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Effect of 8-OH-DPAT on temporal discrimination following central 5-hydroxytryptamine depletion

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Abstract

The 5-hydroxytryptamine (5-HT)$_{1A}$ receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) alters performance in discrete-trials timing schedules. 5-HT$_{1A}$ receptors occur both presynaptically and postsynaptically, but it is not known which receptor population mediates the effects of 8-OH-DPAT on timing. Rats received intra-raphe injections of 5,7-dihydroxytryptamine ($n=16$) or sham lesions ($n=14$). They were trained in a discrete-trials psychophysical procedure in which levers were presented at a predetermined time after the onset of each trial (2.5, 7.5, . . ., 47.5 s). A response on lever A was reinforced if lever presentation occurred <25 s after trial onset; a response on lever B was reinforced if lever presentation occurred >25 s after trial onset. After 70 preliminary sessions, the rats received 8-OH-DPAT (25, 50, 100, 200 μg kg^{-1} sc) and saline vehicle. The percentage of responses on lever B (%B) increased as a function of time from trial onset. Under the baseline (vehicle-treatment) condition, performance did not differ between the two groups. 8-OH-DPAT did not alter the indifference point (time corresponding to %B = 50%), but dose-dependently increased the Weber fraction in both groups. Forebrain concentrations of 5-HT and 5-HIAA in the lesioned group were approximately 10% of control levels. The results suggest that the effect of 8-OH-DPAT on performance on discrete-trials timing schedules is mediated by postsynaptic 5-HT$_{1A}$ receptors. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: 5-HT$_{1A}$ receptors; 8-OH-DPAT; 5,7-dihydroxytryptamine; Timing; Discrete-trials psychophysical procedure

1. Introduction

There is increasing evidence that the ascending 5-hydroxytryptaminergic (5-HTergic) pathways contribute to the regulation of interval timing behaviour. Recent experiments have shown that destruction of the 5-HTergic pathways has qualitatively different effects on performance in different types of timing schedule, suggesting that 5-HTergic mechanisms may contribute to several behavioural processes that are involved to differing degrees in different types of timing paradigm (see Al-Ruwaitea et al., 1997; Ho et al., 1998).

Two classes of timing schedule which appear to be differentially sensitive to manipulation of central 5-HTergic function are *immediate* and *retrospective* timing schedules. In immediate timing schedules, the subject is required to regulate its own behaviour in time (''temporal differentiation of behaviour''), whereas in retrospective timing schedules, the subject is required to discriminate the durations of exteroceptive stimuli (''temporal discrimination'') (Killeen and Fetterman, 1988; Killeen et al., 1997). Performance on both types of timing schedule can be characterized by a measure of the central tendency of timing behaviour, the *indifference point* (T_{50}), and a measure of the variability of performance, the Weber fraction (see Al-Ruwaitea et al., 1997; Hinton and Meck, 1997; Killeen et al., 1997). The Weber fraction is usually defined as the ratio of the limen to T_{50}, the limen being derived from the slope of the psychometric function (see Section 2.8 for details).

Chiang et al. (2000) recently examined the effects of the 5-HT$_{1A}$ receptor agonist 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT) on both temporal differentiation (free-operant psychophysical procedure: Bizo and White, 1994a,b; Stubbs, 1976) and temporal discrimination (interval bisection task: Catania, 1970; Church and Deluty, 1977),

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and found that the drug had qualitatively different effects on performance on the two types of timing task. In the case of the free-operant psychophysical procedure, 8-OH-DPAT produced a dose-dependent reduction of the indifference point, together with an increase in the Weber fraction. In contrast, on the interval bisection task, 8-OH-DPAT increased the Weber fraction, but had no effect on the indifference point.

The pharmacological mechanisms underlying these effects of 8-OH-DPAT on timing are uncertain. It is likely that the effects are mediated by 5-HT_{1A} receptors, because 8-OH-DPAT is a rather selective agonist of these receptors (De Vry, 1995: see Section 4 for consideration of other actions of 8-OH-DPAT). Stimulation of 5-HT_{1A} receptors on the cell bodies and dendrites of 5-HTergic neurones in the raphe nuclei (somatodendritic autoreceptors) suppresses 5-HT release in the forebrain (Bonvento et al., 1992), and this is believed to be the basis of many of 8-OH-DPAT's behavioural effects (see De Vry, 1995). However, 5-HT_{1A} receptors also occur on postsynaptic membranes in structures innervated by the 5-HTergic pathways (Pompeiano et al., 1992). It seems that postsynaptic receptors are responsible for some of 8-OH-DPAT's behavioural effects, as evidenced by the survival of these effects following neurotoxic destruction of 5-HTergic neurones (Carli and Samanin, 2000).

The present experiment attempted to determine whether 8-OH-DPAT's ability to impair temporal discrimination performance is mediated by pre- or postsynaptic receptors. The effect of 8-OH-DPAT was compared between intact rats and rats whose 5-HTergic pathways had been ablated by injection of the selective neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) into the median and dorsal raphe nuclei. Destruction of the 5-HTergic pathways should eliminate or greatly reduce the contribution of somatodendritic 5-HT_{1A} autoreceptors, thus attenuating any effects of 8-OH-DPAT that might be mediated by a presynaptic action of the drug. In contrast, the lesion should not attenuate any effects that 8-OH-DPAT might exert via postsynaptic 5-HT_{1A} receptors (see De Vry, 1995; Carli and Samanin, 2000).

2. Method

The experiment was carried out in accordance with UK Home Office regulations governing experiments on living animals.

2.1. Subjects

Thirty female Wistar rats aged approximately 4 months and weighing 250–290 g at the start of the experiment were housed individually under a constant cycle of 12 h light and 12 h darkness (lights on 07:00–19:00 h), and were maintained at 80% of their initial free-feeding body weights by providing a limited amount of standard rodent diet after each experimental session. Tap water was freely available in the home cage.

2.2. Surgery

The rats received either lesions of the dorsal and median raphe nuclei ($n = 16$) or sham lesions ($n = 14$). Our methods for the surgical preparation of the rats have been described in detail elsewhere (Wogar et al., 1992). Each rat was anaesthetised with 4% halothane in oxygen, and placed in a stereotaxic apparatus; anaesthesia was maintained with 2% halothane in oxygen during the surgery. The following stereotaxic coordinates (Paxinos and Watson, 1982) were used to locate the median and dorsal raphe nuclei: AP +1.2, L 0.0, DV +1.5 (median) or +3.5 (dorsal), measured from the interaural line, with the incisor bar fixed 3.3 mm below the interaural line. The neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) was injected into the median and dorsal raphe nuclei of the rats in the lesioned group; the control group received sham injections into the same areas. The dose of 5,7-DHT injected into the dorsal and median raphe nuclei was 4 μg base dissolved in 2 μl vehicle (0.9% w/v sodium chloride solution with 0.1% ascorbic acid) in each case. The injection rate was 10 nl s^{-1} (total injection time, 200 s), and the cannula was left in position for a further 3 min after completion of the injection.

2.3. Apparatus

The rats were trained in operant conditioning chambers (Campden Instruments, Sileby, UK) of internal dimensions $20 \times 23 \times 22.5$ cm. One wall of the chamber contained a recess into which a motor-operated dipper could deliver 50 μl of a liquid reinforcer. Apertures were situated 5 cm above and 2.5 cm on either side of the recess; a motor-driven retractable lever could be inserted into the chamber through each aperture. Each lever could be depressed by a force of approximately 0.2 N. The chamber was enclosed in a sound-attenuating chest; masking noise was provided by a rotary fan. A CUBE microcomputer (Paul Fray, Cambridge, UK) located in an adjoining room controlled the schedules and recorded the behavioural data.

2.4. Behavioural training

Two weeks after surgery, the food deprivation regimen was started and the rats were gradually reduced to 80% of their free-feeding body weights. They were trained to press the levers, and were exposed to a discrete-trials continuous reinforcement schedule for two sessions. Then they underwent daily training sessions under the discrete-trials psychophysical procedure, as described below.

Fifty-minute training sessions took place 7 days a week, at the same time each day during the light phase of the daily cycle (between 07:00 and 12:00 h). The reinforcer, a 0.6-M solution of sucrose in distilled water, was prepared daily

before each session. Each session consisted of fifty trials, successive trials being initiated at 60-s intervals. Each trial started with the illumination of a lamp above the central reinforcer recess. After a predetermined interval had elapsed (see below), the levers were inserted into the chamber. A single response on either lever resulted in withdrawal of both levers and extinguishing of the light; the chamber remained in darkness until the start of the next trial. Lever insertion took place once in each trial, at one of the following "entry points" following the start of the trial: 2.5, 7.5, 12.5, 17.5, 22.5, 27.5, 32.5, 37.5, 42.5 or 47.5 s. If lever insertion took place at any of the first five entry points (i.e., less than 25 s after trial onset), a response on lever A resulted in reinforcer delivery, whereas a response on lever B did not; conversely, if lever insertion took place at any of the last five entry points (i.e., more than 25 s after trial onset), a response on lever B resulted in reinforcer delivery, whereas a response on lever A did not. If no response occurred within 5 s of lever insertion, the levers were withdrawn and the light was extinguished (this seldom occurred after the first few sessions of training). The positions of levers A and B (left versus right) were counterbalanced across subjects. In each session, there were 40 trials in which both levers were presented (four trials with each entry point, in pseudorandom sequence). The remaining trials were forced-choice trials in which only one lever was presented (lever A in five trials and lever B in the other five), the entry points occurring in a pseudo-random sequence.

2.5. Drug treatment

The drug treatment regimen started after 70 sessions of preliminary training under the discrete-trials psychophysical procedure. Treatments were given by subcutaneous injection (0.1 ml/kg body weight) using a 26-gauge needle, 15 min before the start of the experimental session. Injection of 8-OH-DPAT was given on Tuesdays and Fridays, and injection of the vehicle alone (0.9% sodium chloride solution) on Mondays and Thursdays; no injections were given on Wednesdays, Saturdays or Sundays. Each rat received four doses of 8-OH-DPAT in the order of increasing doses (25, 50, 100 and 200 $\mu g\ kg^{-1}$; doses refer to weights of the salt, 8-OH-DPAT HBr). Each dose was administered on 8 occasions in order to accrue a sufficient number of trials to obtain reliable estimates of the timing indices for individual rats (Chiang et al. 2000).

2.6. Biochemical assays

At the end of the behavioural experiment, the rats were killed, their brains were removed, and the following regions were dissected out on ice: parietal cortex, hippocampus, amygdala, nucleus accumbens and hypothalamus. The concentrations of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), noradrenaline and dopamine in each region were measured by high-performance liquid chromatography combined with electrochemical detection. The method was as described by Wogar et al. (1992), with the exception that the mobile phase for the indoleamine assay was 0.1 M sodium citrate, buffered to pH 2.45, containing 75% (w/v) acetonitrile and 1 mM octane sulphonic acid (ion pair agent); *N*-ω-methyl-5-hydroxytryptamine was used as the internal standard in the indoleamine assay.

2.7. Drugs

5,7-dihydroxytryptamine creatine sulphate and (±)8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide were obtained from Sigma Chemical Company (Poole, UK).

2.8. Data analysis

2.8.1. Behavioural data

The %B data from each treatment condition (vehicle alone, and 25, 50, 100 and 200 $\mu g\ kg^{-1}$ 8-OH-DPAT) were analysed by three-factor analysis of variance (group × treatment × time-bin) with repeated measures on the second and third factors. A two-parameter logistic function was fitted to the %B data obtained from each rat: $\%B = 100/(1+[t/T_{50}]^{-\varepsilon})$, where t is time from trial onset, T_{50} (the indifference point) is a parameter expressing the time at which %B = 50%, and ε is the slope of the function (Al-Zahrani et al., 1996). The curve-fitting procedure yielded estimates (± S.E. est.) of the values of T_{50} and the slope, from which the Weber fraction was determined as follows. The limen was defined as half the difference between T_{75} and T_{25} (T_{75} and T_{25} being the values of t corresponding to %B = 75% and %B = 25%), and the Weber fraction was calculated as the ratio of the limen to T_{50}. The values of T_{50} and the Weber fraction were analysed by two-factor analyses of variance (group × treatment) with repeated measures on the latter factor.

2.8.2. Biochemical data

The concentrations of 5-HT, 5-HIAA, noradrenaline and dopamine in each brain region were compared between the two groups using Student's t test.

3. Results

3.1. Behavioural data

Fig. 1 shows, for each group, the relation between %B and time from the onset of the trial, under each treatment condition. Analysis of variance of these data revealed a significant main effect of time-bin [$F(9,252) = 604.8$, $P < .001$], but no significant main effect of group [$F < 1$] or treatment [$F(4,112) = 1.6$, $P > .1$]. The treatment × time-bin interaction was significant [$F(36,1008) = 8.1$, $P < .001$], reflecting "flattening" of the psychometric curves under the higher doses of 8-OH-DPAT (see Fig. 1). There was a small but significant group × time-bin interaction [$F(9,252) = 3.0$,

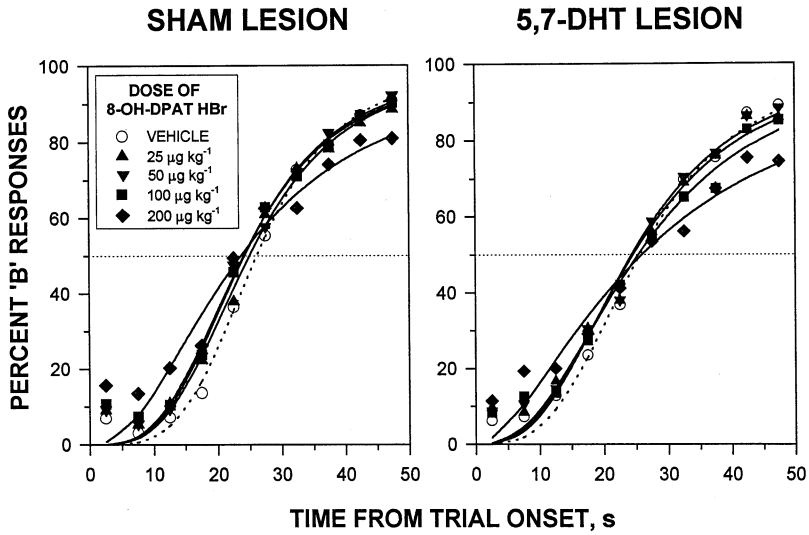

Fig. 1. Effect of 8-OH-DPAT on proportional choice of lever B as a function of time from trial onset (s). *Left-hand graph*: sham-lesioned group; *right-hand graph*: 5,7-DHT-lesioned group. Open circles: vehicle-alone treatment; filled symbols: 8-OH-DPAT treatment, subcutaneously (see inset key for doses). Horizontal dotted lines indicate indifference (50% choice of lever B). Smooth curves are best-fit logistic functions. 8-OH-DPAT flattened the curve without significantly displacing the indifference time (see text).

$P < .02$], reflecting a tendency for the psychometric curves to be slightly flatter in the lesioned than the sham-lesioned group. Neither the group × treatment interaction nor the three-way interaction was statistically significant [F's < 1].

Fig. 2 shows the group mean values of T_{50} and the Weber fraction derived from the logistic functions fitted to the data from the individual rats under each treatment condition. T_{50} was not significantly affected by 8-OH-DPAT in either group: analysis of variance showed no significant main effect of group [$F < 1$] or treatment [$F(4,112) = 1.5$, $P > .1$], and no significant interaction [$F(4,112) = 1.6$, $P > .1$]. However, the Weber fraction increased with increasing doses of 8-OH-DPAT in both groups. Analysis of variance revealed a significant main effect of treatment [$F(4,112) = 14.3$, $P < .001$], while the main effect of group and the interaction effect were not statistically significant [F's < 1]; analysis of the simple main effects indicated that the effect of treatment was statistically significant in both groups [*sham-lesioned group*: $F(4,52) = 6.8$, $P < .001$; *lesioned group*: $F(4,60) = 8.9$, $P < .001$], and multiple comparisons with the vehicle-alone treatment (Dunnett's test, $k = 5$) revealed a significant increase in the Weber fraction following 200 μg kg^{-1} 8-OH-DPAT in each group [*sham-lesioned group*: $t(48) = 4.8$, $P < .001$; *lesioned group*: $t(52) = 5.1$, $P < .001$].

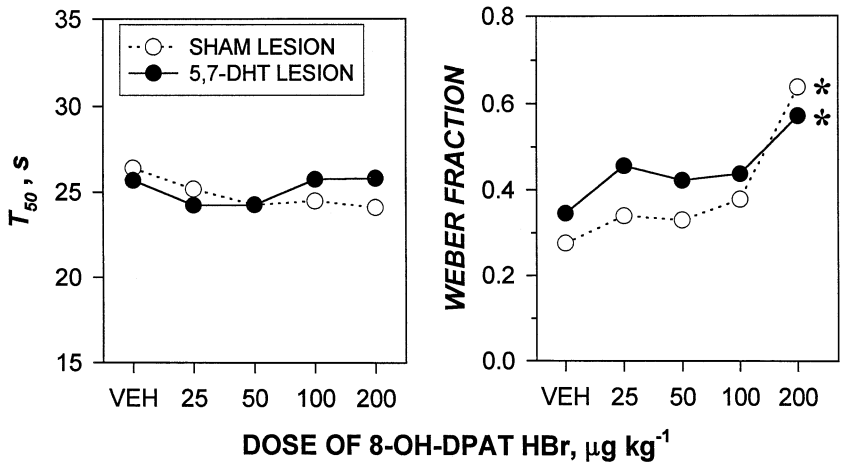

Fig. 2. Effect of 8-OH-DPAT on indices of temporal discrimination. *Left-hand graph*: indifference time, T_{50} (s); *right-hand graph*: Weber fraction. Open circles: sham-lesioned group; filled circles: 5,7-DHT-lesioned group. 8-OH-DPAT did not significantly alter T_{50} in either group, but significantly increased the Weber fraction in both groups (significance of difference from vehicle control, * $P < .01$; see text).

Table 1
Concentrations of 5HT, 5HIAA, noradrenaline and dopamine (ng g^{-1} wet weight of tissue, mean ± S.E.M.) in brain regions of the two groups

Region	Control	Lesioned	% Control	Control	Lesioned	% Control
A	5HT			5HIAA		
Parietal cortex	390 ± 16	46 ± 8	12*	305 ± 13	21 ± 6	7*
Hippocampus	529 ± 25	39 ± 5	7*	457 ± 25	35 ± 4	8*
Amygdala	1066 ± 35	97 ± 30	9*	642 ± 27	65 ± 18	10*
N. accumbens	1280 ± 84	112 ± 57	9*	848 ± 40	52 ± 26	6*
Hypothalamus	1303 ± 73	192 ± 39	15*	771 ± 37	132 ± 22	17*
B	Noradrenaline			Dopamine		
Parietal cortex	390 ± 14	352 ± 15	94	165 ± 19	151 ± 16	92
Hippocampus	601 ± 27	534 ± 27	102	23 ± 2	18 ± 2	78
Amygdala	858 ± 33	774 ± 22	90	571 ± 38	539 ± 35	95
N. Accumbens	503 ± 81	472 ± 52	94	6774 ± 593	6435 ± 339	95
Hypothalamus	2460 ± 175	2179 ± 75	89	415 ± 27	388 ± 18	93

Significance of difference between the two groups (t test).
* $P < .001$.

3.2. Biochemical data

Table 1A shows the concentrations of 5-HT and 5-HIAA, and Table 1B the concentrations of noradrenaline and dopamine, in the brains of the rats belonging to the two groups. The levels of 5-HT and 5-HIAA were significantly reduced in the lesioned group, compared to the sham-lesioned group, in all areas assayed [$t(28) > 4.0$, $P < .001$ in each case]. There was no significant effect of the lesion on the levels of the catecholamines.

4. Discussion

The timing schedule used in this experiment was a discrete-trials variant of the free-operant psychophysical procedure (Stubbs 1976, 1979, 1980; Bizo and White, 1994a,b, 1997). The timing task took the form of a conditional discrimination based on the length of time that had elapsed between the illumination of a light which marked the start of the trial and presentation of the levers. Responses on lever A were reinforced following stimulus durations < 25 s, whereas responses on lever B were reinforced following stimulus durations of >25 s. In keeping with performance of other temporal discrimination tasks, the rats' preference for lever B increased as a sigmoid function of stimulus duration, indifference between the two levers (%B = 50%) being attained approximately at the middle of the duration range (25 s), when reinforcer allocation was transferred from lever A to lever B (see Gibbon, 1977; Killeen et al., 1997). The Weber fraction (approximately 0.3 under the vehicle-alone condition) was similar to that seen in other temporal discrimination tasks (see Al-Ruwaitea et al., 1997; Killeen et al., 1997).

In the case of the sham-lesioned group, the effect of 8-OH-DPAT was to increase the size of the Weber fraction without altering the locus of the indifference time, T_{50}. This pattern of effect resembles that observed by Chiang et al. (2000) in the case of another temporal discrimination task, the interval bisection task, using the same range of doses of 8-OH-DPAT as that used in the present experiment. However, it differs from the effect which these authors found in the case of the free-operant psychophysical procedure; in that case, 8-OH-DPAT dose-dependently reduced the value of T_{50}, as well as increasing the Weber fraction. It may be noted that the duration range (2.5–47.5 s) used in the present experiment was similar to that used by Chiang et al. (2000) in the free-operant psychophysical procedure, and considerably longer than the range which they employed in the interval bisection task (2–8 s). This strongly suggests that the different effects of 8-OH-DPAT in immediate and retrospective timing schedules reflect the different forms of timing behaviour (i.e. temporal differentiation vs. temporal discrimination), and not merely the different time ranges that are often employed in these schedules.

Injection of 5,7-DHT into the median and dorsal raphe nuclei resulted in a profound depletion of 5-HT and 5-HIAA from the forebrain, the extent of which was similar to that seen in previous experiments using our protocol (e.g., Chiang et al., 1999). The lesion had little effect on baseline temporal discrimination performance. (As noted above, the significant group × time-bin interaction appears to reflect a slightly flatter psychometric function in the lesioned group than the sham-lesioned group; however, this was not manifested in a significant between-group difference in either T_{50} or the Weber fraction.) The present results are in broad agreement with previous experiments which have shown that central 5-HT depletion does not preclude the attainment of accurate temporal discrimination (see Al-Ruwaitea et al., 1997). However, there is evidence that central 5-HT depletion can affect performance on retrospective timing schedules under some circumstances. Thus, Morrissey et al. (1994) and Ho et al. (1995) reported that 5-HT depletion reduced the value of T_{50} in an interval bisection task in

which rats discriminated between a 2- and 8-s light stimulus. This effect was shown to be mediated by a facilitatory effect of the lesion on rats' tendency to move across the chamber during stimulus presentation, which seems to occur only within a fairly restricted range of stimulus durations (Graham et al., 1995; Ho et al., 1995; see also Al-Ruwaitea et al., 1997).

The principal finding of this experiment was that destruction of the 5-HTergic pathways did not significantly alter the effect of 8-OH-DPAT on timing performance, suggesting that the deleterious effect of 8-OH-DPAT on temporal discrimination is unlikely to have been mediated by an action of the drug on somatodendritic 5-HT_{1A} autoreceptors. The possibility cannot be totally excluded that the small proportion of 5-HTergic neurones, which survived the neurotoxic effect of 5,7-DHT, may have possessed a sufficient number of 5-HT_{1A} receptors to mediate an effect of 8-OH-DPAT. However it seems unlikely that this made a significant contribution to the overall effect of 8-OH-DPAT seen in this experiment, because central 5-HT depletion of a similar extent to that seen in this experiment has been found to reduce or abolish some other behavioural effects of 8-OH-DPAT administered in the same range of doses as that used in this experiment (Cervo and Samanin, 1991; Currie et al., 1998; Carli and Samanin, 2000).

A plausible alternative explanation for 8-OH-DPAT's effect on temporal discrimination is that it may be mediated by postsynaptic 5-HT_{1A} receptors. 5-HT_{1A} receptors are present on postsynaptic membranes in several structures that are innervated by the 5-HTergic pathways, including the cingulate cortex and hippocampus (Pompeiano et al., 1992). These receptors mediate membrane hyperpolarization, and appear to operate in opposition to 5-HT_2 receptors, the two receptor types often co-existing on the membrane of the same neurone (Araneda and Andrade, 1991). 5-HT_{1A} and 5-HT_2 receptor agonists are known to have opposite effects on some behavioural functions (e.g., Marek et al., 1989), but qualitatively similar effects on others (e.g., Evenden, 1999). The effects of 5-HT_2 receptor agonists and antagonists on temporal discrimination have yet to be explored.

8-OH-DPAT is a rather selective agonist of 5-HT_{1A} receptors. It has low affinity for α_1- and α_2-adrenoceptors and D_2 dopamine receptors (Brown et al., 1990; Assié and Koek, 2000), and its affinity for most 5-HT receptor subtypes other than the 5-HT_{1A} receptor is several orders of magnitude lower than its affinity for 5-HT_{1A} receptors (see Hoyer et al., 1994; Barnes and Sharp, 1999). A major exception to this generalization is the 5-HT_7 receptor, for which 8-OH-DPAT has a high affinity (Thomas et al., 1999). 5-HT_7 receptors may contribute to some of the postsynaptic actions of 8-OH-DPAT; they have, for example, been implicated in 8-OH-DPAT's facilitatory effect on passive avoidance behaviour (Otano et al., 1999). Whether 5-HT_7 receptors play any role in 8-OH-DPAT's effects on timing behaviour remains an open question pending further experiments using selective antagonists.

The present experiment was specifically concerned with the effect of 8-OH-DPAT on temporal discrimination. As discussed earlier, Chiang et al. (2000) found that 8-OH-DPAT had a qualitatively different effect on temporal differentiation performance, dose-dependently reducing the value of T_{50} in the free-operant psychophysical procedure. A further experiment is needed to determine whether the effect of 8-OH-DPAT on T_{50} in immediate timing schedules is sensitive to ablation of the ascending 5-HTergic pathways.

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