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A comparison of the effects of 8-OH-DPAT pretreatment on different behavioural responses to 8-OH-DPAT

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Abstract

The effects of daily pretreatments with the prototypical 5-HT_{1A} receptor agonist 8-hydroxy-(di-*n*-propylamino) tetralin (8-OH-DPAT) (1.0 mg/kg s.c.) on behavioural responses to challenge by 8-OH-DPAT (0.5 mg/kg s.c.) due to activation of 5-HT_{1A} receptors were determined. The responses had strikingly different susceptibilities to pretreatment. These were not explicable by different effects on pre- and postsynaptic responses. Thus, two components of the 5-HT syndrome due to action at postsynaptic sites (i.e. flat body posture and reciprocal forepaw treading) were substantially attenuated 1 day after a single pretreatment with 8-OH-DPAT, but the tail-flick response, though due to action at postsynaptic 5-HT_{1A} sites, was completely unimpaired by 14 pretreatments while the hypothermic response which also probably involves postsynaptic sites showed progressively increased attenuation on 14 pretreatments. 8-OH-DPAT-induced hyperphagia which depends on activation of presynaptic sites was unimpaired by the pretreatment schedule. The results are discussed in relation to receptor reserve, second messenger changes and effects at NMDA receptors. They imply a need for caution in the use of chronic effects of 5-HTergic drugs on specific 5-HT_{1A} receptor-dependent responses as indices of mechanisms for the therapeutic actions of the drugs.

Keywords: 5-HT (5-hydroxytryptamine, serotonin); 5-HT_{1A} receptor; 5-HT syndrome; 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin); Hyperphagia; Hypothermia; Tail-flick

1. Introduction

The effects of pretreating rats with 5-HT_{1A} receptor agonists on subsequent responses to challenge by a 5-HT_{1A} receptor agonist are of particular interest as the antidepressant and anxiolytic effects of these substances (Jacobson et al., 1985; Amsterdam, 1992) and of the selective serotonin reuptake inhibitor antidepressants (Feighner and Boyer, 1991) are apparent only after treatment for a number of days. However, the relevant literature is somewhat confusing. For example, the hyperphagic response to the prototypical 5-HT_{1A} receptor agonist 8-hydroxy-(di-*n*-propylamino) tetralin (8-OH-DPAT), a behavioural index of presynaptic 5-HT_{1A} receptor activation (Dourish et al., 1986; Hutson et al., 1988) was attenuated after giving a single dose of the drug on the previous day (Kennett et al., 1987) consistent with the rapid selective decrease of these presynaptic sites by 8-OH-DPAT found by Beer et al. (1990). On the other hand, neither the hyperphagic response (Uphouse et al., 1991) nor a neurochemical effect of activating the presynaptic sites, i.e. reduced, 5-HT synthesis at terminal-rich sites (Larsson et al., 1990) were altered by a single pretreament with 8-OH-DPAT. Other 5-HT_{1A} receptor agonists, i.e. gepirone (Welner et al., 1989), and ipsapirone (Fanelli and Mc Monagle-Strucko, 1992; Schechter et al., 1990) significantly decreased presynaptic sites or function but only after prolonged treatment. Also, the induction of male copulatory behaviour by 8-OH-DPAT, which probably occurs via presynaptic 5-HT_{1A} receptor activation, was not attenuated by pretreatment for 15 days (Johansson et al., 1990). Furthermore, although postsynaptic 5-HT_{1A} receptors were not decreased even on repeated treatment with 8-OH-DPAT (Larsson et al., 1990) or other 5-HT_{1A} agonists (Welner et al., 1989; Fanelli and Mc Monagle-Strucko, 1992), numerous behavioural responses to their activation are reported to be readily attenuated, e.g. components of the 5-HT syndrome (forepaw treading and flat body posture) and

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hypothermia (Larsson et al., 1990), corticosterone secretion (Kelder and Ross, 1992) and the blockade of acquisition of a passive avoidance response (Jackson et al., 1994). However, Kennett et al. (1987) found that a single 8-OH-DPAT pretreatment did not attenuate the 5-HT syndrome when elicited by giving the drug 24 h later.

The above findings were obtained with rats from different sources, kept under different conditions, given different drug treatments and with responses scored in different ways. We have, therefore, compared, in a single study, the effects of pretreatment with 8-OH-DPAT (1 mg/kg s.c.) for 1, 3 and 14 days on responses to the activation of 5-HT_{1A} receptors by a challenge dose of 8-OH-DPAT (0.5 mg/kg). Responses investigated were the hyperphagic effect of activating presynaptic 5-HT_{1A} receptors (Dourish et al., 1986; Hutson et al., 1988) and the following effects of activating postsynaptic 5-HT_{1A} receptors: spontaneous tail-flick (Millan et al., 1991; Bervoets et al., 1993), hypothermia (Hjorth, 1985; Hutson et al., 1987; Bill et al., 1991; O'Connell et al., 1992; Millan et al., 1993) and flat body posture and reciprocal forepaw treading (Tricklebank et al., 1985).

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Charles River, UK) weighing 250–350 g were housed individually under a 12-h light-dark cycle (lights on 06:00 h) under constant temperature (21 ± 1°C) with rat diet 22F (Labsure, Poole, Dorset, UK) and water freely available for at least 5 days before commencing pretreatment by daily s.c. injections of 8-OH-DPAT HBr (1.0 mg/kg unless stated otherwise, Research Biochemicals) dissolved in 0.9% NaCl given between 12:00 and 14:00 h and in a volume of 1 ml/kg. Challenge doses of 8-OH-DPAT (0.5 mg/kg s.c.) were given 24 h after the last injection. The following four responses were determined on groups of rats which had been pretreated with 8-OH-DPAT for 1, 3 or 14 days. Only one response was determined/rat.

2.2. Hyperphagia

A weighed amount of food pellets was placed in each hopper immediately before injection of the challenge dose of 8-OH-DPAT and the weight consumed determined 2 h later. Three control groups were used for each 8-OH-DPAT pretreatment group as follows; 0.9% NaCl pretreatment, 8-OH-DPAT challenge: 0.9% NaCl pretreatment, 0.9% NaCl challenge; 8-OH-DPAT pretreatment, 0.9% NaCl challenge. An experiment was also performed in which a single pretreatment dose of 2.0 mg/kg was used and challenges given 24 and 48 h later to separate groups of rats.

2.3. Spontaneous tail-flick

Tail-flicks were counted on rats placed individually in an opaque Perspex retaining tube from which the tail hung freely through a groove cut in a rubber bung which closed the end of the tube. The dimensions of the tube were such that the rats were minimally restricted but unable to turn or move forward or back. These dimensions varied critically with rat weight, animals weighing 270 ± 10 g (S.D.) and 330 ± 15 g (S.D.) requiring tubes of 60 mm diameter × 145 mm length and 65 mm diameter × 150 mm length, respectively.

Rats were placed in the tube immediately after injection of the 8-OH-DPAT challenge and tail-flicks counted continuously starting 5 min later for 5 min. A tail-flick was defined as a rapid continuous movement of the tail from below to above the horizonal and down again (Millan et al., 1991). After a preliminary experiment to establish dose dependency, the effects of the 8-OH-DPAT challenge after 8-OH-DPAT pretreatments were determined. Controls were pretreated with 0.9% NaCl instead of 8-OH-DPAT. Controls challenged with 0.9% NaCl were not used as in preliminary experiments such rats did not exhibit tail-flicks.

2.4. Hypothermia

Rats were briefly retained in a Perspex tube (60 mm internal diameter) and rectal temperature measured with a lubricated digital thermometer probe (Philip Harris Scientific, London, UK) inserted 3 cm into the rectum. Readings were taken 15 min before and 30 min after a 8-OH-DPAT challenge dose. Control groups were as in Section 2.2. An experiment was also performed using a pretreatment dose of 2.0 mg/kg as in Section 2.2.

2.5. Components of the 5-HT syndrome

At least 3 days prior to initiation of 8-OH-DPAT pretreatment rats were housed singly in clear Perspex cages (430 × 190 × 160 mm high). After 8-OH-DPAT challenge, behaviour was recorded on video tape and flat body posture and reciprocal forepaw treading scored over four 1-min periods at 8 min intervals starting 8 min after 8-OH-DPAT injection. Control groups were as in Section 2.3. as rats challenged with 0.9% NaCl did not exhibit the above behavioural components.

2.6. Statistics

The effects of 8-OH-DPAT pretreatments on the hyperphagic response to 8-OH-DPAT challenge were assessed by Kruskal-Wallis analysis of variance followed by Mann-Whitney *U*-test. The dose-response curve for tail-flick was assessed by significant one-way analysis of variance (ANOVA) followed by Duncan's test and the effect of 8-OH-DPAT pretreatments on the tail-flick re-

sponse to the challenge by Student's *t*-test. Effects on hypothermia were assessed by significant one way ANOVA followed by Duncan's test and effects on components of the 5-HT syndrome by Mann-Whitney *U*-test.

3. Results

3.1. Hyperphagia

The challenge dose of 8-OH-DPAT (0.5 mg/kg) given 24 h after the end of pretreatment significantly increased feeding (Fig. 1A) but the increases were not appreciably altered by 1, 3 or 14 days of pretreatment with 8-OH-DPAT (1.0 mg/kg). When the pretreatment dose was increased to 2.0 mg/kg, rats given a single pretreatment and challenged 24 and 48 h later showed significant hyperphagic responses which were smaller than those of animals pretreated with 0.9% NaCl by 50 and 42%, respectively (Fig. 1B), but the decreases were not significant.

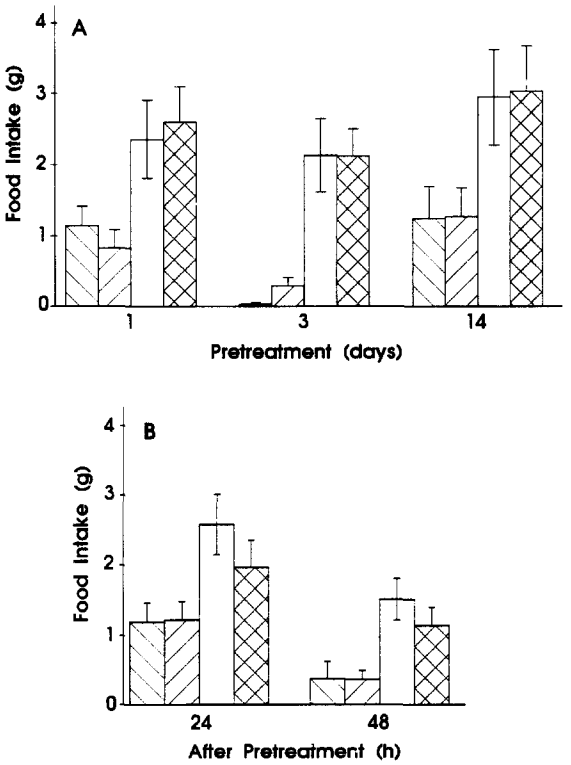

Fig. 1. Effects of daily pretreatment with 8-OH-DPAT (s.c.) or 0.9% NaCl on hyperphagic response to challenge by 8-OH-DPAT (0.5 mg/kg s.c.) or 0.9% NaCl given 1 day after the last pretreatment. Food intake was determined over 2 h. Values are mean ± S.E.M. ($n = 7–9$/group). Pretreatments and challenges were as follows; NaCl, NaCl (hatched columns, lines running from NW to SE): 8-OH-DPAT, NaCl (hatched columns, lines running from SW to NE): NaCl, 8-OH-DPAT (unhatched columns): 8-OH-DPAT, 8-OH-DPAT (cross-hatched columns). Pretreatment doses were 1.0 (A) and 2.0 mg/kg (B). Groups challenged with 8-OH-DPAT differed significantly from groups challenged with NaCl. $P < 0.05$ (Kruskal-Wallis ANOVA followed by individual comparisons by Mann-Whitney *U*-test), but did not differ significantly from each other.

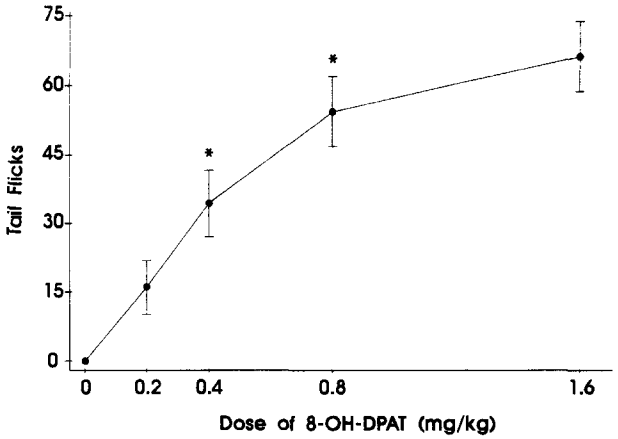

Fig. 2. Effect of 8-OH-DPAT at different doses on tail-flicks. The drug was given and tail-flicks/5 min counted starting 5 min after injection. Values are mean ± S.E.M. ($n = 6–7$/ group). Significant differences from values for the next lowest drug dose: * $P < 0.05$ (significant one-way ANOVA followed by Duncan's test).

3.2. Spontaneous tail-flicks

Single injections of 8-OH-DPAT caused tail-flicks with dose-dependent frequency in the range 0.2–1.6 mg/kg (Fig. 2). The effect of a challenge dose of 8-OH-DPAT (0.5 mg/kg) was not altered by 1, 3 or 14 days of 8-OH-DPAT (1.0 mg/kg) pretreatment (Fig. 3).

3.3. Hypothermia

The challenge dose of 8-OH-DPAT (0.5 mg/kg) when given 1 day after 0.9% NaCl vehicle was significantly hypothermic (Fig. 4A). After 1 and 3 pretreatments with 8-OH-DPAT (1.0 mg/kg), the responses to challenge remained significant but were slightly and somewhat more

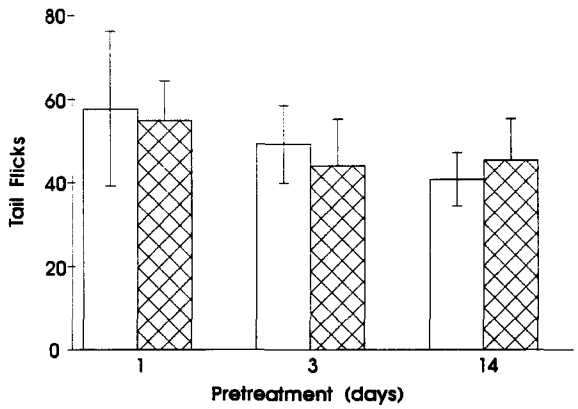

Fig. 3. Effect of daily pretreatment with 8-OH-DPAT (1.0 mg/kg s.c.) or 0.9% NaCl on tail-flicks on challenge by 8-OH-DPAT (0.5 mg/kg s.c.) 1 day after the last pretreatment. Tail-flicks/5 min were counted as in Fig. 2. Values are mean ± S.E.M. ($n = 7/11$ group). Pretreatments: NaCl (unhatched columns), 8-OH-DPAT (cross-hatched columns). Responses were not significantly affected by drug pretreatment (Student's *t*-test).

markedly attenuated. After 14 pretreatments, the challenge no longer caused appreciable hypothermia.

When rats were given a larger single pretreatment dose of 8-OH-DPAT (2.0 mg/kg), the hypothermic response to challenge 1 day later by 8-OH-DPAT (0.5 mg/kg) was marginally more attenuated than when the standard pretreatment dose was used but if the interval between pretreatment and challenge was increased to 2 days the attenuation was more well defined (Fig. 4B).

3.4. Components of the 5-HT syndrome

The challenge dose of 8-OH-DPAT when given 1 day after 0.9% NaCl caused flattened body posture and reciprocal forepaw treading (Fig. 5). The effect on flattened posture was significantly decreased after a single 8-OH-DPAT pretreatment and became progressively more marked on multiple pretreatment so that after 14 pretreatments it was essentially absent. A single pretreatment caused reciprocal forepaw treading to be rather more strikingly attenuated than flattened posture but (unlike the latter behaviour) attenuation was not increased on repeated pretreatment.

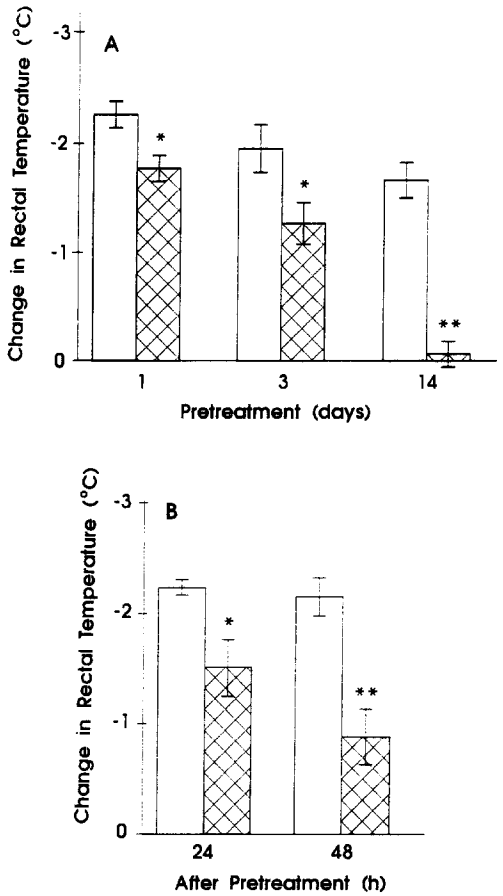

Fig. 4. Effects of daily pretreatment with 8-OH-DPAT (s.c.) or 0.9% NaCl on hypothermic response determined 30 min after challenge with 8-OH-DPAT (0.5 mg/kg s.c.) 1 day after the last pretreatment. General conditions as described in Section 2.4. Values are mean ± S.E.M. (n = 8–10/group). Pretreatment doses were 1.0 mg/kg (a) and 2.0 mg/kg (b). Groups pretreated with 8-OH-DPAT (cross-hatched columns) showed significantly smaller hypothermic response than corresponding groups pretreated with NaCl (unhatched columns): * $P < 0.05$, ** $P < 0.01$ (significant one-way ANOVA followed by Duncan's test). Rats challenged with NaCl showed small hyperthermic effects which did not attain significance and were comparable whether the animals has been pretreated with NaCl or 8-OH-DPAT (results not shown).

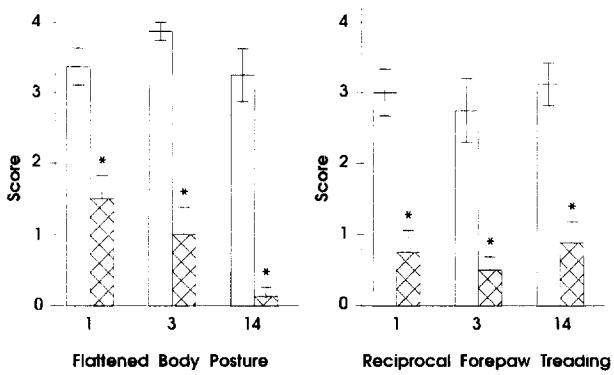

Fig. 5. Effects of daily pretreatment with 8-OH-DPAT (1.0 mg/kg s.c.) or 0.9% NaCl on flat body posture and reciprocal forepaw treading on challenge by 8-OH-DPAT (0.5 mg/kg s.c.) 1 day after the last pretreatment. General conditions as described in Section 2.5. Values are mean ± S.E.M. (n = 12–14/group). Groups pretreated with 8-OH-DPAT (cross-hatched columns) showed significantly smaller responses than corresponding groups pretreated with NaCl (unhatched columns): * $P < 0.01$ (Mann-Whitney U-test).

4. Discussion

Different behavioural responses to activation of rat 5-HT_{1A} receptors by 8-OH-DPAT had strikingly different vulnerabilities to attenuation by 8-OH-DPAT pretreatment. These did not simply reflect differences between presynaptic and postsynaptic 5-HT_{1A} sites. For example, components of the 5-HT syndrome (i.e. reciprocal forepaw treading and flat body posture) and the tail-flick response both result from activation of postsynaptic sites (Tricklebank et al., 1985; Bervoets et al., 1993) but the former effects were substantially attenuated by a single 8-OH-DPAT pretreatment (Fig. 5) while tail flick was unaffected even by repeated pretreatment (Fig. 3). Its resistance was not merely due to an excessive challenge dose as the dose used elicited only about a half-maximal response (Fig. 1) so that attenuation would have readily been revealed. Furthermore, hyperphagia on 8-OH-DPAT challenge, which is mediated by presynaptic 5-HT_{1A} sites (Dourish et al., 1986; Hutson et al., 1988) was as resistant to pretreatment with 8-OH-DPAT (1.0 mg/kg for 1, 3 and 14 days) as the tail-flick response which is mediated by postsynaptic receptors (Bervoets et al., 1993) which the effects of a large range of agonists and antagonists indicate to be of the 5-HT_{1A} type (Millan et al., 1991).

The lack of effect of the above pretreatments on the hyperphagic response to 8-OH-DPAT (0.5 mg/kg) disagrees with the essentially complete prevention by a single

pretreatment of the responses to challenge with 0.06 and 1.0 mg/kg doses previously found (Kennett et al., 1987) and with a recent brief report that a single dose of 8-OH-DPAT (0.25 mg/kg) given to female rats attenuated the hyperphagic effect of challenge given 7 days later (Maswood et al., 1995). It is conceivable that there was less effective uptake or more rapid elimination of 8-OH-DPAT in the present study so that the pretreatment dose was not sufficient to cause attenuation. Although this explanation is conjectural, it is relevant that increasing the pretreatment dose to 2.0 mg/kg led to about a 50% attenuation (albeit non-significant) of the hyperphagia on challenge (Fig. 1B). Nevertheless, the present findings clearly point to 8-OH-DPAT hyperphagia being less vulnerable to attenuation by pretreatment than the hypothermic (see below) and 5-HT syndrome responses.

Differential vulnerabilities of postsynaptic 5-HT_{1A} receptor-dependent responses to 8-OH-DPAT pretreatment were revealed not only by its different actions on the 5-HT syndrome and tail-flick responses but also by the attenuation of the hypothermic response which evidence now indicates to be due to activation of postsynaptic 5-HT_{1A} receptors (see Section 1.). Thus, unlike the rapid attenuation of the 5-HT syndrome, its attenuation only became substantial after repeated pretreatment. Attenuation of the hypothermia was probably not completely developed under the standard conditions used as Fig. 1B indicates that it was greater when the interval between pretreatment and challenge was increased to 48 h (Fig. 4B). These findings agree qualitatively with Larsson et al. (1990) and Forster et al. (1994a) who used different dose and time schedules.

The significant attenuation by a single pretreatment with 8-OH-DPAT (1.0 mg/kg) of flat body posture and reciprocal forepaw treading on challenge with 8-OH-DPAT (0.5 mg/kg) 24 h later (Fig. 5) is consistent with their essentially complete absence on challenge by 8-OH-DPAT (0.3 mg/kg) given 1 day after pretreatment over 24 h with 8-OH-DPAT (1.0 mg/kg × 3) (Larsson et al., 1990). On the other hand, a single 8-OH-DPAT pretreatment did not alter reciprocal forepaw treading or other components of the 5-HT syndrome on challenge (Kennett et al., 1987). The discrepancy could be due to the higher challenge dose of 1.0 mg/kg used in the latter study as the 8-OH-DPAT dose-response relationships for forepaw treading and flat body posture (Tricklebank et al., 1985) taken together with the effect of pretreatment on their ED_{50} values (Forster et al., 1994b) suggests negligible attenuation under these conditions.

The effects of 8-OH-DPAT pretreatment on behavioural responses (other than tail-flick) to activation of postsynaptic 5-HT_{1A} receptors contrasts sharply with the lack of effect of 5-HT_{1A} agonists on receptor numbers in various 5-HT terminal regions (Welner et al., 1989; Larsson et al., 1990; Fanelli and Mc Monagle-Strucko, 1992). However, discrepancies between effects on receptor numbers and on responses to their activation are common. In the present case, behavioural attenuation could depend on at least two mechanisms. (1) Changes at NMDA receptors as the NMDA receptor antagonist dizocilpine [+MK801: (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine] given before 8-OH-DPAT pretreatment blocked the attenuation of the hypothermia on challenge (Renyi et al., 1992). (2) Second messenger changes as suggested by the blockade by 8-OH-DPAT pretreatment of the inhibition of postsynaptic 5-HT_{1A} receptor-dependent forskolin-stimulated adenyl cyclase activity by 5-HT (Newman et al., 1992). Like the attenuation of the hypothermic response, this became more prominent on repeated pretreatment with 8-OH-DPAT (1.0 mg/kg s.c.).

The discrepancies between Beer et al. (1990) who found a decrease of presynaptic 5-HT_{1A} receptor numbers after a single treatment with 8-OH-DPAT (1.0 mg/kg s.c.) and the lack of the significant effect on both 5-HT release at terminals (Hjorth, 1991; Kreiss and Lucki, 1992) and on 8-OH-DPAT hyperphagia on challenge in the present study could be due to the large receptor reserve of the presynaptic sites (Meller et al., 1990). A discrepancy also exists between the lack of attenuation of the hyperphagic response after as long as 14 days of 8-OH-DPAT pretreatment (Fig. 1) and the finding that pretreatment for 7 days was sufficient to oppose the reduction of 5-HT release (Kreiss and Lucki, 1992).

Evidence points to the possible involvement of receptor reserve in responses to activation of postsynaptic sites as Meller et al. (1992) associated an absence of spare postsynaptic receptors with the rapid attenuation of 8-OH-DPAT-induced hypothermia. However, they used mice, a species in which evidence on whether the responsible 5-HT_{1A} receptors are presynaptic or postsynaptic is contradictory (Matsuda et al., 1990; Bill et al., 1991). Furthermore, receptor reserve is not implicated to the same extent in all 5-HT_{1A} receptor-dependent postsynaptic responses as the sites responsible for inhibition of hippocampal adenyl cyclase activity by 8-OH-DPAT lack receptor reserve (Yocca et al., 1992) but substantial reserve (Meller and Bohmaker, 1994) is associated with the hypercorticosteronaemic effect of 8-OH-DPAT which is also postsynaptically mediated (Haleem et al., 1989; Kelder and Ross, 1992).

The findings described in this paper have potential clinical implications. The range of vulnerabilities of 5-HT_{1A} receptor-dependent responses to 8-OH-DPAT pretreatment suggests the need for caution in the use of chronic effects of 5-HT_{1A} receptor agonists or other 5-HTergic antidepressants or anxiolytics on specific 5-HT_{1A} receptor-dependent responses (rev. Newman et al., 1993; Schreiber and De Vry, 1993; De Vry, 1995) as indices of mechanisms for the therapeutic actions of these drugs. The findings, especially taken together with more information on dose-response and time relationships for pretreatment and challenge may be relevant to therapeutic mechanisms and may

also suggest ways of directing drug action toward specific responses.

Acknowledgements

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