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Serotonergic Mechanisms in the Nucleus Accumbens Affected by Chronic Desipramine Treatment

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PŁAŹNIK, A., R. STEFAŃSKI, W. PAŁEJKO AND W. KOSTOWSKI. *Serotonergic mechanisms in the nucleus accumbens affected by chronic desipramine treatment.* PHARMACOL BIOCHEM BEHAV **39**(1) 43–48, 1991.—The effects of repeated treatment of rats with desipramine on 5-HT mechanisms within the nucleus accumbens (NAS) have been studied in a functional model. Local microinjections of 5-HT, quipazine as well as 5-HT_{1A} receptor agonist buspirone, 8-OH-DPAT and NDO-008, inhibited rat locomotor activity in the open-field test. The effect of 5-HT and buspirone was blocked by serotonergic receptor antagonists methysergide and cyanopindolol, respectively. Chronic, but not acute treatment of rats with desipramine (10 mg/kg, PO, twice a day for 21 days, tests were performed 24 h after the last dose) significantly attenuated behavioral depression after 5-HT and quipazine microinjections, while the effect of buspirone was left unchanged. On the basis of present data, it may be concluded that whereas both accumbens 5-HT_{1A} and 5-HT_2 receptors appear to be important to regulation of animals' motility, only 5-HT_2 receptors seem to be the most likely targets of antidepressive treatment. These data, along with previously reported changes in limbic noradrenergic and dopaminergic activity after antidepressive treatment, may explain the energizing influence of drugs and electroconvulsive shocks on psychomotor retardation, a part of endogenous depression.

Serotonin Quipazine 5-HT_{1A} receptor agonists Nucleus accumbens Desipramine Microinjections Open field Rats

CONTRIBUTION of 5-HT_{1A} receptor-related mechanisms to the central effects of antidepressive treatment is a matter of controversy. Biochemical data demonstrate no change in 5-HT_1 receptor binding after chronic administration of tricyclic antidepressants (20, 33, 43, 44). In functional studies no modification or attenuation of 5-HT_{1A} receptor-mediated central processes, depending on the specific model reaction, was found (13, 14, 35). In several animal models 5-HT_{1A} receptor agonists have also been claimed to have antidepressant potency (4, 6, 12, 18, 19). It has been shown that prolonged treatment of rats with tricyclics or monoaminooxidase inhibitors decreases the number of 5-HT_2 receptor-binding sites labelled with specific agonists and antagonists [cf. (43)]. This phenomenon was not, however, followed by decrease in 5-HT_2 receptor function (20, 43, 44). On the contrary, increase of these receptors' activity was reported in several functional studies (20, 24, 33, 43, 44). Furthermore, electroconvulsive shocks produce the opposite effect, i.e., the rise in the 5-HT_2 receptor number and enhancement of the 5-HT_2 receptor-mediated central processes [cf. (44)]. This short overview of the data clearly documents the lack of a single theory explaining the 5-HT involvement in the antidepressive treatment.

The aim of the present study was to compare in a functional model the influence of chronic treatment of rats with potent antidepressant desipramine on central processes mediated by serotonin- and 5-HT_{1A}-receptor agonists. For that purpose as a model we have used changes in rats' motility after chemical stimulation of local 5-HT mechanisms within the limbic nucleus accumbens (NAS) (17,30). This limbic area has a considerable amount of 5-HT and high to moderate concentrations of 5-HT_{1A} receptors (25, 28, 36). The specificity of the effects of 5-HT and buspirone was proved with specific antagonists and by comparison with other drugs acting on serotonergic receptors. It is important to stress that the experiment was performed in two parts, 3 years apart. Because of that there are some differences in the procedure of collecting behavioral data: direct observation of animals' motility in the open field for 5 min versus the number of photobeam breaks in the automated open fields in 30 min (divided into six 5-min periods of time). All the other experimental parameters like strain of rats, dosage of antidepressant, implantation and injection technique, and the time of behavioral scoring, were the same in both parts. Moreover, since in both parts of the experiment appropriate control groups were applied, it seemed justified to join all these supplementary data in one report.

METHOD

Animals

Rats weighing 200 ± 20 g at the beginning of the experiment were obtained from a licensed breeder. After cannula implanta-

tion all the animals were kept individually in wire-mesh cages (30 × 30 × 30 cm) to avoid damage to the implanted sockets, with food and water ad lib.

Surgery

The implantation of guide cannulas (0.7 mm ext. dia., 1.5 cm long) was performed under light ethyl ether anesthesia. Cannulas were implanted bilaterally with tips 3.0 mm above the nucleus accumbens septi (NAS) (A 9.0 mm, L 1.0 mm, V 3.5 mm below the skull surface) incisor bar on the level of the interaural line (29). Seven days were allowed for recovery after operation.

Drugs

Intracerebral injections of drugs were given with the use of Hamilton microsyringes connected via polyethylene tubings with two disposable needles (0.3 mm external diameter). The injection needles were lowered 3.0 mm below the tip of the guide cannula, i.e., they were aimed at the level of the commissura anterior within the NAS. During the injection rats were restrained manually (60 s). The injection needle remained in place for the additional 60 s before it was removed and the stylet replaced. The following drugs were used in the experiment: serotonin sulphate (5-HT, Serva), quipazine maleate (Serva), methysergide maleate (Sandoz), buspirone hydrochloride (Mead Johnson), 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, Troponwerke), 3-dipropylamino-5-hydroxychroman (NDO-008, Astra) (40). All drugs were dissolved in sterile water immediately before administration, and injected in a volume of 0.5 μl/side. Control rats studied in parallel received 0.5 μl of bidistilled water. The doses were calculated on the basis of a salt form of the drugs. Desipramine hydrochloride (DMI, Ciba-Geigy) was dissolved in distilled water and administered in a dose of 10 mg/kg (5 ml/kg) per os, twice a day (0800 and 1500 h) for 21 days. Twenty-four hours after the first (acute treatment) and 21st dose (chronic treatment), the animals were microinjected with drugs and 5 min later subjected to behavioral testing. Control rats studied in parallel received 5 ml/kg of a distilled water per os. Each animal was microinjected and tested 2 times, with a 3-week interval for antidepressant or water treatment.

Open-Field Tests

The experiment was performed in two parts with 3-year intervals. The difference between both parts concerned the way in which behavior was scored. All other parameters including strain of rats, dosage of antidepressant, implantation and injection procedure were the same. In the first part (serotonin, quipazine, methysergide) behavioral data were collected by direct observation of animals' motility in the open field for 5 min, starting 5 min after microinjection. Open-field performance was examined in an arena (80 × 80 × 20 cm) divided into 16 squares, in a sound-proof chamber and under white noise conditions. The locomotor activity of rats was measured by the number of squares crossed during a 5-min observation period. The experimenter observed the animals through a one-way window. In the second part of the experiment (buspirone, cyanopindolol, 8-OH-DPAT, NDO-008), the exploratory locomotion of rats was being examined immediately after injection for 30 min, in 5-min periods of time. The measurements were carried out automatically, in a round arena (diameter 80 cm, 40 cm high wall) equipped with 3 symmetrically placed photocells, in a sound-proof chamber, under white-noise conditions, always at the same time of a day (9:00 a.m.–1:00 p.m.). The animals were habituated to handling for several days before the start of the experiment. The behavior of rats was additionally monitored by the TV system from an adjacent room.

Histological Analysis

At the end of the test, all the rats were sacrificed, their brains fixed in 5% formalin, and dissected out into 40 μm slices. Checks were then made for injection placements with the aid of the Meoflex (42×) (this apparatus is a combination of a magnifying glass and a slide projector).

Statistical Analysis

All data are expressed as mean ± S.E.M. Statistical analysis was made with one-way and two-way ANOVA followed by Duncan's multiple range test for independent measures.

RESULTS

Histological analysis showed that the injection sites were essentially the same as observed in our previous experiment (34), and that they were placed in the anterio-medial part of the NAS, in the close vicinity of the commissura anterior. Only the animals with their injection sites within the limits of the NAS were considered in the statistical analysis. About 10% of animals were rejected due to incorrect placement of injections.

Microinjections of 5-HT dose-dependently decreased rat motility (Fig. 1) in the open field. The effect appeared as quickly as 5 min after administration, and could be observed during the whole 20-min observation period (Fig. 1). However, the difference between control and 5-HT rats did reach the level of statistical significance during the first 5 min only. Quipazine injections likewise depressed rats' motility in a dose-related manner (Fig. 1). The effect of serotonin was absent in animals which were subjected to the simultaneous administration of both serotonin and 5-HT antagonist methysergide (Fig. 2). Two-way analysis of variance showed that there was a significant main effect of 5-HT, $F(1,19)=4.60$, $p<0.05$. However, no significant effect of methysergide, $F(1,19)=2.90$, N.S., and of methysergide × 5-HT interaction was found, $F(1,19)=0.77$, N.S. Chronic but not acute pretreatment of rats with desipramine antagonized the suppressant effect of both 5-HT and quipazine microinjections on locomotion (Figs. 3 and 4). Additionally performed experiments confirmed the specificity of the desipramine effect, since the prolonged treatment of animals with saline only did not change the inhibitory influence of both serotonergic agonists on rat behavior (Figs. 3 and 4, right parts).

Buspirone potently decreased animals' motility (Fig. 5). The same phenomenon was found after 8-OH-DPAT (Fig. 5), and less potently after NDO-008 (Fig. 5) administration. The effect of 8-OH-DPAT was dose-dependent and statistically significant, while in the case of NDO-008 only a similar tendency could be observed. Cyanopindolol in a dose not active by itself applied with buspirone significantly attenuated the inhibitory influence of 5-HT_{1A} receptor agonist on behavior (Fig. 6). Two-way analysis of variance indicated that there was a significant main effect of buspirone, $F(1,26)=11.1$, $p<0.01$, but not of cyanopindolol, $F(1,26)=0.28$, N.S. Significant buspirone × cyanopindolol interaction was found in this experiment, $F(1,26)=5.98$, $p<0.05$. Neither acute, nor chronic pretreatment of rats with desipramine modified the behavioral suppression present after local administration of buspirone (Fig. 7). Two-way analysis of variance showed that there was a significant main effect

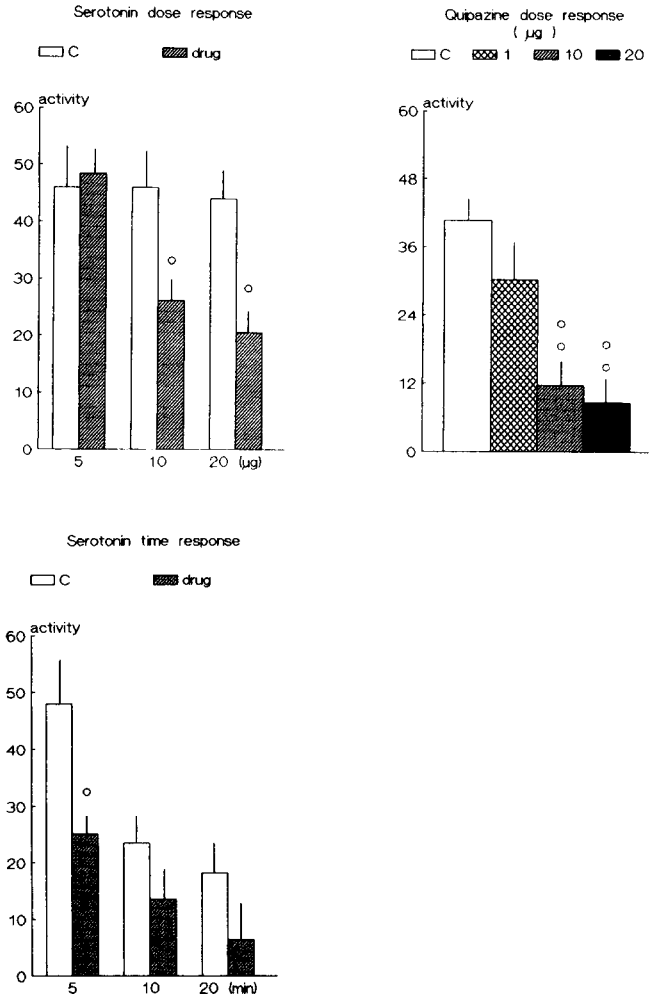

FIG. 1. The effect of intra-accumbens injections of serotonin and quipazine on rat motility in the open field; dose- and time-response study. Data are expressed as mean ± S.E.M. Ordinate: number of squares crossed during 5-min experimental session; abscissa (upper part of the figure): the doses of drugs; abscissa (lower part of the figure): time in min; o: differs from control, o, $p<0.05$; oo, $p<0.01$. Number of rats; serotonin dose-response study: control (C) 5 μg: 8; serotonin (S) 5 μg: 8; C 10 μg: 8; S 10 μg: 8; C 20 μg: 6; S 20 μg: 8; quipazine dose-response study: C 6, quipazine (Q) 1 μg: 6; Q 10 μg: 6; Q 20 μg: 6; serotonin time-response study: C: 8; S 10 μg: 8.

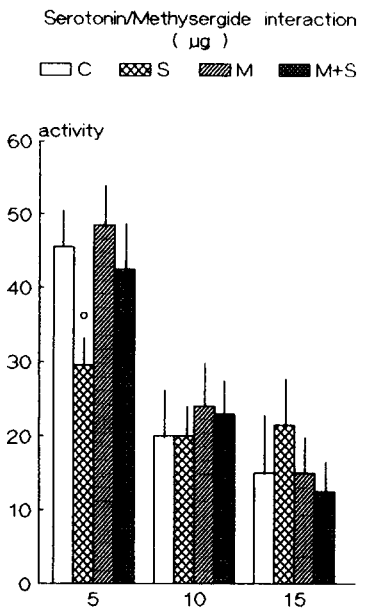

FIG. 2. The effect of intra-accumbens injections of serotonin (10 μg) with methysergide (10 μg) on rat motility in the open field. C: control, S: serotonin, M: methysergide. o, $p<0.01$. Number of rats; C: 5, S: 6, M: 6, M + S: 6. All other abbreviations as in Fig. 1.

of buspirone in animals treated acutely, $F(1,20)=20.48$, $p<0.01$, or chronically, $F(1,28)=82.59$, $p<0.01$, with vehicle or antidepressant. No significant effect of desipramine [acute exp., $F(1,20)=0.27$, N.S.; chronic exp., $F(1,28)=2.12$, N.S.], or of buspirone × desipramine interaction was found [acute exp., $F(1,20)=2.11$, N.S.; chronic exp., $F(1,28)=2.20$, N.S.]. It is important to stress that the statistical analysis performed for each of the 5-min periods of the 30-min experimental session revealed changes or tendencies in rats' behavior similar to that shown in the figures as the total scores of animals' motility.

DISCUSSION

It has been shown previously that microinjections of 5-HT into the NAS inhibited rat motility (30), and antagonized the stimulatory effect on locomotion of dopaminergic agonists (5a,17). The present data corroborate these findings and they further indicate that both 5-HT_2 and 5-HT_{1A} receptors may significantly contribute to this phenomenon. All 5-HT_{1A} agonists studied, except for a newly discovered NDO-008 (40), have

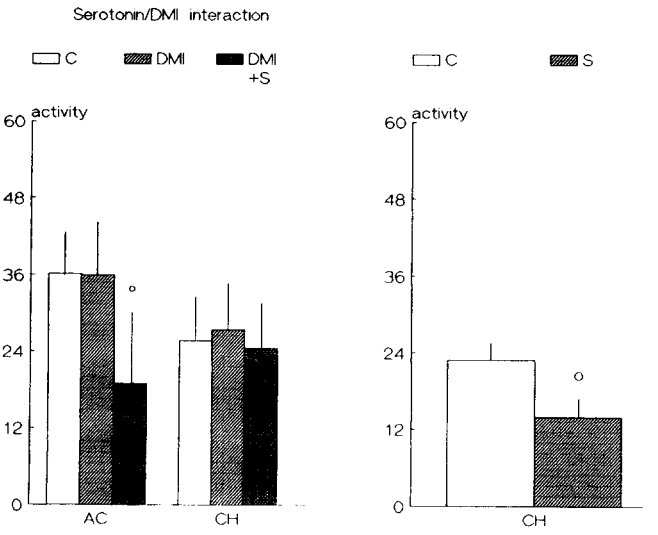

FIG. 3. The effect of acute and chronic treatment of rats with desipramine upon locomotor suppression produced by local injections of serotonin. S: serotonin-treated rats (10 μg), C: control, saline-treated rats, DMI: desipramine-treated rats, AC: acute treatment, CH: chronic treatment. All other abbreviations as in Fig. 1. Number of rats; serotonin versus desipramine interaction: AC C: 8, AC DMI: 8, AC DMI + S: 6, CH C: 12, CH DMI: 7, CH DMI + S: 6; chronic saline versus serotonin treatment: C: 8, S: 10.

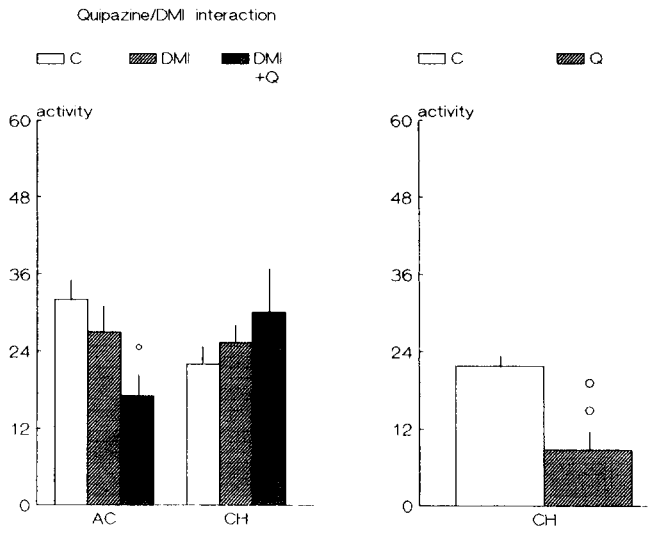

FIG. 4. The effect of acute and chronic treatment of rats with desipramine upon locomotor suppression produced by local injections of quipazine. Q: quipazine-treated rats (10 μg), C: control, saline-treated rats, DMI: desipramine-treated rats, AC: acute treatment, CH: chronic treatment. All other abbreviations as in Fig. 1. Number of rats; quipazine versus desipramine interaction: AC C: 6, AC DMI: 8, AC DMI+Q: 6, CH C: 6, CH DMI: 8, CH DMI+Q: 6; chronic saline versus quipazine treatment: C: 9, Q: 8.

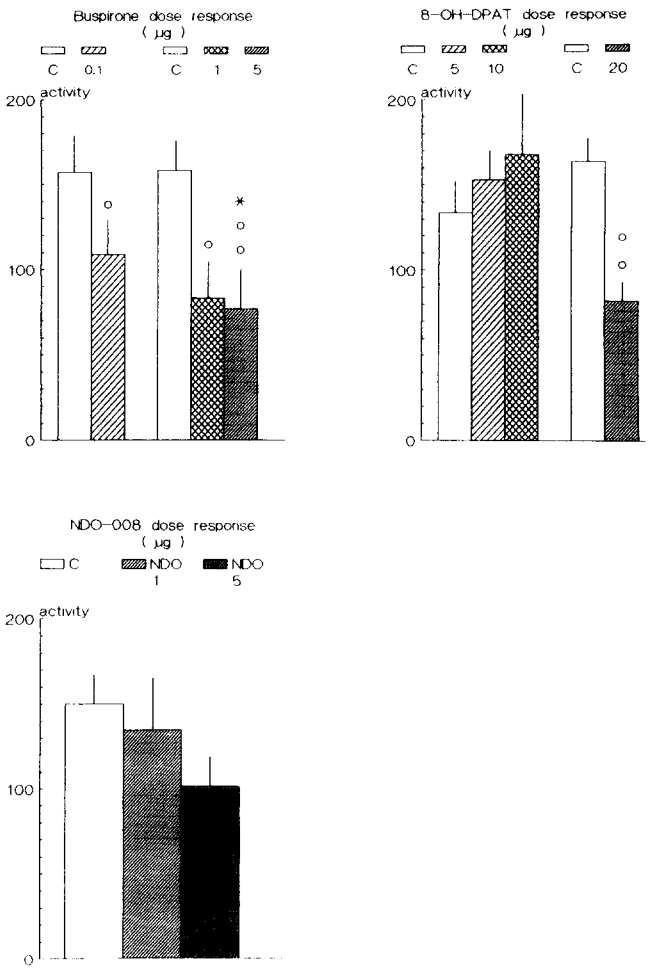

FIG. 5. The effect of intra-accumbens injections of buspirone, 8-OH-DPAT and NDO-008 on rat motility in the automatic open field. All data are shown as mean ± S.E.M. Ordinate: number of photobeam interruptions during 30-min session, C: control, o: differs from control; *differs from buspirone 0.1 μg. o, *$p<0.05$, oo,$p<0.01$. Number of rats; buspirone study, C 0.1: 8, Busp 0.1 μg: 8; C: 8, Busp 1 μg: 7, Busp 5 μg: 8; 8-OH-DPAT study, C 5 μg: 6, 8-OH-DPAT 5 μg: 5, 8-OH-DPAT 10 μg: 6, C 20 μg: 12, 8-OH-DPAT 20 μg: 10; NDO-008 study, C: 6, NDO 1 μg: 4, NDO 5 μg: 6.

significantly attenuated animals' motor activity when given to the NAS. The same behavioral reaction could be observed after peripheral injections of 5-HT_{1A} receptor agonists (7,16). Moreover, the effect of buspirone has been blocked by cyanopindolol—a nonselective 5-HT_{1A} receptor antagonist. This indicates that the antiadrenergic and antidopaminergic properties of buspirone and other 5-HT_{1A} receptor agonists probably are not of importance to the discussed behavioral reaction (2, 10, 15). The lack of influence of chronic DMI on buspirone hypoactivity confirms such a conclusion. Accordingly, it is well recognized that antidepressants enhance the activity of mesolimbic DA system, thus attenuating the behavioral effects of dopaminergic antagonists (5, 23, 43). 5-HT-induced hypokinesia does not appear in rats subjected to the concomitant injections of methysergide, a 5-HT receptor blocker, either. Since methysergide in the brain tissue is about 15 times more potent at displacing binding to the 5-HT_2 receptors than to the 5-HT_1 receptors (K_i value of approximately 7.5 nM), 5-HT effect may be considered as being mediated via 5-HT_2 receptors (22). The same conclusion can be drawn from the part of the experiment with quipazine, a nonselective 5-HT receptor agonist, inhibiting monoamine oxidase and 5-HT reuptake among others (9). All these data point, therefore, at the accumbens 5-HT_2 and 5-HT_{1A} receptors as mediators of the influence of local 5-HT innervation on the processes of motor activity regulation. However, lack of a clear-cut dose-response curve after microinjections of drugs may question the specificity of the effects of 5-HT agonists in the present experiment. Nevertheless, it seems that in the case of microinjections, local concentration of drug higher than total dose administered is a critical factor determining the drug-induced central effects. In the case of peripheral injections, the drugs are more evenly distributed throughout the organism, and the dose-response criterion may be more directly applied. Furthermore, in most instances, the significant difference between various doses of drugs can be observed.

Chronic but not acute pretreatment of rats with desipramine antagonized behavioral suppression after 5-HT and quipazine injections, while the buspirone effect was left unchanged. These data are in agreement with many others demonstrating a concomitantly occurring decrease in the number of central 5-HT_2 receptors and attenuation of 5-HT agonist-induced behavioral reactions (3, 11, 26, 27, 37, 39). This phenomenon comprises spinal reflexes, as well as associative and cognitive processes controlled in an inhibitory way by brain 5-HT systems. The opposite findings involving sensitization of 5-HT-related behaviors have been reported mainly with drugs that are strong 5-HT receptor antagonists (amitriptyline, mianserin, trazodone, doxepin) (8, 11, 24, 27). The fact that a similar sensitization effect appeared after chronic treatment with 5-HT receptor antagonist, metergoline, supports the notion that compensatory supersensitivity is responsible for this phenomenon and that this is probably limited to some antidepressants only (38,39).

The accumbens 5-HT_{1A} receptors stimulated by buspirone appear to be unsusceptible to chronic desipramine treatment. This finding contrasts with the data reported recently by Good-

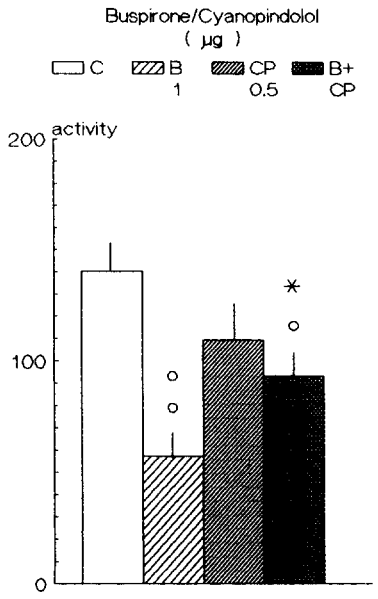

FIG. 6. The effect of intra-accumbens injections of buspirone with cyanopindolol on rat motility in the automatic open field. C: control, B: buspirone, CP: cyanopindolol. All other abbreviations as in Fig. 4. Number of rats; C: 7, B 1 μg: 8, CP 0.5 μg: 8, B+CP: 7.

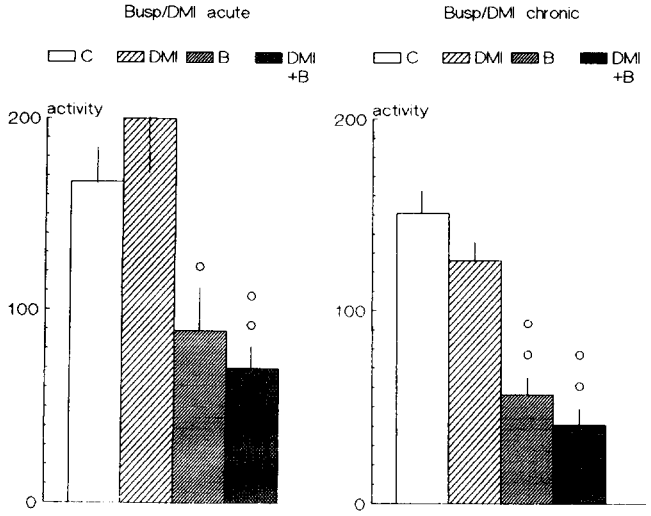

FIG. 7. The effect of acute and chronic treatment of rats with desipramine upon locomotor suppression produced by local injections of buspirone. C: control, DMI: desipramine, B: buspirone (5 μg). All other abbreviations as in Fig. 4. Number of rats; B/DMI acute C: 6, DMI: 6, B: 6, DMI+B: 6; B/DMI chronic C: 7, DMI: 8, B: 9, DMI+B: 8.

win et al. (13,14). Accordingly, a uniform decrease in central 5-HT_{1A} receptor activity after repeated injections of desipramine, amitriptyline, zimelidine, mianserin and electroconvulsive shocks was found in functional models of 8-OH-DPAT-induced hypothermia and stereotypic motor responses. Kennett et al. (18,19) reported that both chronic pretreatment of rats with desipramine and a single injection of 8-OH-DPAT and ipsapirone attenuated the inhibitory effect of restraint stress on animals' locomotor activity in the open field. It was hypothesized, therefore, that 5-HT_{1A} receptor agonists may have properties of a rapid antidepressant, due to desensitization of 5-HT_{1A} presynaptic receptor-mediated mechanisms controlling 5-HT release (6, 18, 19). Thus it was suggested that the desensitization of 5-HT_{1A} receptors may be a common mechanism of the therapeutic efficacy of all kinds of antidepressive treatment. However, the present data indicate that this effect of antidepressants is limited and most probably applies to the function of some populations of 5-HT_{1A} receptors in the specific brain areas only. Arguments for such a conclusion are provided by the present paper as well as by the findings that the repeated treatment of rats with imipramine, clomipramine, citalopram and mianserin failed to modify 8-OH-DPAT-induced increase in the corticosterone secretion (35), and the hypothermic response to this 5-HT_{1A} receptor agonist (45). The activation of 5-HT_{1A} receptors within the hypothalamus is known to cause increase of ACTH, corticosterone and cortisol secretion in rats and human beings (41). Moreover, these hormones function as markers of central serotoninergic activity, and they are also considered to be involved in the pathomechanisms of affective disorders (41). Furthermore, a significant increase in [^{3}H] 8-OH-DPAT binding following a 21-day treatment with amitriptyline, measured by autoradiography in the whole brain and dorsal hippocampus, was reported recently (42). Finally, 5-HT_{1A} receptors were found to be already subsensitive in depressed patients (hypothermic response to ipsapirone) and that amitriptyline further impaired 5-HT_{1A} receptor-mediated hypothermia (21). This finding argues against the therapeutic role of 5-HT_{1A} receptor down-regulation during antidepressive treatment.

In sum, it is concluded that the effect of chronic desipramine treatment on 5-HT system within the mesolimbic area probably does not involve 5-HT_{1A} receptors. Based on the previous data, and on the part of the experiment with 5-HT and quipazine, 5-HT_2 receptors appear to be the most likely targets for the action of desipramine. Such an effect might lead to an enhancement of disinhibitory processes within the brain, e.g., to the attenuation of inhibitory influence of limbic 5-HT on dopamine-related mechanisms controlling motor behavior. Such mechanisms, together with the previously reported changes in the reactivity of limbic noradrenergic and dopaminergic innervation after chronic antidepressants (31,32), could explain the energizing influence of drugs and electroconvulsive shocks on psychomotor retardation, a pivotal symptom of endogenous depression in humans.

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