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Antidepressant-like action of 8-OH-DPAT, a 5-HT_{1A} agonist, in the learned helplessness paradigm: evidence for a postsynaptic mechanism

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In animal models of depression, the 5-HT_{1A} agonists, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), buspirone, gepirone and ipsapirone administered i.p. have been shown to mimic the behavioural effects of antidepressants. For instance, in the present study, using the learned helplessness paradigm, 8-OH-DPAT dose-dependently reversed helpless behaviour. To assess the possible role of pre- or postsynaptic 5-HT_{1A} receptors in this effect, the ability of 8-OH-DPAT to reduce helpless behaviour was investigated following (1) i.p. administration (0.125 or 0.25 mg/kg/day) in rats whose ascending 5-HT neurons were partially destroyed by previous 5,7-dihydroxytryptamine (5,7-DHT) injection (5 μg free base in 0.6 μl) into the raphe nuclei or (2) after local microinjection (0.1 or 1.0 μg in 0.5 μl) into the raphe nuclei or into the septum. The reversal of helpless behaviour by 8-OH-DPAT (i.p.) was still observed in 5,7-DHT-treated rats with telencephalic 5-HT uptake reduced by 50–75% depending on the region. 8-OH-DPAT microinjected into the raphe nuclei did not reverse helpless behaviour; in contrast, 8-OH-DPAT microinjected into the septum reversed helpless behaviour. These results suggest that the ability of 8-OH-DPAT to reverse helpless behaviour probably involved the stimulation of postsynaptic rather than presynaptic 5-HT_{1A} receptors.

INTRODUCTION

The analysis of the role of serotonin (5-HT) neurons in the control of behaviour has been complicated by the discovery of multiple of recognition sites for 5-HT. Based on radio-ligand binding studies, Peroutka and Snyder[29] postulated the existence of two classes of 5-HT recognition sites: those labelled by [^{3}H]5-HT were termed 5-HT_1 and those labelled by [^{3}H]spiperone were termed 5-HT_2 sites. Recently, various subtypes of the 5-HT_1 site have been identified including the 5-HT_{1A} site labelled by 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT)[13,28].

Various drugs which specifically block 5-HT uptake show antidepressant activity[20]. Furthermore, various tricyclic antidepressants enhance the electrophysiological responses to 5-HT in the brain after chronic treatment[6]. These findings favour the hypothesis of a deficit in 5-HT neurotransmission in depression[35].

In contrast, various tricyclic antidepressants

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acts as 5-HT antagonists[10,24]. Furthermore, a reduction in the number of 5-HT_2 receptors has been found after long-term treatment with various antidepressants[30]. These findings have led to the suggestion that an excess of 5-HT at some receptors, probably the 5-HT_2 type, could be involved in depressive illness.

The 5-HT_{1A} agonist 8-OH-DPAT has been found to selectively reduce brain 5-HT synthesis[15] by activation of autoreceptors located on serotonergic cell bodies. 8-OH-DPAT also produced behavioural effects compatible with reduced central 5-HT function[7,8]. On the other hand, 5-HT_{1A} sites also have been found postsynaptically to 5-HT neurons[26,37] and 8-OH-DPAT showed an antidepressant-like action in rats[12,17]. From these findings it is unclear whether the antidepressant effects of 8-OH-DPAT, like those of tricyclic antidepressants, resulted from an augmentation or diminution of 5-HT neurotransmission.

The learned helplessness paradigm[32] is a behavioural model highly sensitive to antidepressants. To establish whether pre- or postsynaptic 5-HT receptors were involved in the antidepressant action of 5-HT_{1A} agonists, the ability of 8-OH-DPAT to reduce helpless behaviour was investigated in the present study. Two approaches were taken. In the first, the effects of i.p. injection of 8-OH-DPAT were assessed in rats whose ascending 5-HT neurons were partially destroyed by previous injection of 5,7-dihydroxytryptamine (5,7-DHT) into the raphe nuclei. In the second, the effects of microinjections of 8-OH-DPAT into the raphe nuclei or the septum were assessed. The septum was chosen as a high concentration of postsynaptic 5-HT_{1A} receptors has been found there[36].

MATERIALS AND METHODS

Animals

Male Wistar A.F. rats (Centre d'élevage R. Janvier, France) weighed 200–220 g at the beginning of experiments. Animals were housed in groups of 10 per cage under standard conditions: room temperature (21 ± 1 °C); light/dark cycle (12 h/12 h); water and food ad libitum.

Apparatus and general experimental procedures

Helplessness induction. Inescapable electric footshocks were delivered via stainless steel grids (1.5 cm mesh) in 20 × 10 × 10 cm chambers with Plexiglas walls and covers. A constant-current shocker was used to deliver 60 scrambled, randomized inescapable shocks (15 s duration, 0.8 mA) every minute ± 15 s. Control rats were placed for 1 h in identical chambers and no shocks were administered. Helpless induction was performed in the morning, on day 1.

Conditioned avoidance training. To evaluate escape and avoidance performance, avoidance training was initiated 48 h (day 3)after inescapable shocks. Automated two-way shuttle-boxes (60 × 21 × 30 cm) were constructed 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 opening. Animals were placed singly into the shuttle-box, allowed to habituate to the test environment for 5 min (for the first session only) and then were subjected to 30 avoidance trials with between-trial intervals of 30 s. During the first 3 s of each trial, a light signal was presented, allowing the animals to avoid shocks by moving to the other side of the box. If a response did not occur within this period, the light remained on and a 0.8-mA shock (3 s duration) was applied to the grid floor. If no response occurred during shock presentation, the shock and light signal were terminated automatically after 3 s. An escape failure has been previously defined as failure to escape within a 30- to 60-s period after shock onset. The first few seconds following shock onset, however, are critical for detecting interference effects in animals pre-exposed to inescapable shocks especially under a fixed ration one (FR1) schedule[22,34]; therefore, the briefer 3-s duration was employed here. Avoidance sessions were performed for 3 consecutive days. (days 3, 4 and 5) in the morning, and the number of escape failures, referred to as 'no crossing response', were recorded.

Statistical analyses. Results were expressed as mean number of escape failures (± S.E.M.)

recorded over 30 trials during each shuttle-box session. Between-groups comparisons were performed using two-way (treatment × session) analyses of variance (ANOVA) followed by Dunnett's *t*-test.

Drug administration. 8-OH-DPAT (Research Biochemicals Inc., Coger, France) was injected either i.p. (in aqueous solution) in a volume of 0.5 ml/100 g body weight or microinjected (in saline solution) in a volume of 0.5 μl per rat.

Rats were randomly chosen for the various treatment conditions. Control rats did not receive shocks and were given vehicle. Experimental animals for the 8-OH-DPAT alone and 5,7-DHT studies received inescapable shocks and were injected (i.p.) either with 8-OH-DPAT or vehicle (aqueous solution) given on 5 consecutive days, i.e. 6 h after inescapable shocks on day 1 and then, twice a day in the morning (30 min before shuttle-box sessions) and between 18.00 h and 19.00 h. Half the daily dose was given at each injection, except on day 1 when the daily dose was given as a single bolus. For the microinjection studies either 8-OH-DPAT or vehicle (saline solution) were given on 5 consecutive days, once a day just before shuttle-box sessions.

Systemic administration of 8-OH-DPAT

In this study the effects of 6 doses of 8-OH-DPAT (0; 0.03; 0.06; 0.125; 0.25; 1.0 mg/kg, i.p.) were assessed in animals having received inescapable shocks. The number of animals receiving each dose, respectively, was 43, 10, 13, 16, 10 and 10.

5,7-DHT lesion studies

Three weeks before being subjected to the learned helplessness paradigm, the rats were pretreated with desipramine (25 mg/kg, i.p.) and anesthetized with chloral hydrate (400 mg/kg, i.p.). They were then place into a stereotaxic apparatus and 5,7-DHT dissolved in saline containing 0.2% ascorbic acid was infused (5 μg of free base in 0.6 μl over a 3-min period) into the midbrain. Stereotaxic coordinates according to König and Klippel[19] were A = 0.16, L = 0 and H = − 1.2. The incisor bar was set 5 mm above the horizontal plane passing through the interaural line. The injection cannula was lowered at an angle of 12° 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[11]. Sham-operated animals were prepared in the same manner but no 5,7-DHT infusion was performed.

Biochemistry. Following the last shuttle-box session, rats were killed by decapitation, and the brain was quickly removed and dissected on ice. [^{3}H]5-HT uptake was measured in the hippocampus, the cerebral cortex (anterior part) and the striatum, as previously described[14]. Briefly, tissues were homogenized in 10 vols. (v/w) of 0.32 M sucrose using a Potter-Elvejhem apparatus fitted with a Teflon pestle. Homogenates were centrifuged at 1000 *g* for 10 min at 4 °C, and the crude synaptosomal pellets were obtained by centrifuging the resulting supernatants at 12000 *g* for 20 min at 4 °C. Each pellet was gently resuspended in 10 vols. of Krebs-Henseleit medium, and uptake assays were carried out using 75-μl aliquots of each suspension. Using [^{3}H]5-HT (15 nM; 26.2 Ci/mmol, Radiochemical Centre Amersham) as the substrate, synaptosomes were incubated for 4 min at 37 °C in a total volume of 0.5 ml Krebs-Henseleit medium supplemented with 10 μM pargyline, and under a constant atmosphere of O_2 : CO_2 (95 : 5). Blanks were obtained by adding 10 μM citalopram to the incubating mixture.

Assays were stopped by rapid filtration through GF/B filters. After washing with 3 ml of ice-cold Krebs-Henseleit medium, filters were dried and immersed in 4 ml of Aquasol (New England Nuclear) for radioactivity counting. Triplicate determinations were made in all cases. Proteins were estimated using the Folin phenol procedure[21] with bovine serum albumin (Sigma) as the standard.

Microinjection studies

At least one week prior to the initiation of testing, rats were stereotaxically implanted under chloral hydrate (400 mg/kg) anaesthesia with a single guide cannula (modified 23-g needle) with

the tip aimed at a point 2 mm above the target structure. As the target structures were located along the midline, cannulae were introduced into the brain at an angle of 15° to the sagittal plane to avoid damage to the sagittal sinus. Using the atlas of Paxinos and Watson[27], co-ordinates for dorsal raphe guide cannulae were 7.8 mm posterior to bregma, 1.7 mm lateral to the midline and 6.6 mm ventral to the surface of the skull, the corresponding co-ordinates for septal implants were 0.5 mm anterior, 1.2 mm and 2.8 mm, respectively. The incisor bar was set at 3.3 mm below the horizontal plane passing through the interaural line. Cannulae were secured with watchmaker's screws placed into the skull and dental acrylic cement. When injections were not being made, the guide cannulae were blocked with an obturator pin (30 g wire).

Microinjections of 8-OH-DPAT were made with a 2-μl Hamilton microsyringe in a volume of 0.5 μl during 30 s. The injection needle (30 g) extended 2 mm below the tip of the guide cannula. Each solution was prepared immediately before use and 0.9% NaCl was applied as solvent.

Following behavioral testing, cannulae placements were confirmed using standard histological techniques.

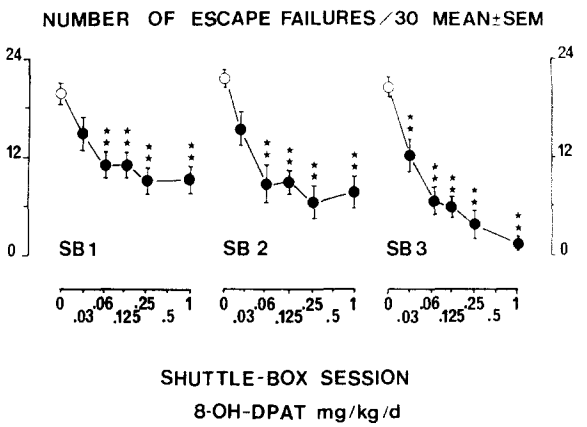

Fig. 1. Reversal by 8-OH-DPAT of escape failures as a function of the daily dose injected and the number of exposures to daily shuttle-box sessions. Data are the mean number (± S.E.M.) of escape failures for each of the 3 consecutive daily shuttle-box sessions (SB 1–3). Escape failure refers to the absence of the shuttle response during the electric foot-shock presentation (30 per session; 0.8 mA; 3 s duration). 8-OH-DPAT was injected (i.p.) on 5 consecutive days, i.e. 6 h after inescapable shocks on day 1 and then, twice a day in the morning (30 min before shuttle-box sessions) and between 18.00 h and 19.00 h. Stars indicate that 8-OH-DPAT-treated rats (●) differed significantly from the corresponding vehicle-treated rats (○). $^{**}P < 0.01$ (Dunnett's t-test).

RESULTS

Analysis of variance revealed that non-drugged rats pre-exposed to inescapable shocks (experimental rats) exhibited more escape failures than controls with no shock ($P < 0.01$). The most pronounced differences were generally observed during the third shuttle-box session (S-BS). During the first, second and third S-BS, the mean ± S.E.M. number of escape failures for control and experimental groups was: 8.3 ± 1.08 and 21.2 ± 1.62; 6.4 ± 0.87 and 19.7 ± 1.49; 4.9 ± 0.52 and 20.1 ± 1.53, respectively.

Systemic administration of 8-OH-DPAT

8-OH-DPAT induced ad dose-related reduction in the number of escape failures in rats pre-exposed to inescapable shocks (Fig. 1). ANOVA indicated significant treatment ($F_{5,96} = 29.79$; $P < 0.001$), session ($F_{2,192} = 8.75$; $P < 0.001$)

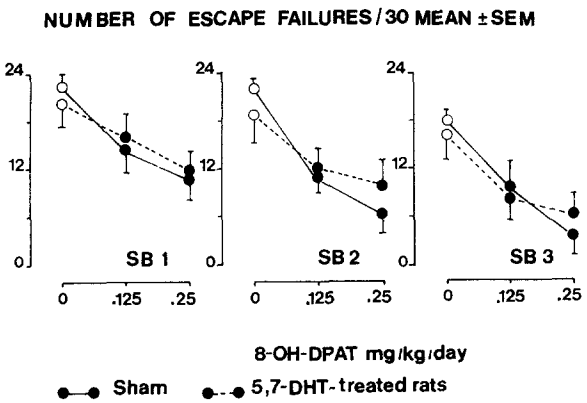

Fig. 2. Reversal by 8-OH-DPAT (0.125; 0.25 mg/kg/day) of escape failures as a function of the number of exposures to daily shuttle-box sessions (SB 1–3) in sham-operated (●——●) or 5,7-DHT (●---●)-lesioned rats. Data are the mean number (± S.E.M.) of escape failures. All animals were exposed to inescapable shock pretreatment at day 1 and then treated daily with 8-OH-DPAT (●) or vehicle (○).

and treatment × session interaction effects ($F_{10,192} = 4.44$; $P < 0.001$).

Post-hoc analyses revealed that during the first and second shuttle-box sessions all doses of 8-OH-DPAT greater than 0.03 mg/kg/day significantly reduced the number of escape failures. During the third shuttle-box session all doses of 8-OH-DPAT significantly reduced the escape deficit induced by inescapable shocks (Fig. 1).

5,7-DHT lesion studies

An ANOVA comparing sham-operated ($n = 40$) and lesioned rats ($n = 15$) trained for learned helplessness revealed that the number of escape failures was not significantly affected by the lesion ($F_{1,53} = 1.05$; $P = 0.31$). Nor were there any significant interactions involving the group variable.

ANOVA indicated that for sham-operated ($n = 16$ and 9) or lesioned ($n = 19$ and 20) rats pre-exposed to inescapable shocks and given 8-OH-DPAT (0.125; 0.25 mg/kg/day), the number of escape failures during the 3 shuttle-box sessions was significantly reduced when compared with sham-operated ($n = 40$) and lesioned rats ($n = 15$) given vehicle. Significant treatment ($F_{5,113} = 15.52$; $P < 0.001$), session ($F_{2,226} = 14.64$; $P < 0.001$) and treatment × session interaction effects ($F_{10,226} = 4.81$; $P < 0.001$) were observed (Fig. 2).

Biochemistry. As indicated in Table I, a randomly selected subgroup of 19 rats given a raphe nucleus infusion of 5,7-DHT exhibited a significant reduction in hippocampal, striatal and cortical [^{3}H]5-HT uptake in comparison to a randomly selected subgroup of 10 sham control rats. Reductions ranged from 49 to 92%.

Microinjection studies

A representative septal and raphe cannula placement is shown in Fig. 3. Only animals with cannula tips in these regions were included in the analysis. The number of animals with septal cannulae receiving 0, 0.1 or 1.0 μg injections of 8-OH-DPAT was, 9, 11 and 8, respectively. The numbers in corresponding raphe groups were 17, 6 and 8, respectively.

Septal injections. 8-OH-DPAT induced a dose-related reduction in the number of escape failures in rats pre-exposed to inescapable shocks (Fig. 4A). ANOVA indicated a significant treatment ($F_{2,25} = 12.95$; $P < 0.001$) and session effect ($F_{2,50} = 17.18$; $P < 0.001$) and no significant treatment × session interaction ($F_{4,50} = 2.26$; $P = 0.08$).

Post-hoc analyses revealed that the number of escape failures was significantly reduced by 8-OH-DPAT microinjected into the septum during the 3 shuttle-box sessions at doses of 0.1 or 1 μg/0.5 μl: at the first S-BS, $t_{2,25} = 1.62$ (non-significant) and 2.92; at the second S-BS, $t_{2,25} = 4.19$ and 5.98; at the third S-BS, $t_{2,25} = 3.37$ and 4.65 (Fig. 4A).

Raphe injections. ANOVA indicated no significant effect: treatment, $F_{2,28} = 0.08$; $P = 0.92$, session $F_{2,56} = 1.37$; $P = 0.26$ or treatment × session interaction, $F_{4,56} = 1.05$; $P = 0.39$ (Fig. 4B).

TABLE I

The effects of 5,7-DHT infusion into the midbrain raphe area (5 μg of free base in 0.6 μl saline containing 0.2% ascorbic acid) on [^{3}H]5-HT uptake in synaptosomal preparations of various brain structures; rats of all shock and drug conditions included

	[^{3}H]5-HT uptake pmol/mg prot./4 min (mean ± S.E.M.)		
	Hippocampus	*Striatum*	*Cerebral cortex*
Control sham ($n = 10$)	2.37 ± 0.37	4.30 ± 0.12	2.95 ± 0.26
5,7-DHT-lesioned ($n = 19$)	0.85 ± 0.19***	1.84 ± 0.27***	0.80 ± 0.18***

*** $P < 0.001$/control sham (Student's t-test).

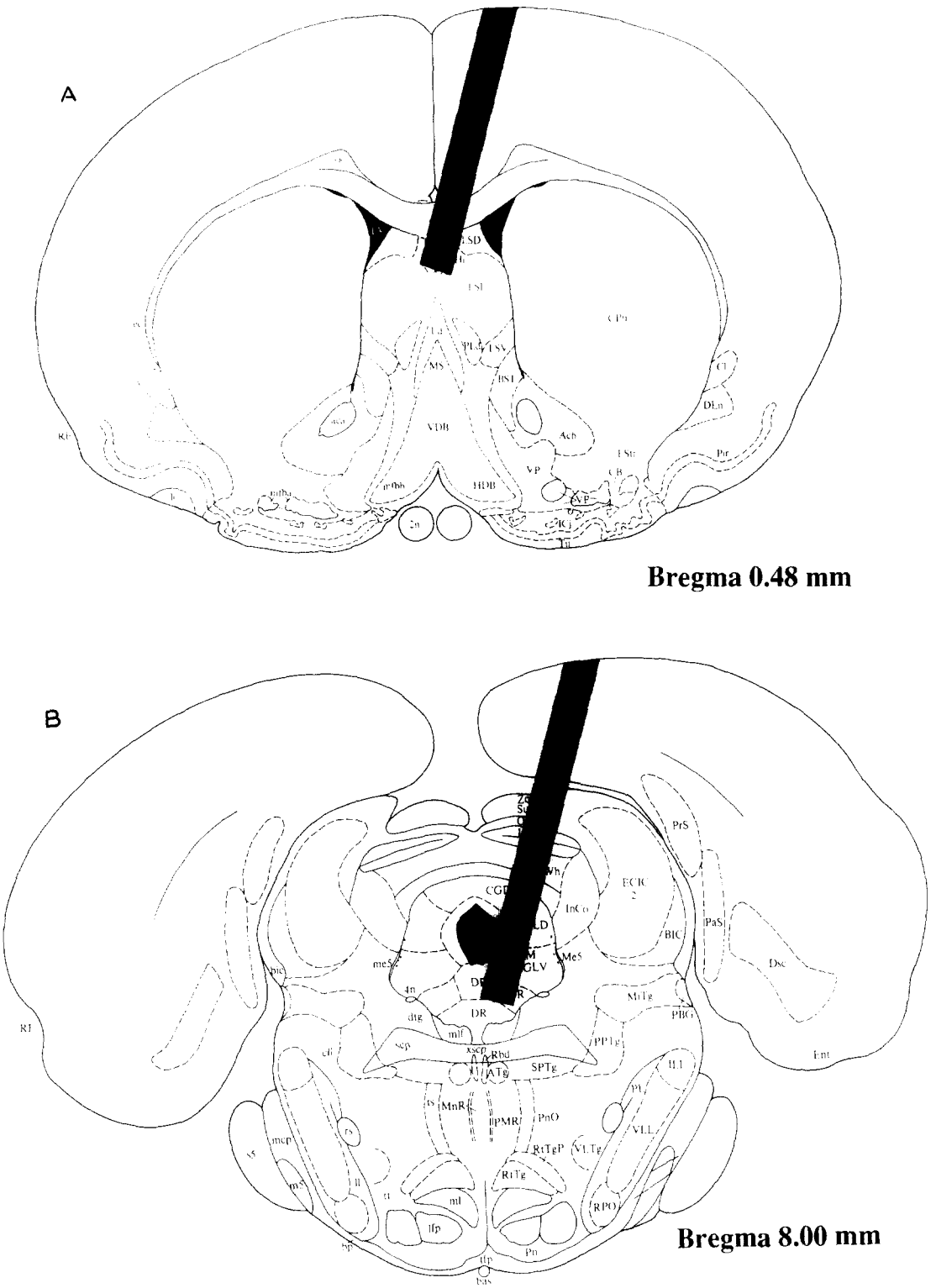

Fig. 3. Representative examples of septal (A) and raphe (B) cannulae placements for rats in the microinjection study. The black area indicates the maximum penetration of the guide and injection cannulae. The guide cannula would have ended 2 mm dorsal to the indicated terminal area. Sections were copied from the atlas of Paxinos and Watson[27] at the co-ordinates from bregma as indicated.

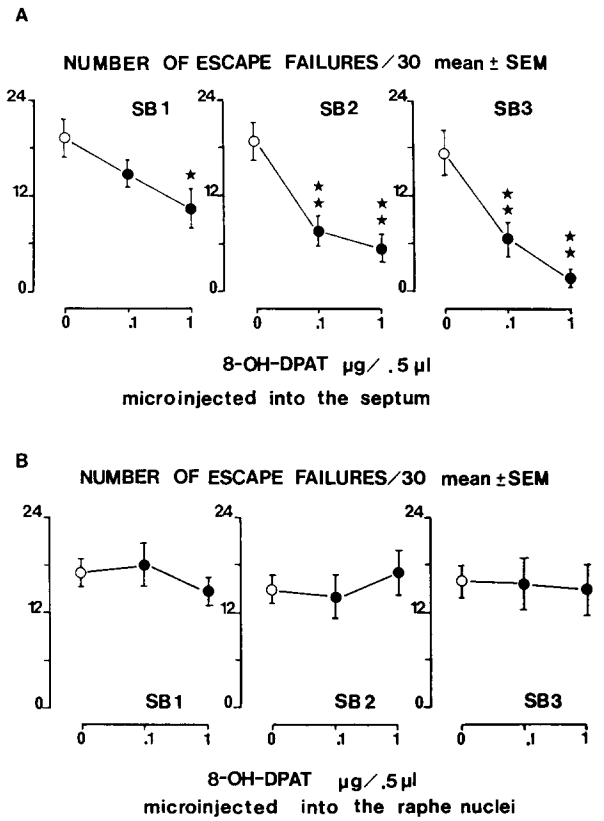

Fig. 4. A: effects of microinjections of 8-OH-DPAT into the septum on reversal of escape failures as a function of the number of exposures to daily shuttle-box sessions (SB 1–3). B: effects of microinjections of 8-OH-DPAT into the raphe nuclei on reversal of escape failures as a function of the number of exposures tot daily shuttle-box sessions (SB 1–3). Data are the mean number (± S.E.M.) of escape failures at each of the 3 consecutive daily shuttle-box sessions. Escape failure referred to the absence of the response required of the rat to change compartments during the electric foot-shock presentations. 8-OH-DPAT was microinjected (0.1; 1 µg/0.5 µl) 6 h after daily from the end of the inescapable shock session and daily thereafter before each test session. Stars indicate that 8-OH-DPAT-treated rats (●) differed significantly from the corresponding vehicle-treated rats (○) at $^{*}P < 0.05$; $^{**}P < 0.01$ (Dunnett's *t*-test).

DISCUSSION

Previous studies have shown that 5-HT receptor subtypes located both postsynaptically and presynaptically – on serotoninergic somas and/or dendrites in the dorsal raphe nucleus for the 5-HT_{1A} receptors, on serotoninergic nerve terminals for the 5-HT_{1B} receptors (for a review, see ref. 28) – probably participate in the central mechanisms of action of antidepressant drugs[2]. Using the learned helplessness paradigm, we presently confirmed the participation of 5-HT_{1A} receptors since their subchronic stimulation by the selective agonist 8-OH-DPAT (at doses ranging from 0.03 to 1.0 mg/kg, i.p.) was as efficient as subchronic administration of classical antidepressants to eliminated behavioural deficits in rats submitted to inescapable electric foot-shocks[22,32,34]. In contrast, the selective 5-HT_{1B} agonist[25] CGS 12066B (0.06 to 1 mg/kg/day) does not share this property (P. Martin, unpublished observations), indicating that 5-HT_{1B} receptors do not mediate the behavioural effects of antidepressants in the learned helplessness paradigm.

Previous data in the literature have shown that 5-HT_{1A} agonists exhibit antidepressant-like properties in two other rat models of depression, the restraint stress-induced open field locomotor deficit[17] and the immobility induced by forced swimming[3]. Altogether, these results and those presently obtained with the learned helplessness paradigm strongly support that 5-HT_{1A} agonists are potential antidepressant drugs. Indeed, preliminary observations in humans are in line with the proposal since clearcut antidepressant effects of chronic administration of the 5-HT_{1A} agonists gepirone and buspirone have been reported by several groups[1,4,31].

Interestingly, the antidepressant-like effects of 8-OH-DPAT and other 5-HT_{1A} agonists have been observed after the chronic or subchronic administration of these drugs, i.e. when pre- and postsynaptic 5-HT_{1A} receptors underwent differential adaptive changes. Thus, Kennett et al.[18] have shown that the acute hyperphagic response to 8-OH-DPAT, which depends on the activation of the *presynaptic* 5-HT_{1A} autoreceptors within the anterior raphe nuclei[16], is markedly decreased 24 h after a prior treatment with large doses of 8-OH-DPAT or of other 5-HT_{1A} agonists. Furthermore, the same pretreatment also prevented the 8-OH-DPAT-induced decrease in 5-HIAA levels normally observed within the anterior raphe area of acutely treated rats[18]. Finally, M. Beer (cited in Curzon[5]) did find a decreased density of [^{3}H]8-OH-DPAT specific binding sites in the

anterior raphe area of rats treated with 8-OH-DPAT 24 h before death. In contrast, extensive electrophysiological[6] and biochemical[9] investigations have shown that *postsynaptic* 5-HT_{1A} receptors within forebrain limbic structures (notably the hippocampus and the septum) do not desensitize after repeated administrations of a 5-HT_{1A} agonist. Altogether these data suggest that the postsynaptic but not the presynaptic 5-HT_{1A} receptors were functional under the drug regimen presently used for revealing the antidepressant-like properties of 8-OH-DPAT in the learned helplessness paradigm. Accordingly, a postsynaptic, rather than a presynaptic, action of 8-OH-DPAT might be involved in the antidepressant effects of this drug. Indeed, when the presynaptic 5-HT_{1A} autoreceptors were fully functional, i.e. in untreated rats, an acute treatment with 8-OH-DPAT failed to reduce the behavioural deficit induced by inescapable foot-shocks (P. Martin, unpublished observation).

A more direct demonstration of the selective involvement of postsynaptic rather than presynaptic 5-HT_{1A} receptors in the antidepressant-like properties of 8-OH-DPAT was presently attempted by examining the behavioural effects of this drug after the lesion of ascending serotoninergic neurones. Thus, the daily administration of 8-OH-DPAT in rats whose forebrain serotoninergic systems were partially destroyed by previous 5,7-DHT microinjection into the anterior raphe nuclei still eliminated escape failures induced by inescapable foot-shocks. This effect was observed in spite of a decrease in [^{3}H]5-HT uptake ranging from approximately 50 to 90% in the various telencephalic structures. Although partial, this lesion has been previously shown to reduce the density of presynaptic [^{3}H]8-OH-DPAT binding sites within the dorsal raphe nucleus[36] without affecting the postsynaptic [^{3}H]8-OH-DPAT binding sites. Furthermore, in the same learned helplessness paradigm, the antidepressant-like effects of a drug acting presynaptically on serotoninergic systems: indalpine (a potent and selective 5-HT uptake inhibitor), is markedly impaired after such 5,7-DHT lesions[23]. By contrast, the intact behavioural effects of 8-OH-DPAT in the lesioned animal further suggest that postsynaptic rather than presynaptic 5-HT_{1A} receptors mediated these effects.

Finally, 8-OH-DPAT was injected directly into the presynaptic area: anterior raphe nuclei, or into a postsynaptic area: septum, in an attempt to reproduce the behavioural effects of a systemic injection of this drug. Clearly the intraseptal injection but not that in the anterior raphe area significantly reduced the behavioural deficit induced by inescapable foot-shocks. Other limbic areas might be involved as well since evidence has been reported for the involvement of the hippocampus, where 5-HT_{1A} receptors are particularly abundant[36], in behavioural recovery from stress-induced deficits[33].

In conclusion, the present data support that the antidepressant-like properties of 8-OH-DPAT involve its agonist effects on postsynaptic 5-HT_{1A} receptors, notably those located in limbic structures. By contrast, previous data have shown that the anxiolytic properties of this drug are mediated by the stimulation of the presynaptic 5-HT_{1A} autoreceptors within the anterior raphe area. Therefore the mixed antidepressant-anxiolytic effects of 5-HT_{1A} agonists seem to depend on the stimulation of 5-HT_{1A} receptors differently located in the central nervous system.

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