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Prevention of the Serotonin Syndrome in Rats by Repeated Administration of Monoamine Oxidase Inhibitors but not Tricyclic Antidepressants

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Abstract. The serotonin syndrome, a behavioral response produced by the activation of serotonin receptors, and ^{3}H-serotonin binding were examined after repeated treatment of rats with different types of antidepressant drugs. The serotonin syndrome was produced by the direct-acting serotonin receptor agonists 5-methoxy-N,N-dimethyltryptamine (5-MeDMT) or *d*-lysergic acid diethylamide (LSD). Repeated, but not acute treatment of rats with monoamine oxidase inhibitors (nialamide, pargyline, and phenelzine) prevented the serotonin syndrome in response to either 5-MeDMT or LSD and also reduced ^{3}H-serotonin binding in the brain stem and spinal cord. Pretreatment of rats with *p*-chlorophenylalanine blocked the ability of nialamide treatment to inhibit the serotonin syndrome caused by 5-MeDMT. By contrast, neither the serotonin syndrome or ^{3}H-serotonin binding was affected significantly by the repeated administration of tricyclic antidepressants (amitriptyline, desmethylimipramine, and chlorimipramine) or iprindole. Repeated monoamine oxidase inhibitor treatments may prevent the serotonin syndrome by causing a reduction of ^{3}H-serotonin receptor binding sites in the brain stem and/or spinal cord.

Key words: Serotonin syndrome – Monoamine oxidase inhibitors – Tricyclic antidepressants – ^{3}H-serotonin binding – Depression

Late-developing pharmacological effects due to the repeated administration of antidepressant drugs have been examined recently in experimental animals, because such effects may explain the widely accepted belief that there is a "lag period" between the initiation of antidepressant treatment and clinical improvement (Oswald et al. 1972). For example, the repeated administration of antidepressants to rats reduces responses elicited by the activation of β-adrenergic receptors (Frazer et al. 1974; Vetulani and Sulser 1975; Moyer et al. 1981) possibly due, at least in part, to a reduction in the number of β-adrenergic binding sites (Banerjee et al. 1977; Frazer 1981).

In contrast to this relatively consistent effect of repeated antidepressant treatments on β-adrenergic receptor binding sites and responsiveness, antidepressant drug-induced changes in 5-hydroxytryptamine (serotonin) receptor sites correlate poorly with their effect on presumed serotonergic responses. For example, repeated administration of tricyclic antidepressants reduced the binding of ^{3}H-spiroperidol to what has been termed the "serotonin$_2$" receptor site (Peroutka and Snyder 1980), and did not alter the binding of ^{3}H-serotonin to the "serotonin$_1$" receptor (Wirz-Justice et al. 1978; Savage et al. 1979, 1980a). However, repeated administration of tricyclic antidepressants has been reported to enhance serotonin-mediated electrophysiological or behavioral responses (De Montigny and Aghajanian 1978; Friedman and Dallob 1979; Mogilnicka and Klimek 1979). On the other hand, binding sites for ^{3}H-serotonin are lowered when rats are repeatedly given the other major class of antidepressant drugs, monoamine oxidase inhibitors (MAOI; Savage et al. 1979, 1980a). The purpose of the present experiments was to determine if a behavioral correlate of this decreased ^{3}H-serotonin binding exists.

To do this, we examined whether antidepressants would modify the serotonin syndrome, a set of behavioral signs elicited through the activation of serotonin receptors (Grahame-Smith 1971; Jacobs 1976; Sloviter et al. 1978). Serotonin receptors in the brain stem and/or spinal cord appear to be involved in producing the serotonin syndrome (Jacobs and Klemfuss 1975; Deakin and Green 1978). Accordingly, we investigated the effect on rats of different types of antidepressant treatments on both the serotonin syndrome produced by the direct-acting serotonin agonists 5-methoxy-N,N-dimethyltryptamine (5-MeDMT) and *d*-lysergic acid diethylamide (LSD) (Trulson et al. 1976; Sloviter et al. 1980) and on ^{3}H-serotonin binding sites in the brain stem and spinal cord.

Materials and Methods

Male albino Sprague-Dawley rats (320–400 g; Ace Animals, Boyertown, PA) were housed in groups in of four with free access to food and water. The animal colony was maintained on a 12 h light cycle (lights on 7 AM).

Drug Treatments. All drugs were administered IP. In initial experiments, the ability of 5-MeDMT (9 mg/kg) or LSD (4 mg/kg) to produce the serotonin syndrome was evaluated in separate groups of rats either 1 h or 24 h after a single injection of nialamide (40 mg/kg) or 1 h after a single injection of 10 mg/kg amitriptyline (AT). In other rats, the presence of the serotonin syndrome was assessed 24 h following the final administration of either nialamide (40 mg/kg × 2) or AT (10 mg/kg × 2) for 7 days. Control rats received injections of 0.9% NaCl for 7 days.

A dose-response curve for 5-MeDMT was obtained in separate groups of rats that had received nialamide (40 mg/

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kg × 2) or 0.9% NaCl for 7 days. The animals were tested with 5-MeDMT 24 h after the last saline or nialamide injection.

The serotonin syndrome produced by 5-MeDMT (3 mg/kg) was evaluated in separate groups of rats following seven daily injections of saline or one of the following antidepressant drugs: pargyline (25 mg/kg); nialamide (40 mg/kg); phenelzine (10 mg/kg), desmethylimipramine (DMI, 10 mg/kg × 2); chlorimipramine (CMI, 10 mg/kg × 2); or iprindole (10 mg/kg × 2). Evaluation of the serotonin syndrome after 5-MeDMT was conducted 24 h following the last drug or saline injection.

Rats pretreated with the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine (PCPA, Koe and Weissman 1966) were given the drug at a dose of 300 mg/kg 3 days prior to initiation of treatment with nialamide and then again at a dose of 150 mg/kg on days 1, 3, and 5 of treatment with nialamide (40 mg/kg × 2/day).

Behavioral Testing. The appearance of the serotonin syndrome was assessed for time periods of up to 30 min after the administration of either 5-MeDMT or LSD. In control rats, the syndrome usually occurred within 5 min of injection. The animals were observed for the signs of the serotonin syndrome in individual clear plexiglas cages (45 × 24 × 20 cm), with the floor covered by fresh sawdust, by an observer who was blind to the drug treatments. Rats had to display at least four of the following six behaviors for the serotonin syndrome to be rated as present, in an all-or-none fashion: (1) repetitive dorso-ventral treading of the forepaws; (2) abduction of the hind limbs; (3) rigidity of the hind limbs; (4) tremor; (5) side-to-side movements of the head; (6) Straub tail. This is a previously published method for evaluating this behavioral syndrome (Jacobs 1976).

^{3}H-Serotonin Binding. Binding experiments were conducted using separate groups of rats that were not given 5-MeDMT or LSD. Specific binding of ^{3}H-serotonin to tissue homogenates was measured using the assay method of Bennett and Snyder (1976), as modified by Nelson et al. (1978) and as described previously (Savage et al. 1980a). Briefly, rats were decapitated and the brain stem or the entire spinal cord were removed and homogenized in 7 ml of an isotonic sucrose-TRIS buffer solution (280 mM sucrose, 25 mM TRIS, 5 mM $MgCl_2$; pH 7.4 at 25° C). In later experiments, binding was measured in the spinal cord after dissection and removal of the cervical area. The final concentration of ^{3}H-serotonin (New England Nuclear, Boston, MA; 26.7 Ci/mM) used in the incubation was 5 nM in brain stem experiments or 2.5 nM in spinal cord experiments. For experiments in which the data were analyzed by the method of Scatchard (1949), five different concentrations of ^{3}H-serotonin (0.5 – 10 nM) were used in the binding assay. Specific binding of ^{3}H-serotonin was determined as the difference in the amount of radioactivity bound in the absence and presence of 2 μM unlabeled serotonin. In control rats, specific binding was about 60% of total binding in the brain stem and about 50% of total binding in the spinal cord.

Protein. The protein content of the tissue aliquots used in the serotonin binding experiments was measured by the method of Lowry et al. (1951) using bovine serum albumin as the protein standard.

Statistics. Statistical evaluations were done by either Student's *t*-test or χ^2 analysis.

Drugs. The following drugs were obtained from their corresponding suppliers: 5-methoxy-N,N-dimethyltryptamine, nialamide, pargyline HCl (Sigma, St. Louis, MO); AT HCl (Merck, Sharp and Dohme, West Point, PA); DMI HCl (USV, Tuckahoe, NY); CMI HCl (Ciba-Geigy, Summit, NJ); phenelzine sulfate (Warner-Lambert, Morris Plains, NJ); iprindole HCl (Wyeth, Philadelphia, PA); LSD (NIDA, Washington, D.C.).

Results

In the first experiment, the appearance of the serotonin syndrome was examined in rats treated with either saline or two different types of antidepressant drugs, AT or nialamide. As shown in Fig. 1, the serotonin syndrome was produced in all control rats after injection of either 5-MeDMT (9 mg/kg) or LSD (4 mg/kg). By contrast, repeated administration of nialamide prevented the ability of either 5-MeDMT or LSD to cause the serotonin syndrome in all rats tested. Acute administration of nialamide did not alter the ability of either agonist to produce the serotonin syndrome. Morever, neither acute or chronic treatment of rats with AT blocked the appearance of this behavioral syndrome in response to 5-MeDMT or LSD. When rats showed the serotonin syndrome, all six symptoms were usually displayed prominently. However, rats treated repeatedly with nialamide failed to show any of the behavioral symptoms that are characteristic of the serotonin syndrome, although locomotor hyperactivity was typically observed in nialamide-treated rats in response to the serotonin agonists. Thus, repeated administration of a MAOI antidepressant, but not a tricyclic antidepressant, prevented the development of the serotonin syndrome caused by two different serotonin receptor agonists.

^{3}H-serotonin binding sites in the brain stem or spinal cord were measured to determine whether the blockade of the serotonin syndrome produced by repeated nialamide administration might be due to a drug-induced decrease in ^{3}H-serotonin receptor sites. The results of these experiments are shown in Table 1. Repeated administration of nialamide produced a significant reduction in specific ^{3}H-serotonin binding sites in the brain stem and the spinal cord. Neither acute administration of nialamide or repeated administration of AT produced significant changes in ^{3}H-serotonin binding in these areas.

The reason that repeated nialamide treatment reduced ^{3}H-serotonin binding was assessed by incubating homogenates of spinal cord with five different concentrations of ^{3}H-serotonin. The results of these studies are shown in Table 2. Nialamide treatment did not significantly affect the dissociation constant (K_D) in the spinal cord, but the maximum number of binding sites (B_{max}) was decreased significantly in the spinal cord of rats given MAOI repeatedly.

The ability of various doses of 5-MeDMT to produce the serotonin syndrome was examined in rats treated repeatedly with either saline or nialamide (Fig. 2). All control rats displayed the serotonin syndrome at doses of 3 mg/kg 5-MeDMT or greater. By contrast, a significant blockade of the serotonin syndrome was observed in nialamide-treated rats in response to doses of 5-MeDMT as high as 27 mg/kg. At this dose, all six saline-pretreated rats displayed the serotonin syndrome, whereas only one of six nialamide-treated rats displayed this behavioral syndrome ($\chi^2 = 5.49$, $P < 0.02$).

In the next experiment, the ability of 5-MeDMT (3 mg/kg) to produce the serotonin syndrome was examined following

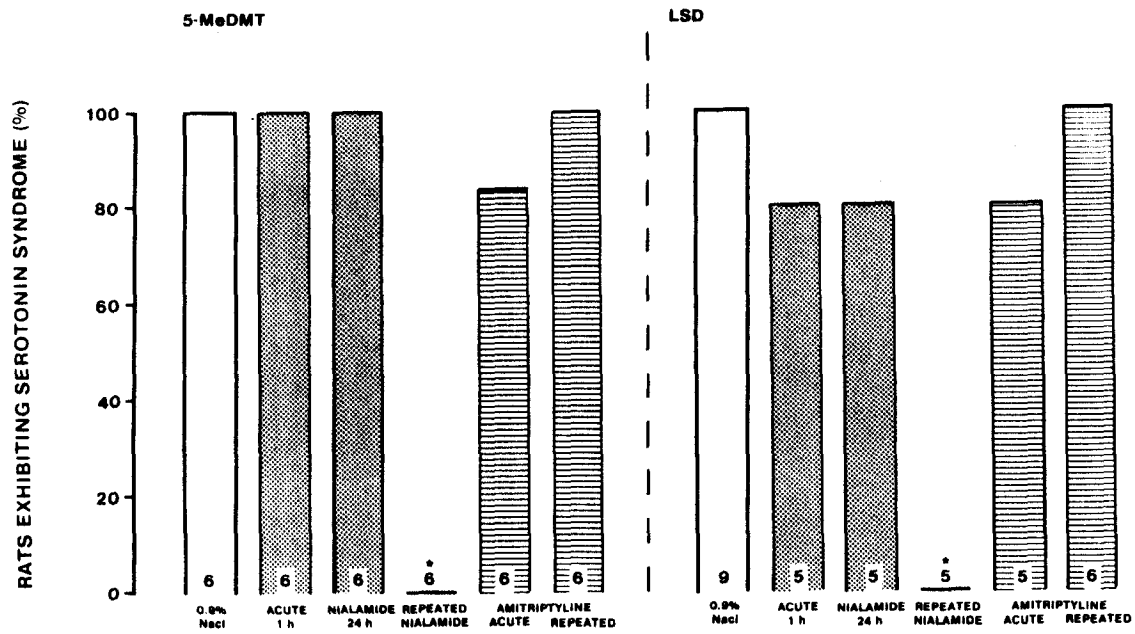

Fig. 1. Effect of treatment of rats with antidepressants on the serotonin syndrome induced by either 5-MeDMT (9 mg/kg) or LSD (4 mg/kg). Results are expressed as the percentage of rats in each group exhibiting the syndrome. The number of rats tested in each group is shown in the individual bars. Rats were tested either 1 h or 24 h after a single injection of nialamide, 1 h after the acute administration of amitriptyline, or 24 h after repeated administration of nialamide or amitriptyline. Asterisk indicates that the value differs significantly from that obtained in control rats ($P < 0.01$, χ^2-test)

Table 1. Specific binding of ^{3}H-serotonin in spinal cord or brain stem after antidepressant drug treatments. All rats were decapitated 24 h after the final drug or saline injection. The tissue was removed, homogenized in buffer, and specific binding of ^{3}H-serotonin was measured at a ^{3}H-serotonin concentration of 2.5 nM for the spinal cord and 5.0 nM for the brain stem. Values are expressed as mean ± SEM and the number of experiments is given in parentheses

Pretreatment	Specific ^{3}H-serotonin binding (fmol/mg protein)	
	Spinal cord	Brain stem
Saline	49 ± 5.2 (6)	85 ± 4.6 (9)
Nialamide		
Acute	49 ± 4.9 (4)	–
Repeated	23 ± 2.5[a] (6)	41 ± 4.1[a] (5)
Amitriptyline	51 ± 3.6 (4)	82 ± 2.6 (7)

[a] Compared to saline-treated rats, $P < 0.001$

Table 2. Effect of repeated administration of nialamide on ^{3}H-serotonin binding in rat spinal cord. Rats were treated with either 0.9% NaCl or nialamide (40 mg/kg twice daily) for 7 days and decapitated 24 h after the final injection. The spinal cord was removed and homogenates prepared and incubated with different concentrations of ^{3}H-serotonin. The binding data were analyzed by the method of Scatchard (1949). Values are expressed as mean ± SEM

Pretreatment	N	Specific ^{3}H-serotonin binding	
		B_{max} (fmol/mg protein)	K_D (nM)
Saline	5	118 ± 6.5	1.2 ± 0.12
Nialamide	5	77 ± 11.5[a]	1.7 ± 0.32

[a] Compared to saline-treated rats, $P < 0.025$

repeated treatment of rats with other antidepressant drugs. Separate groups of rats were treated for 7 days with pargyline, nialamide, or phenelzine (MAOI antidepressants); DMI or CMI (tricyclic antidepressants); or the atypical antidepressant iprindole. As shown in Fig. 3, repeated treatment with all three MAOI produced a significant blockade of the serotonin syndrome elicited by 5-MeDMT. However, neither of the tricyclic antidepressants or iprindole altered this behavioral syndrome significantly.

The binding of ^{3}H-serotonin was measured in the thoracic-lumbar area of the spinal cord of rats following repeated administration of nialamide, phenelzine, CMI, or iprindole. Both nialamide and phenelzine, which produced blockade of the serotonin syndrome, also produced a significant reduction of ^{3}H-serotonin binding in the spinal cord (Fig. 4). Treatment of rats with CMI or iprindole did not significantly alter the number of ^{3}H-serotonin binding sites in the spinal cord.

Previous work has demonstrated that pretreatment of rats with PCPA compromises the ability of MAOI to decrease ^{3}H-serotonin binding sites in brain (Savage et al. 1980b). Accordingly, we studied whether such pretreatment would affect the ability of repeated nialamide administration to block the serotonin syndrome produced by 5-MeDMT (3 mg/kg). The results of this experiment are shown in Fig. 5. Rats pretreated with saline and then nialamide repeatedly showed the previously demonstrated blockade of the serotonin syndrome. By contrast, rats administered PCPA prior to and during treatment with nialamide exhibited the serotonin syndrome in response to 5-MeDMT.

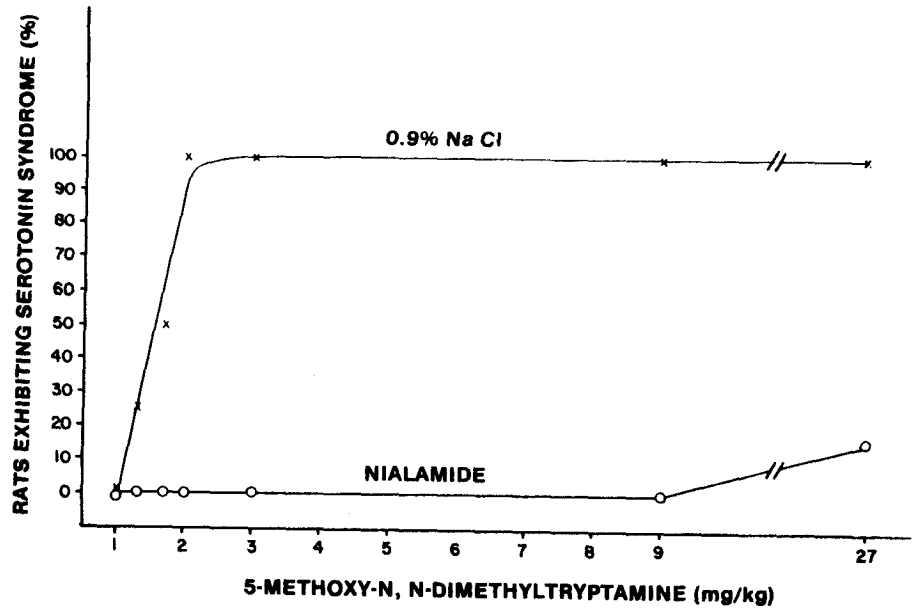

Fig. 2
Effect of repeated treatment of rats with nialamide on the serotonin syndrome induced by various doses of 5-MeDMT. Results are expressed as in Fig. 1. Rats were administered either nialamide or saline for 7 days and tested 24 h after the last injection. Four to nine rats were tested at each dose of 5-MeDMT

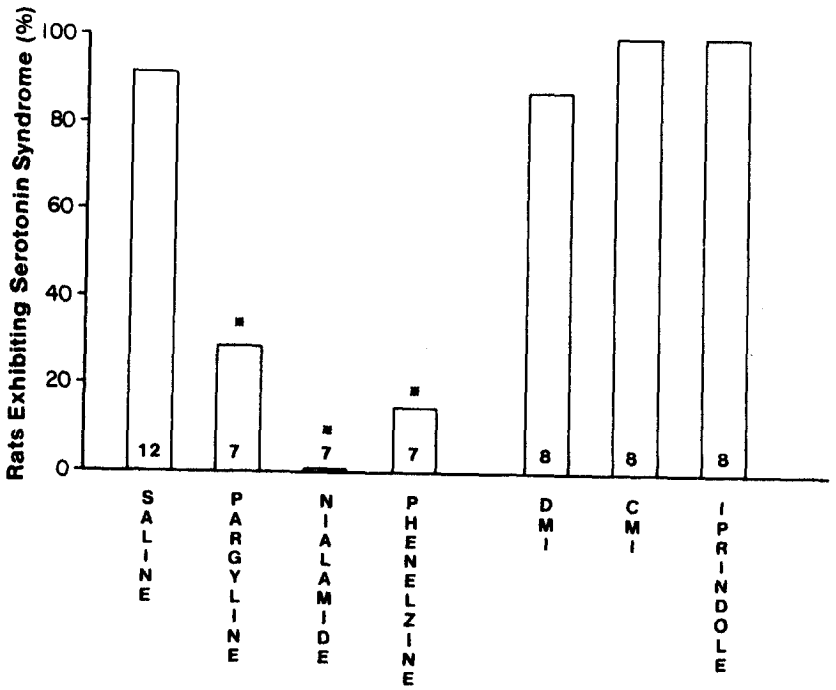

Fig. 3
Effect of treatment with antidepressant drugs on the serotonin syndrome induced by 5-MeDMT (3 mg/kg). Results are expressed as in Fig. 1. Rats were injected with antidepressant drugs for 7 days and tested 24 h after the final injection. Asterisk indicates that the value differs significantly from that obtained in control rats ($P < 0.025$, χ^2-test)

Discussion

This study demonstrates that repeated administration of MAOI antidepressants to rats blocked the ability of the direct-acting serotonin agonists 5-MeDMT and LSD to produce the serotonin syndrome, and caused a reduction in ^{3}H-serotonin binding in the spinal cord and brain stem. Converging lines of evidence suggest that the ability of MAOIs to prevent the serotonin syndrome is probably related functionally to a reduction in the number of available ^{3}H-serotonin receptor sites. Firstly, repeated, but not acute, MAOI administration blocked the appearance of the serotonin syndrome and reduced ^{3}H-serotonin binding. Secondly, administration of PCPA prior to and during repeated nialamide treatment prevented the MAOI-induced blockade of the serotonin syndrome. We have shown previously that PCPA treatment prevents MAOI from reducing ^{3}H-serotonin binding sites in cerebral cortex (Savage et al. 1980b). It is likely that a similar result would occur in the brain stem and spinal cord. Finally, repeated administration to rats of the tricyclic antidepressants AT, DMI, or CMI, as well as the atypical antidepressant drug iprindole, failed to alter the appearance of the serotonin syndrome after 5-MeDMT or reduce ^{3}H-serotonin receptor sites. Thus, the results from these experiments lead us to suggest that the ability of MAOIs to block the development of the serotonin syndrome is a consequence of these drugs decreasing the number of ^{3}H-serotonin binding sites available to bind with the serotonin receptor agonists.

However, a numerically concordant association between the MAOI-induced change in ^{3}H-serotonin binding and blockade of the serotonin syndrome was not obtained in these

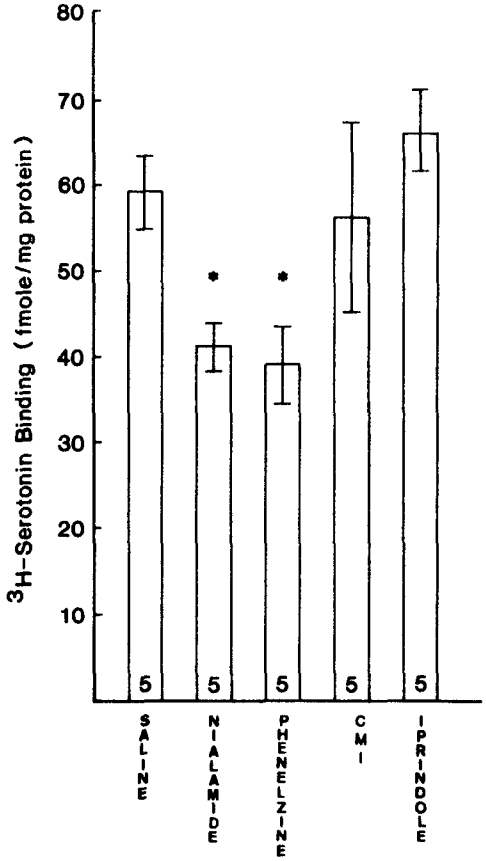

Fig. 4. ^{3}H-serotonin binding in rat spinal cord following repeated administration of antidepressant drugs. Values represent specific ^{3}H-serotonin binding ± SEM. Rats were treated with antidepressant drugs or saline for 7 days and assayed for ^{3}H-serotonin binding 24 h after the last injection. Binding of ^{3}H-serotonin was determined in tissue homogenate prepated from the thoracic-lumbar areas of the spinal cord and incubated in the presence of 2.5 nM ^{3}H-serotonin. Asterisk indicates that the value differs significantly from that measured in control rats ($P < 0.025$, Student's t-test)

experiments. Specific ^{3}H-serotonin binding sites were decreased, on the average, by no more than 50% after repeated MAOI administration, whereas the syndrome was prevented completely by MAOI. Even when 5-MeDMT was given in a dose approximately tenfold higher than that needed to cause the serotonin syndrome consistently in control rats, it failed to produce the serotonin syndrome in rats that were repeatedly administered nialamide (Fig. 2). Even though the reduction in ^{3}H-serotonin binding caused by repeated MAOI administration is due to a decrease in the number of ^{3}H-serotonin receptor sites (Table 2), a significant number of specific binding sites for ^{3}H-serotonin would be expected to remain present in rats repeatedly given nialamide. Such quantitative differences between drug-induced changes in ligand binding sites and monoaminergic responsiveness have been observed with other receptor systems as well (Moyer et al. 1981).

The simplest explanation for the absence of a perfect correlation between MAOI-induced changes in serotonin binding sites and resulting behavioral changes is that only a minimum number of serotonin receptors are required to be activated to produce the serotonin syndrome. However, other factors may be involved. For example, ^{3}H-serotonin may bind to more than just a single population of serotonin receptor sites that may be altered differentially by repeated treatment with MAOIs. Pedigo et al. (1981) identified a compartment of ^{3}H-serotonin binding that is sensitive to neuroleptics. If this compartment is involved in the production of the serotonin syndrome, it would explain why some neuroleptics block the serotonin syndrome (Grahame-Smith 1971; Jacobs 1974). Alternatively, MAOIs may change the "coupling" of the serotonin receptor and whatever biochemical effector systems are ultimately involved in producing the serotonin syndrome.

In contrast to the results of this study, head twitches or wet dog shakes produced in rodents by activation of serotonin receptors are increased following repeated administration of tricyclic antidepressants (Friedman and Dallob 1979; Mogilnicka and Klimek 1979). Similarly, electrophysiological responses to iontophoretically applied serotonin in vari-

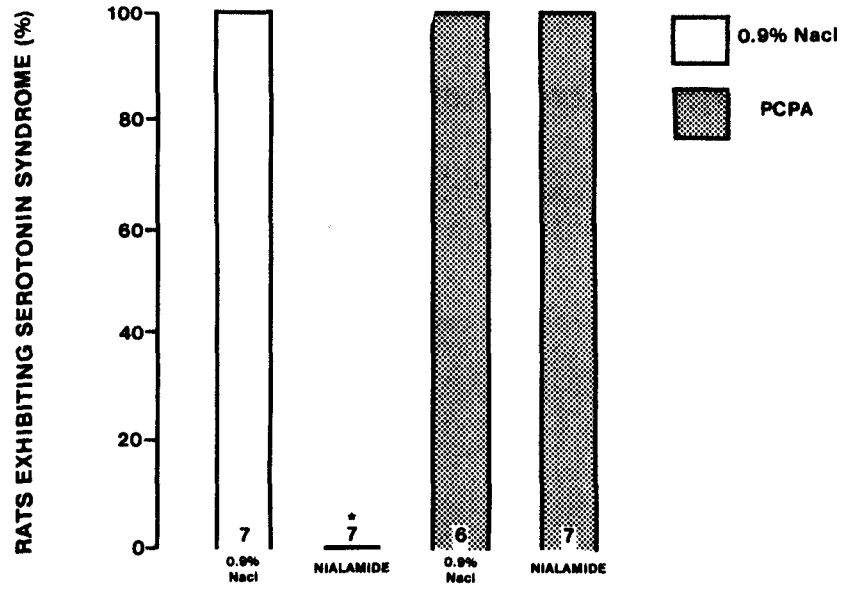

Fig. 5
Effect of repeated treatment of rats with nialamide or PCPA on the serotonin syndrome induced by 5-MeDMT (3 mg/kg). Results are expressed as in Fig. 1. Rats were injected with nialamide or saline for 7 days. PCPA (300 mg/kg) was administered 3 days prior to the initiation of nialamide treatment and again (150 mg/kg) on treatment days 1, 3, and 5. Animals were tested for the serotonin syndrome with 5-MeDMT 24 h after the last injection. Asterisk indicates that the value differs significantly from that found in control rats ($P < 0.01$, χ^2-test)

ous brain regions of the rat are enhanced following repeated tricyclic drug treatment (De Montigny and Aghajanian 1978). It should be pointed out that the tricyclic compounds can block serotonin receptors (Peroutka and Snyder 1980) so that serotonin receptor supersensitivity might develop upon prolonged administration of these drugs, which could account for the enhanced responses to serotonin receptor activation noted upon withdrawal of the drug. However, no ligand binding studies have demonstrated an increased number of serotonin receptor sites after repeated tricyclic antidepressant drug administration (Wirz-Justice et al. 1978; Savage et al. 1979, 1980a; Peroutka and Snyder 1980).

The differential ability of MAOI and tricyclic antidepressant drug treatments to block the serotonin syndrome makes it likely that this syndrome is produced by activation of serotonin$_1$ receptors, rather than the recently described serotonin$_2$ receptors in the CNS (Peroutka and Snyder 1979). Whereas only MAOIs appear to decrease the number of serotonin$_1$ sites, tricyclic compounds, MAOIs, and iprindole cause a decrease in the number of serotonin$_2$ sites (Peroutka and Snyder 1980). Since, in the present study, only repeated MAOI administration prevented serotonin agonists from inducing the serotonin syndrome, it appears that the production of this syndrome involves the activation of serotonin$_1$ receptor sites.

It has been suggested that ^{3}H-serotonin may bind to a site that should not be called a receptor, because no functional consequences have been ascribed to it (Leysen 1981). The demonstration that the ^{3}H-serotonin binding site is linked to a physiological consequence, i.e., production of the serotonin syndrome, suggests that the ^{3}H-serotonin binding site does correspond to a serotonin receptor site.

The mediation of the serotonin syndrome by serotonin$_1$ receptors differs from observations on another behavioral model of serotonin receptor activation. Based on correlations between the ability of drugs to block the development of head twitches in mice produced by 5-hydroxytryptophan and to displace ^{3}H-spiroperidol binding to rat frontal cortical membranes, Peroutka et al. (1981) suggested that head twitches in mice are mediated by serotonin$_2$ receptors. In view of these data and those obtained in the present study, it seems that head twitches in mice and the complex set of signs in the rat termed the serotonin syndrome are mediated by different serotonin receptors.

The ability of MAOIs to reduce ^{3}H-serotonin receptors cannot be related to a common mechanism for the therapeutic efficacy of different classes of antidepressant drugs, since tricyclic and atypical antidepressants did not produce this effect (Wirz-Justice et al. 1978; Savage et al. 1979, 1980a). This result differs from that seen when β-adrenergic receptors are measured, in which case most effective forms of antidepressant treatments reduce the number of β-adrenergic receptor sites (Frazer 1981). Nevertheless, the specific effect of MAOI on ^{3}H-serotonin binding sites may have therapeutic relevance, given the observations that the clinical characteristics of patients who respond to MAOI may be different from those who respond to tricyclics (Robinson et al. 1978; Quitkin et al. 1979). Consistent with this view is the suggestion by Aprison et al. (1978) that hypersensitive serotonergic receptors underlie a subset of depressive disorders. The status of the serotonergic system in depressed patients who respond to MAOI should receive further study.

Interestingly, the serotonin syndrome in the rat may be useful as an animal model for studying drug-induced hallucinations in humans (Sloviter et al. 1980). Our findings that the serotonin receptor-activating properties of two hallucinogens (5-MeDMT and LSD) were blocked by repeated MAOI administration suggests that long-term MAOI administration might block the actions of LSD and similar hallucinogenic drugs in humans. Previous studies indicate that this may occur (Sai-Halasz 1963; Resnick et al. 1964). Our data, taken together with these clinical results, indicate that the ability of repeated MAOI treatment to antagonize drug-induced or naturally occurring hallucinations should receive careful experimental attention.

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