Pharmacology Biochemistry & Behavior, Vol. 25, pp. 1–6, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

The Lesion of Serotonergic Neurons Does Not Prevent Antidepressant-Induced Reversal of Escape Failures Produced by Inescapable Shocks in Rats

P. SOUBRIE, P. MARTIN, S. EL MESTIKAWY,* M. H. THIEBOT, P. SIMON AND M. HAMON*

*Département de Pharmacologie and *INSERM, U288 Neurobiologie cellulaire et fonctionnelle CHU Pitié-Sâlpêtrière, 91, Bd de l'Hôpital, 75013, Paris, France*

Received 3 February 1986

SOUBRIE, P., P. MARTIN, S. EL MESTIKAWY, M. H. THIEBOT, P. SIMON AND M. HAMON. *The lesion of serotonergic neurons does not prevent antidepressant-induced reversal of escape failures produced by inescapable shocks in rats.* PHARMACOL BIOCHEM BEHAV **25**(1) 1–6, 1986.—The present study was aimed at testing the hypothesis (based mainly on biochemical evidence) of the implication of brain serotonergic neurons in the induction of learned helplessness (escape deficit) and its reversal by antidepressants in rats. After desipramine (25 mg/kg IP)-pretreatment rats were either sham-operated or infused with 5,7-dihydroxytryptamine (5,7-DHT, 3 μg of free base in 0.4 μl saline containing 0.02% ascorbic acid) into the midbrain raphe area. Three weeks later, experimental animals were exposed to 60 randomized inescapable shocks (0.8 mA; 15 sec duration), control rats being not shocked, and, 48 hr later, they were subjected to daily shuttle-box sessions (30 trials/day; ITI=30 sec) on 3 consecutive days in order to assess escape deficits. After inescapable shock pretreatment separate groups of rats were given twice daily injections of clomipramine (total daily dose: 32 mg/kg), desipramine (24 mg/kg), imipramine (32 mg/kg), nialamide (32 mg/kg) or saline. After behavioral testing, animals were sacrificed, and tryptophan hydroxylase activity was assayed in the cerebral cortex, the hippocampus and the striatum. We found that damage to serotonergic neurons associated with a 70% loss of tryptophan hydroxylase activity altered neither escape deficits produced by prior exposure to inescapable shock, nor the ability of either antidepressant studied to reverse escape failures in the shuttle-box paradigm. These findings cast some doubts on the hypothesized crucial role of serotonergic neurons in helpless behavior and its reversal by antidepressants.

Serotonergic neurons Learned-helplessness Escape deficits Antidepressant drugs 5,7-Dihydroxytryptamine Rats

AMONG the behavioral procedures that have been investigated as potential animal models of depression, it would be difficult to find another model that has stimulated more research activity, theoretical interest and argument than that generated by the learned helplessness paradigm [9, 12, 27]. This model, originally described by Seligman and coworkers in dogs, is based on the finding that exposure to uncontrollable stress produces performance deficits in subsequent learning tasks, which are not seen in subjects exposed to an identical, but controllable, stressor [12]. The appeal of the paradigm comes mainly from the attractive value of the concept of uncontrollability in relation to affective disorders and the fact that such performance deficits have been proven to be sensitive to a large variety of antidepressant therapies [8, 21, 27]. On this account, the paradigm is increasingly used to gain insight into the neurobiological bases of depressive states. Consonant with the biochemical and pharmacological foundations of aminergic hypotheses of depression, much animal research implicated noradrenergic and serotonergic neurons in the induction of helpless behavior and/or its attenuation by antidepressants [1, 2, 7, 15, 18, 19, 26].

Most relevant animal data for the implication of serotonergic neurons derive from studies on serotonin metabolism and 3H-imipramine binding, suggesting a reduction in serotonin transmission in animals that expressed helpless behavior [16, 18–20]. Moreover, a relationship between reversal of learned helplessness by antidepressants and enhancement of serotonin transmission has been proposed [15, 18, 19]. Contradictory results, however, have been reported. It has been found that alteration of brain serotonin metabolism following uncontrollable stress did not correlate with helplessness per se [26]. Moreover, serotonin depletion with parachlorophenylalanine, unlike noradrenaline depletion, did not facilitate the induction of helpless behavior [1] whereas the serotonin precursors, L-tryptophan and 5-hydroxytryptophan, did [3]. On the other hand, parachlorophenylalanine but not alpha methylparatyrosine reportedly reversed the therapeutic effect of antidepressants in depressed patients [22]. Since one current research tend-

TABLE 1

MEAN TRYPTOPHAN HYDROXYLASE ACTIVITY (± SEM)
(nmol 5-HTP/mg PROT/15 MIN)

	Cerebral Cortex	Hippocampus	Striatum
Sham-operated	0.229 ± 0.015	0.297 ± 0.020	0.240 ± 0.011
5,7-DHT-treated			
*all lesioned-rats (1)	0.115 ± 0.011	0.178 ± 0.012	0.096 ± 0.009
*rats lesioned by 70% (2)	0.049 ± 0.009	0.075 ± 0.006	0.029 ± 0.004
Imipramine group (Fig. 2)	0.036 ± 0.010	0.061 ± 0.022	0.031 ± 0.013

Effects of 5,7-dihydroxytryptamine (5,7-DHT) infusion into the midbrain (3 μg in 0.4 μl) on tryptophan hydroxylase activity in the rat cerebral cortex, hippocampus and striatum, all shock- and drug-conditions included.

(1)—Non-lesioned rats (tryptophan hydroxylase activity at more than 80% of control values) have been discarded.

(2)—Animals with at least 70% loss of tryptophan hydroxylase in one of the three structures assayed are only considered.

TABLE 2

MEAN NUMBER (± SEM) OF ESCAPE FAILURES/30

	N	SB1	SB2	SB3
Experimental rats				
(60 inescapable shocks)				
Sham	(16)	21.7 ± 2.6	21.3 ± 2.5	22.1 ± 2.8
5,7-DHT*	(10)	17.5 ± 2.7	21.8 ± 2.7	18.6 ± 3.7
Control rats				
(no shock)				
Sham	(8)	9.7 ± 1.4	8.3 ± 1.6	5.9 ± 1.8
5,7-DHT*	(7)	8.1 ± 1.3	6.4 ± 1.8	5.7 ± 1.3

Effects of 5,7-dihydroxytryptamine (5,7-DHT) infusion into the midbrain (3 μg in 0.4 μl) on escape deficits on 3 consecutive shuttle-box sessions (SB) produced by inescapable shock pretreatment. Escape failure refers to failure of the rat to change compartments during electric foot-shocks (0.8 mA, 3 sec duration) out of 30 two-way avoidance trials.

*Only the performances of 5,7-DHT-lesioned rats with a 70% loss of tryptophan hydroxylase activity in one of the brain structures assayed are considered.

ency is increasingly concerned with the application to human depression of the neurobiological correlates of learned helplessness in animals, the present study was aimed at investigating in rats the consequences of selective damage to serotonergic neurons on learned helplessness acquisition and on its reversal by tricyclic antidepressants and monoamine oxidase inhibitors.

METHOD

The experiments were carried out on male Wistar AF rats (CERJ, France) weighing 180–200 g at the beginning of the experiment. The animals were housed in groups of 10/cage under standard conditions: room temperature: 21 ± 1°C; light/dark cycle: 12 hr/12 hr; water and food ad lib.

Inescapable Shock Pretreatment

Electric footshocks were delivered in 20×10×10 cm chambers with Plexiglas walls and cover. The floors were stainless steel grids (1.5 cm mesh). A constant-current shocker was used to deliver 60 scrambled, randomized inescapable shocks (15 sec duration, 0.8 mA, every minute ±15 sec) to the grid floor. Control rats were placed for 1 hour in identical chambers but no shocks were administered. Inescapable shock pretreatment was performed in the morning, on day 1.

Conditioned Avoidance Training

In order to evaluate interference effects, avoidance training was initiated 48 hours (day 3) after inescapable shock pretreatment in automated two-way shuttle-boxes (60×21×30 cm) with Plexiglas walls and a floor consisting of stainless-steel rods spaced 1.0 cm apart. Each shuttle-box was divided into two equal-size chambers by a stainless steel partition with a gate providing access to the adjacent compartment through a 7×7 cm space.

Animals were placed singly in the shuttle-box, allowed to habituate to the test environment for 5 minutes (for the first session only) and then subjected to 30 avoidance trials (inter-trial intervals being 30 sec). During the first 3 sec of each trial, a light signal (used as a CS) was presented, allowing the animals to avoid shocks. If a response did not occur within this period, a 0.8 mA shock (3 sec duration) was applied via the grid floor. If no escape response occurred within this latter period, shock and light CS were terminated. The response (avoidance or escape) required of the rat was to cross the gate into the other compartment of the box. Only 3 sec was permitted for escape since, although escape failure is defined as failure to escape within a 30 to 60 sec period in most procedures used for helplessness assessement, the very first seconds following shock onset seem to be critical for detecting interference effects in animals preexposed to inescapable shocks, especially under a simple FR1 schedule [13,25]. Shuttle-box sessions were performed for 3 consecutive days (day 3, 4 and 5) in the morning, and the number of escape failures referred to as no crossing response during shock delivery was recorded.

Drug Administration

Rats were randomly treated according to one of the following protocols (16 to 20 rats per group): controls with no shock were given saline; experimental animals with inescap-

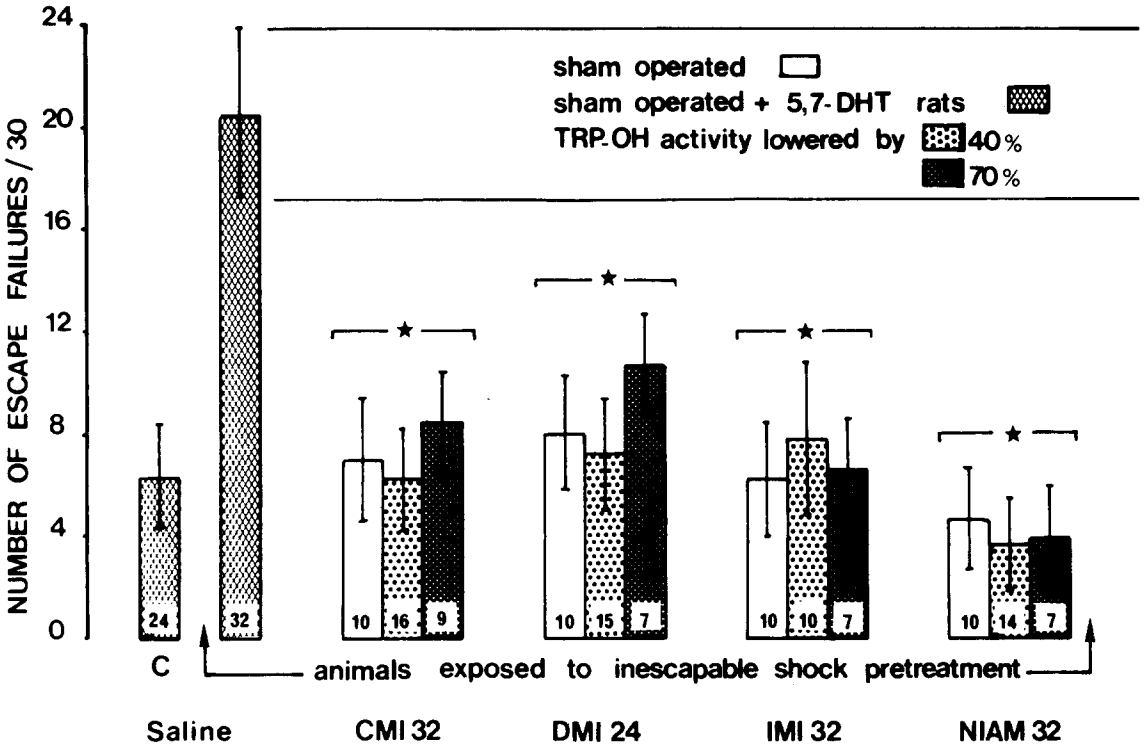

FIG. 1. Effects of 5,7-dihydroxytryptamine (5,7-DHT) infusion on the reversal by tricyclic antidepressants and nialamide of escape deficits produced by inescapable shock pretreatment. Data are the mean number of escape failures (±SEM) out of 30 two-way avoidance trials during the third daily shuttle-box session (day 5). Escape failure refers to failure of the rat to change compartments during the electric foot-shock (0.8 mA, 3 sec duration). C refers to saline-treated rats not subjected to shock pretreatment. Clomipramine (CMI), desipramine (DMI), imipramine (IMI) and nialamide (NIAM) were given twice daily, at a total daily dose of 32 mg/kg (16 + 16), except for desipramine: 24 mg/kg (8 + 16). Three weeks before being subjected to the learned helplessness paradigm rats were either sham-operated or given 5,7-DHT into the midbrain raphe nuclei (3 μg in 0.4 μl) after desipramine pretreatment (25 mg/kg IP). Tryptophan hydroxylase activity (TRP-OH activity) was assayed in three brain structures (cerebral cortex, hippocampus and striatum) following the last shuttle-box session. TRP-OH activity lowered by 40 or 70% refers to the 5,7-DHT lesioned rats with a loss of TRP-OH activity of at least 40 or 70% respectively, in the brain structures assayed (see the Method section). *Indicates that in rats given clomipramine, desipramine, imipramine or nialamide, sham-operated animals or lesioned animals with either a 40 or 70% loss of TRP-OH activity did not differ from each other but differ significantly from their matched saline-treated controls preexposed to shocks. Number of animals are shown at the bottom of columns.

able shocks were injected either with clomipramine, desipramine, imipramine (Ciba Geigy), nialamide (Pfizer) or saline. These injections were performed during five consecutive days: i.e., 6 hr after shock pretreatment on day 1 and then, twice a day in the morning (30 min before shuttle-box session) and the afternoon (except the 5th day). The daily dose administered was fixed at 32 mg/kg (morning 16 mg/kg + afternoon 16 mg/kg) for clomipramine, imipramine and nialamide and at 24 mg/kg (8 + 16) for desipramine. Drugs were injected intraperitoneally in a volume of 1 ml/200 g b.w. Schedules and doses of administration were selected according to previous results [13,14] in order to produce a reversal of escape failures that will be rapid in onset and complete: such a condition being required to assess with sufficient accuracy the magnitude of any antagonistic effect of destroying serotonergic systems. Hence, doses of antidepressants higher than those sufficient to reduce escape failures in various protocols including the present one were used.

5,7-Dihydroxytryptamine (5,7-DHT) Lesion

Three weeks before being subjected to the learned helplessness paradigm the rats were pretreated with desipramine (25 mg/kg IP) and anaesthetized with chloral hydrate (400 mg/kg IP). They were then placed in a stereotaxic apparatus, operated and 5,7-DHT dissolved in saline containing 0.02% ascorbic acid was infused (3 μg of free base in 0.4 μl over a 3 min period) into the midbrain (stereotaxic coordinates according to König and Klippel [10]: A=0.16; L=0; H=−1.2, the incisor bar being set 5 mm above the inter-aural plane and the injection cannula being lowered at a 12° angle to the sagittal plane) in order to destroy ascending serotonergic projections of the dorsal and median raphe nuclei. Under these conditions, 5,7-DHT is known to destroy serotonergic neurons with minimal damage to other monoaminergic cells [5]. Sham-operated animals were prepared in the same manner but no 5,7-DHT infusion was performed.

Tryptophan Hydroxylase Assay

Following the last shuttle-box session, rats were killed by decapitation, the brain quickly removed and dissected on ice. Tryptophan hydroxylase activity was measured in the cerebral cortex, hippocampus and striatum according to

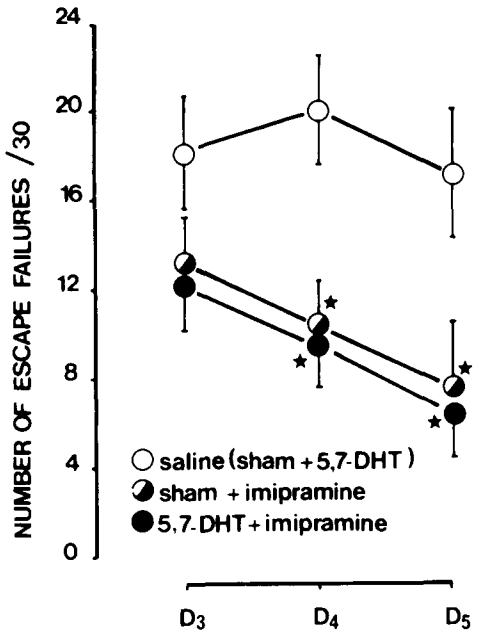

FIG. 2. Reversal by imipramine (32 mg/kg) of escape failures as a function of the number of exposures to daily shuttle-box sessions. Data are the mean number (±SEM) of escape failures. All the animals were exposed to inescapable shocks pretreatment at day 1 (D1). The 5,7-DHT + imipramine group only refers to rats with at least a 70% loss in tryptophan hydroxylase activity in one of the brain structures assayed (see Table 1 and the Method section). *Indicates that rats given imipramine (sham-operated or lesioned) differ at $p<0.01$ from their saline matched controls in their ability to escape from shocks.

Hamon *et al.* [6] in the 35,000×g supernatant of tissue homogenates with 0.15 mM tryptophan and 0.16 mM 6-methyl-tetrahydropterin (6-MPH4) as the cofactor. These structures were selected to appreciate the magnitude of the lesion of the two major ascending serotonergic pathways originating either from the dorsal or the median raphe nucleus. In addition, the hippocampus and the cerebral cortex were assayed according to the role ascribed to their afferent serotonergic fibres in learned helplessness and its prevention or reversal by antidepressant drugs [15, 16, 18, 20]. After the assay, the rats were divided into two sub-groups according to the intensity of the lesion. The first group was constituted by eliminating non-lesioned rats (with a tryptophan hydroxylase activity at more than 80% of control values), the second one by including only the animals with at least a 70% loss of tryptophan hydroxylase activity in one of the brain structures assayed.

Statistical analyses were performed by using ANOVA followed by Dunnett's *t*-test.

RESULTS

When rats with a tryptophan hydroxylase activity at more than 80% of the control values in the three brain structures assayed (considered as non-lesioned animals) were not taken into consideration, it appeared that the mean loss of tryptophan hydroxylase activity ranged between 40 and 60% as compared to controls, depending on the structure and the antidepressant-drug condition (Table 1). A sub-group of rats with more severe serotonergic damage (rats with at least a 70% loss of tryptophan hydroxylase activity in a given brain structure) was constituted and considered separately (Table 1).

Analysis of variance revealed that saline-treated rats preexposed to inescapable shocks exhibited significantly ($p<0.01$ for each group) more escape failures than saline with no shocks. This difference was observed whether the rats were sham-operated or lesioned, the number of escape failures in controls or in animals trained for learned helplessness being not significantly affected by the lesion, even in animals with a 70% loss of tryptophan hydroxylase activity (Table 2). On this account and for clarity, the performances of sham animals and 5,7-DHT-treated rats were pooled on Figs. 1 and 2 for each shock-condition but further statistical comparisons have been performed on the performances of the appropriate (shock-lesion-condition) animals.

Analysis of variance indicated that in rats preexposed to shocks and given clomipramine, desipramine, imipramine or nialamide, the number of escape failures at the third shuttle-box session was significantly reduced ($p<0.01$ for each drug) when compared with saline-treated rats, no lesion effect being detectable in either antidepressant-drug condition (Fig. 1). Indeed, statistical analysis revealed that in rats trained for learned helplessness there is, for each antidepressant studied, no significant difference in the number of escape failures between sham-operated rats and animals with either a 40% or a 70% loss in tryptophan hydroxylase activity, but that all these animals differed from their saline-treated matched controls (Fig. 1).

In seven 5,7-DHT infused rats (3 in the imipramine group, 2 in the nialamide group and 1 in the clomipramine and desipramine group), the tryptophan hydroxylase activity was at the null values in each of the three brain structures assayed. The average number of escape failures for these animals was 7.8±2.7 at the third shuttle-box session (D5).

As shown in Fig. 2 for imipramine (but this applies to the other drugs studied) the reduction in escape failures observed at each shuttle-box session was not significantly altered in 5,7-DHT-lesioned rats with a 70% loss in tryptophan hydroxylase activity (Table 1), thus indicating that the lesion did not delay the onset of action of the antidepressants tested.

DISCUSSION

As already reported, we found that subacute administration of tricyclic antidepressants (clomipramine, desipramine and imipramine) and a monoamine oxidase inhibitor (nialamide) prevents animals trained for learned helplessness from exhibiting escape deficits when subsequently tested in the shuttle-box paradigm [8, 21, 27].

The most significant finding of the present study is that destruction of brain serotonergic neurons failed to affect significantly the induction of helpless behavior and the reversal of escape failures by antidepressants. These observations conflict with the hypothesized involvement of serotonergic neurons in learned helplessness acquisition and its elimination by antidepressants [15, 18–20].

The evidence on which this hypothesis rests needs, however, further substantiation. Indeed, although a temporal connection between impairment of escape behavior and reduced serotonergic transmission had been described [16], it is not established that a decrease in serotonin transmission might be able to facilitate escape deficits. In fact, blockade of serotonin synthesis did not increase the number of escape failures caused by inescapable shock pretreatment [1] and,

on the contrary, impaired avoidance acquisition has been observed in animals treated with L-tryptophan or 5-hydroxytryptophan and subjected to subeffective exposure to inescapable stress [3].

These data along with our findings support the conclusion drawn from the separation model in monkeys, that serotonin depletion did not augment depressive-like behavior [11].

Likewise, the hypothesis of a connection between reversal of learned helplessness following antidepressant treatment and restoration or enhancement of serotonin transmission is flawed by the lack of information on some crucial points. A single application of desipramine into the frontal cortex has been reported both to reverse learned helplessness and to increase neo-cortical 5-hydroxyindoleacetic acid levels and restore normal septal serotonin release [15, 18, 19]. The possibility, however, that such biochemical changes can be observed following a behaviorally inactive, single peripheral administration of desipramine has not been investigated. In fact repeated, but not acute, systemic injections of imipramine were found to counteract escape deficits and the reduction in serotonin release caused by inescapable stress [15, 18, 19]. However, release assay was performed twenty-four hours after the last imipramine injection, thus leaving open the question of whether serotonin release—though not escape failures—might not be altered at shorter post-injection intervals. Finally, it has not been demonstrated that antagonism of these putatively crucial biochemical modifications would prevent the reversal effect by antidepressants of escape deficits.

Our findings suggest that the changes in serotonergic transmission that occur in a matter of a few days of treatment with tricyclic antidepressants or monoamine oxidase inhibitors are unlikely to underlie the effects of these drugs in the learned helplessness paradigm.

These assumptions, however, should be tempered by consideration of the following points. First, our results do not allow us to exclude the possibility of a serotonergic influence on escape deficits and on their elimination by antidepressants in rats with intact serotonergic pathways. This would be compatible with the fact that serotonin release might be effective in antagonizing the escape interference as suggested by the findings that application of serotonin to the septum or the frontal cortex reversed escape failure [18]. Second, in 5,7-DHT-lesioned animals, tricyclic antidepressants and nialamide may reverse escape deficits by their action on residual, not damaged, serotonergic neurons. However, no inverse correlation can be found between the severity of the damage as assessed by tryptophan hydroxylase activity and the efficacy of either antidepressant studied in reducing escape failures. In antidepressant-treated animals, the performance of the few rats with tryptophan hydroxylase activity at the null value was not distinguishable from that of sham-operated rats. Moreover, biochemical assay was limited to the striatum, hippocampus and cerebral cortex. Therefore, it cannot be exluded that serotonergic neurons terminating in other (not assayed) critical areas such as the septum [18] could have been spared by the neurotoxin. However the fact that raphe-septal neurons have been found sensitive to the neurotoxic action of 5,7-dihydroxytryptamine ([4], and our experience with the drug), makes this possibility unlikely. Third, from the behavioral changes we are dealing with when considering reversal of escape deficits produced by antidepressants, we can speculate that serotonergic neurons play a minimal role in the onset of action of antidepressants. However, the experimental procedure we used cannot allow us to exclude the possibility of a serotonergic mediation of the maintenance of the antidepressant effects of tricyclics or monoamine oxidase inhibitors. This speculation would be in line with the pervasive—but as yet not replicated—apparent reversal of the therapeutic effect of imipramine and tranylcypromine by the serotonin synthesis inhibitor parachlorophenylalanine [22].

In conclusion, since the drugs employed in the present study are known to interfere inter alia with noradrenergic transmission (see review in [17,24]), our results might suggest that noradrenergic rather than serotonergic neurons might be involved in the onset of the reversal of learned helplessness by antidepressants. An enhanced density of beta-adrenergic receptors in the rat cerebral cortex and hippocampus has been recently described following selective destruction of serotonergic pathways [23]. Since stimulation of beta-adrenergic receptors plays an important role in antidepressant-induced reversal of learned helplessness [7, 13, 14], this beta-receptor up-regulation may compensate for the absence of serotonergic brain innervation and thus contribute to the persistence of the effects of antidepressants in 5,7-dihydroxytryptamine-lesioned rats. However, in light of the large variety of neurochemical systems that can be affected by antidepressants [17,24] it would be premature to conclude from our study, on the exclusive or even preferential noradrenergic mediation of antidepressant-induced reversal of learned helplessness.

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