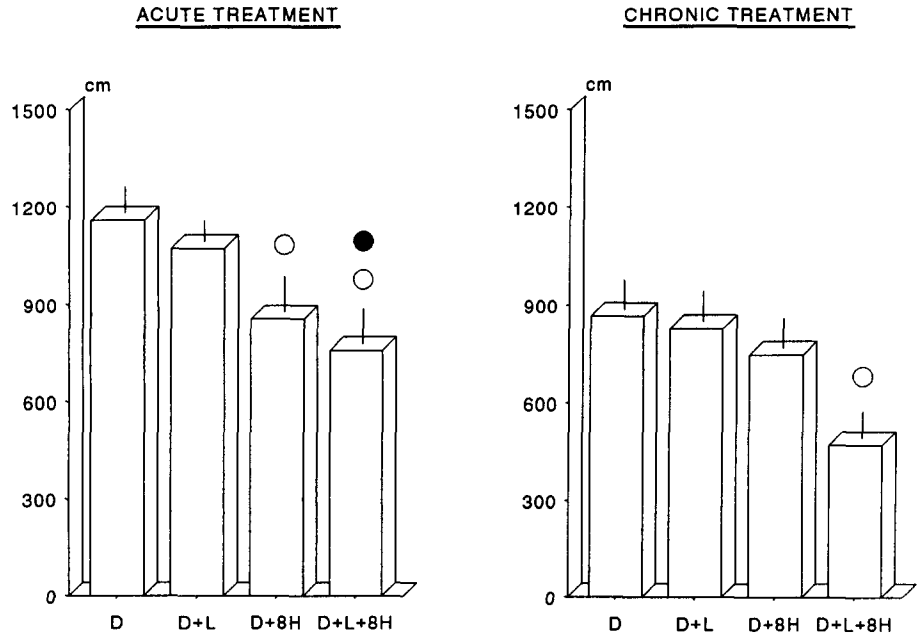

FIG. 8. The effect of acute and chronic treatment of intact or 5,7-DHT-lesioned rats (L) with desipramine (D), on the motor effects of intra-NAS injections of 8-OHDPAT (8H, 10 μg). The number of rats in groups varied from 7 to 10. ○—differs from control (C); ●—differs from D + L group. ○,●—$p < 0.05$. For other explanations see Fig. 1.

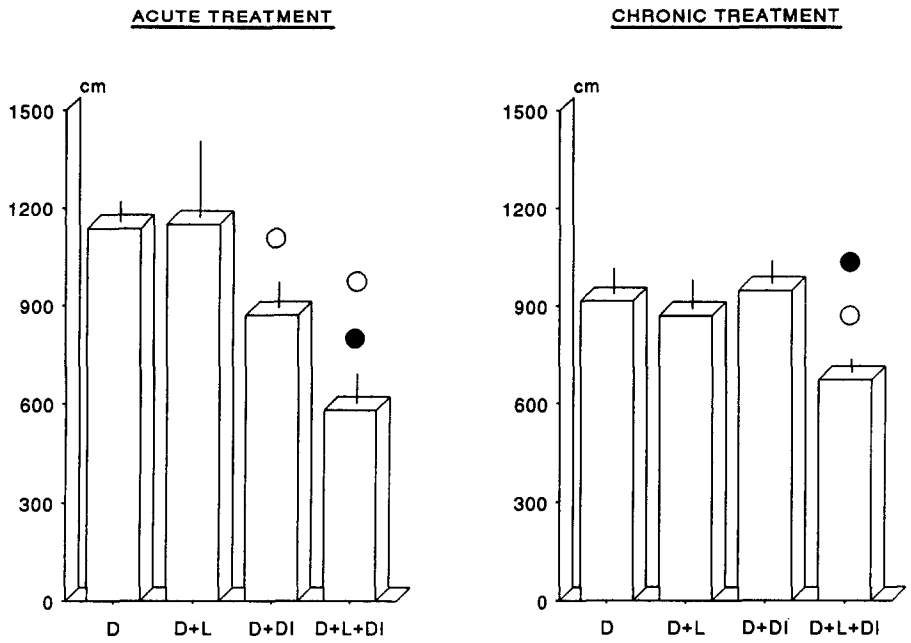

FIG. 9. The effect of acute and chronic treatment of intact or 5,7-DHT-lesioned rats (L) with desipramine (D), on the motor effects of intra-NAS injections of DOI-HCL (DI, 1 μg). The number of rats in groups varied from 8 to 11. ○—differs from control (C); ●—differs from D + L group. ○,●—$p < 0.05$. For other explanations see Fig. 1.

systemic administration of PCPA changed neither 8-OHDPAT-induced lower lip retraction nor DOI-produced head shake response (1). In rats injected intracisternally with 5,7-DHT, DOI still significantly reduced locomotor activity (32). In autoradiographic study, treatment of rats with 5,7-DHT did not cause any change in binding of ^{3}H-DPAT to 5-HT_{1A} receptors in the rat forebrain (13). This data demonstrate postsynaptic localization of 5-HT_{1A} receptor subtype in the limbic structures of the brain. The putative 5-HT_{1A} receptor antagonist NAN-190 while significantly attenuating behavioral effects of 8-OHDPAT, depressed rat motility by itself, at the higher dose tested. Accordingly, in the electrophysiological model NAN-190 was found to reduce neuronal activity in a concentration-dependent manner in the rat dorsal raphe nucleus, thus mimicking the action of the full 5-HT_{1A} receptor agonist 8-OHDPAT (12). However, the effects of 8-OHDPAT could be antagonized when concentration of NAN-190 was too low to produce a marked inhibition. Based on this experiment it was concluded that NAN-190 is a partial 5-HT_{1A} receptor agonist which, due to different intrinsic activity and an interference with receptor occupancy, at some doses may change biological response to a full agonist.

Overall, these data point at the accumbens postsynaptic 5-HT_{1A} and 5-HT_2 receptors (and/or 5-HT_{1C} receptor) as mediators of the influence of local 5-HT innervation on the processes of motor activity regulation. Because locomotor inhibition seems to be related to activation of both receptor subtypes within the NAS, this behavioral reaction can be, therefore, used as a specific tool to study at the functional level, adaptive processes that occur in 5-HT receptor subtypes, in the course of chronic antidepressant treatment.

The present data corroborate and extend our previous findings showing an attenuation by chronic desipramine administration of behavioral depression after 5-HT and quipazine microinjections into the NAS (30). Prolonged but not acute treatment of rats with desipramine—preferentially inhibiting noradrenaline uptake, citalopram—selectively inhibiting 5-HT uptake, and ECS—releasing neurotransmitters, abolished behavioral suppression after local 8-OHDPAT and DOI injections. The mechanism of this phenomenon—common to all kinds of applied antidepressant treatment—remains obscure. Only the part of the results obtained with DOI may be explained by concomitantly occurring decrease in the number of 5-HT_2 receptors. This is a robust biological characteristic of a majority of AD, confirmed in many laboratories [cf. (37)]. It is also well established that oppositely to AD, ECS induce an increase in the 5-HT_2 number, in the rat frontal cortex [cf. (29,37)]. The present data indicate that in spite of these disparate receptor effects, both ECS and AD can similarly affect some central processes, on the functional level. Other possibilities exist that either changes in 5-HT_2 receptors in the limbic area are not important for antidepressive action, or that there are local differences in the reactivity to antidepressant treatment of this receptor population. Recently, it was demonstrated that the effects mediated by 5-HT_2 receptors (L-5-HTP-induced twitches in mice and fenfluramine-, m-CPP-, and TFMPP-induced hyperthermias in rats) were reduced by chronic fluoxetine (18). Fluoxetine given repeatedly attenuated also the m-CPP-induced hypoactivity in rats (a 5-HT_{1C} effect) (18). The part of the experiment with 5,7-DHT and desipramine demonstrates that the discussed effects of antidepressant treatment depend on intact presynaptic terminals of brain 5-HT system. Accordingly, in an another behavioral model, 5,7-DHT lesions significantly weakened antidepressant-evoked reduction in 5-HT_2 receptor-mediated quipazine-induced head shake response in rats (8).

As far as postsynaptic 5-HT_{1A} receptors are concerned, most of the recent data indicate no change in their number or affinity after chronic antidepressant treatment [cf. (25)], though previously both an increase or decrease in 5-HT_{1A} receptor concentration has been reported (27,36). More uniformly, the results of second messenger studies (inhibition of adenylate cyclase coupled to 5-HT_{1A} receptor, or the inhibition by 5-HT of carbachol-stimulated formation of inositol phosphate) indicate receptor subsensivity after AD administration (23–25). Actually, behavioral (serotonin syndrome) and hypothermic response to 8-OHDPAT in rats (a presynaptically mediated reaction), were shown to be significantly reduced after various AD and ECS (11). There are also some data indicating that adaptive processes occur in the population of postsynaptic 5-HT_{1A} receptors only, and may not concern presynaptically localized 5-HT_{1A} autoreceptors (2,20). It should be stressed, however, that negative results have also been observed with chronic administration of AD altering neither the ^{3}H-OHDPAT binding sites on brain membranes, nor the inhibition of forskolin-stimulated adenylate cyclase by 5-HT in the rat hippocampus (26). As in the case of 5-HT_2-mediated reaction, the effect of desipramine on 8-OHDPAT-induced locomotor depression was abolished by serotonergic lesions. It appeared, therefore, that intact presynaptic stores of 5-HT are necessary for expression of antidepressant-induced changes in the accumbens 5-HT_{1A} receptors-related behavior. In contrast to 8-OHDPAT, the effect of buspirone appeared unresponsive to chronically administered desipramine and citalopram. This finding corroborates our previous data on desipramine vs. intra-NAS buspirone interaction (30). The reason for these disparate findings obtained with 8-OHDPAT and buspirone are not clear. It does not seem that the lower efficacy of buspirone at 5-HT_{1A} receptors could fully account for this phenomenon. Rather, the distinct partial agonist properties of buspirone for dopaminergic D_2 receptors and antidopaminergic potency revealed in some behavioral tests, may explain its profile of action (34). It is possible that the competition between dopamine and the drug with lower intrinsic activity at accumbens D_2 receptors (in fact, an antidopaminergic action) may add to behavioral suppression already present after stimulation by buspirone of 5-HT_{1A} receptors. This dual mechanism of buspirone effect may contribute to its resistance to antidepressant treatment. However, such explanation is disputable because it is well recognized that chronic antidepressant treatment enhances the activity of mesolimbic dopaminergic system, thus attenuating the behavioral effects of dopaminergic antagonists (4).

The influence of antidepressant treatment on 5-HT mechanisms within the NAS has not been reflected by changes in biochemical parameters, examined in the present study. A small but significant increase in 5-HIAA concentration in the limbic forebrain after chronic citalopram treatment is an unexpected finding. The turnover index (F, the ratio of 5-HIAA and 5-HT levels, calculated for every sample) was not, however, significantly different from control values [citalopram treated rats $F = 0.76$, control animals $F = 0.64$, $t(10) = 1.86$, $p < 0.09$]. The available data indicate reduction or no change in concentration of indoles after continued administration of selective 5-HT uptake inhibitors or releasers (3, 7). Nevertheless, in electrophysiological studies it was recently observed that long-term citalopram enhances 5-HT neurotransmission in the brain, probably by desensitizing both the terminal and somatodendritic 5-HT autoreceptors (5). Chronic citalopram led also to a significant increase of the basal synthesis of 5-HT in the rat frontal cortex (as shown by changes in accumulation of 5-HTP) (22). The mechanism of this phenomenon may involve adaptive processes in the 5-HT autoreceptors.

In sum, the present data indicate that the activity of 5-HT system related to the 5-HT_{1A} and 5-HT_2 receptors in the limbic nucleus, is diminished after chronic antidepressant treatment. This effect of AD and ECS concerns nervous processes linked with the function of postsynaptically localized 5-HT receptor subtypes, and it depends on intact presynaptic 5-HT innervation. The disinhibitory influence of antidepressant treatment on rat behavior in the applied model contributes significantly to the aforementioned concept of antidepressant action of drugs and ECS (31).

ACKNOWLEDGEMENT

This work was supported by a grant from the State Committee for Scientific Research (KBN), Grant No 40992 91 01.

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