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8-OH-DPAT-induced release of hippocampal noradrenaline in vivo: evidence for a role of both 5-HT_{1A} and dopamine D_1 receptors

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Abstract

Here we investigate the effects of the novel selective 5-HT_{1A} receptor antagonist, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl cyclo-hexanecarboxamide (WAY 100635), and the dopamine D_1 receptor antagonist, *R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol (SCH 23390), on the increase in extracellular noradrenaline in rat hippocampus induced by the 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*N*-propylamino)tetralin (8-OH-DPAT). 8-OH-DPAT (0.1 and 1 mg/kg s.c.) caused a dose-related increase in extracellular noradrenaline. WAY 100635 (0.3 and 1 mg/kg s.c.) did not block the release of noradrenaline induced by the higher dose of 8-OH-DPAT (1 mg/kg s.c.) but abolished the response to the lower dose (0.1 mg/kg s.c.). When administered alone, WAY 100635 (0.3 and 1 mg/kg s.c.) had no effect on extracellular noradrenaline. The postsynaptically mediated 5-HT behavioural syndrome induced by the higher dose of 8-OH-DPAT, in contrast to the increase in noradrenaline, was completely blocked by WAY 100635 (0.3 mg/kg s.c.). Finally, the noradrenaline response to 8-OH-DPAT (0.1 mg/kg s.c.) was blocked by SCH 23390 (0.5 mg/kg s.c.). Our data confirm that noradrenaline can be released by activation of 5-HT_{1A} receptors but show that these receptors are not tonically activated, and may be more sensitive to stimulation than classical postsynaptic 5-HT_{1A} receptors. A role for the dopamine D_1 receptor in the noradrenaline response to 8-OH-DPAT is also suggested.

Keywords: 5-HT_{1A} receptor; 8-OH-DPAT (8-hydroxy-2-(di-*N*-propylamino)tetralin); Noradrenaline; Dopamine D_1 receptor; SCH 23390; Microdialysis

1. Introduction

There is much evidence that 5-HT plays a role in the modulation of central noradrenergic activity (e.g., Renaud et al., 1975; McRae-Degueurce et al., 1985; Reader et al., 1986), with recent work focusing on the involvement of specific 5-HT receptor subtypes (e.g., Rasmussen and Aghajanian, 1986; Gorea and Adrien, 1988; Done and Sharp, 1992, 1994). The interaction between noradrenaline and the 5-HT_{1A} receptor is of particular interest to psychopharmacological studies. Thus, both noradrenaline and the 5-HT_{1A} receptor may have causal roles in psychiatric disorders such as depression and anxiety (Cowen, 1991; Nutt et al., 1992), and 5-HT_{1A} agonists have demonstrated antidepressant and anxiolytic activity in clinical trials (Charney et al., 1990).

Following on from an earlier report that the 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*N*-propylamino)tetralin (8-OH-DPAT), increased noradrenaline turnover in rat hypothalamus (Fuller and Perry, 1989), several studies using microdialysis have shown that this drug increases brain extracellular levels of noradrenaline in the awake (but not the anaesthetised) rat (Done and Sharp, 1994; Chen and Reith, 1995; Suzuki et al., 1995). Indeed, not only 8-OH-DPAT but a wide range of other 5-HT_{1A} ligands have this effect, including the non-benzodiazepine anxiolytics buspirone, gepirone and ipsapirone (Done and Sharp, 1994), the novel 5-HT_{1A} receptor agonist MKC-242 (Suzuki et al., 1995) and the partial 5-HT_{1A} receptor agonists NAN-190 and MDL 73005 (Done and Sharp, 1994; Hajós-Korcsok et al., 1994).

NAN-190 and MDL 73005 have low intrinsic activity at the postsynaptic 5-HT_{1A} receptor, but are almost full agonists at the 5-HT_{1A} autoreceptor (Hjorth and Sharp, 1990; Gartside et al., 1990; Sharp and Hjorth, 1990). Partly on the basis of this evidence, we hypothesised that a presynaptic mechanism (inhibition of 5-HT release) mediated

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the increase in extracellular noradrenaline induced by 5-HT_{1A} ligands (Done and Sharp, 1994). Subsequent studies found, however, that the noradrenaline response to 8-OH-DPAT was not abolished in rats pretreated with either a 5-HT neurotoxin (Suzuki et al., 1995) or a 5-HT synthesis inhibitor (Chen and Reith, 1995), implicating the involvement of 5-HT_{1A} receptors located postsynaptically rather than presynaptically.

There are interesting parallels between the effect of 8-OH-DPAT on extracellular noradrenaline and its effect on extracellular acetylcholine. In particular, recent microdialysis data suggest that 8-OH-DPAT activates release of cortical acetylcholine through stimulation of postsynaptic 5-HT_{1A} receptors (Consolo et al., 1996). Dopamine is also implicated in this facilitation of acetylcholine release since the effect is blocked by the dopamine D_1 (-like) receptor antagonists, SCH 23390 and SCH 39166 (Consolo et al., 1996). A role for the D_1 receptor in certain 5-HT_{1A}-mediated behaviours has also been reported (Muscat et al., 1989; Shippenberg, 1991), indicating that 5-HT_{1A}/D_1 receptor interactions may be common. Whether there is an involvement of the D_1 receptor in modulation of noradrenaline release by 5-HT_{1A} ligands, has not yet been tested.

The evidence for an influence of the 5-HT_{1A} receptor on brain noradrenaline release is based largely on the effects of agonists/partial agonists although a recently published microdialysis study, Suzuki et al. (1995) reported that the 5-HT_{1A} receptor antagonist, WAY 100135, inhibited the noradrenaline response to 8-OH-DPAT. Here we report the effects on brain extracellular noradrenaline of the novel and highly selective 5-HT_{1A} receptor antagonist, WAY 100635 (Fletcher et al., 1995). In view of the increasing number of reports of interactions between 5-HT_{1A} and dopamine D_1 receptors, a D_1 receptor antagonist, SCH 23390, was also tested.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Harlan-Olac, Bicester, UK) were housed in groups of 5–6 under conditions of controlled temperature (21 ± 1°C) and lighting (lights on 08.00–20.00 h); food pellets and water were freely available.

2.2. In vivo microdialysis

Rats (250–280 g) were anaesthetized with halothane, and microdialysis probes (single cannula type, Hospal AN 69 membrane, 4 mm tip length) were stereotaxically implanted into the right hippocampus (coordinates: anterior-posterior −5.0 mm, medial-lateral −4.6 mm, dorso-ventral −8.5 mm, from bregma and dura surface, according to Paxinos and Watson, 1986), and cemented in place using a fast-drying dental cement. To allow s.c. administration of drugs, a piece of polyethylene tubing (approximately 6–8 cm length) was implanted subcutaneously at the back of the neck and cemented to the head piece assembly to hold it in place. A small length of polyethylene tubing (5–10 mm) was attached to both the inlet and outlet of the microdialysis probe, and then sealed temporarily with bone wax to prevent the dialysis tubing from drying out overnight. Once recovered from anaesthesia, the rats were returned to the home cage.

The day following surgery, rats were transferred to a large hemispherical Perspex bowl and left to acclimatise for at least 30 min. The subcutaneous tubing was connected to a syringe, and flushed with saline. The inlet of the dialysis probe was attached to perfusion pump via polyethylene tubing and a liquid swivel. Probes were perfused continuously (2 μl/min) with artificial cerebrospinal fluid containing 1 μM desipramine. Perfusates were collected every 20 min. After a baseline period of 2–3 h, noradrenaline output was relatively constant. Drugs or vehicle were then administered via the subcutaneous cannula and perfusates were collected for a further 2 h. The subcutaneous cannula allowed the animal to be injected without handling, thereby minimising stress and the stimulatory effect of this on noradrenaline.

2.3. HPLC measurement of noradrenaline

Immediately following collection, perfusate samples were analysed for noradrenaline using high performance liquid chromatography (HPLC) with electrochemical detection as described previously (Done and Sharp, 1992). In brief, noradrenaline was separated using a Rainin Dynamax HPLC column (4.6 × 150 mm, Microsorb C_{18} 5 μm particles) and a mobile phase comprising 0.1 M NaH_2PO_4, 2 mM sodium octane sulphonate, 0.5 mM EDTA and 12% (v/v) methanol (final pH 4.6, flow rate 1.2 ml/min). Detection was achieved using a BAS LC-4 electrochemical detector connected to a glassy carbon electrode (+0.7 V versus Ag/AgCl reference). The detection limit of the assay system, defined as the concentration of a compound producing a peak twice the basal noise, was about 0.02 pmol/20 μl sample.

2.4. Measurement of 5-HT behavioural syndrome

Rats were injected subcutaneously with either vehicle or WAY 100635 and placed singly in clear Plexiglas cages positioned between panels of photocells connected to a computer-based activity monitoring system (Opto-Varimex II Activity Monitor, Columbus Instruments), and allowed to habituate for 40 min. 8-OH-DPAT was then administered and, over the following 60 min, activity counts were monitored, and individual components of the 8-OH-DPAT-induced 5-HT behavioural syndrome (head weaving, forepaw treading, flat body posture) were scored on a

4-point rating scale (0 = absent, 1 = equivocal, 2 = definite, 3 = extreme). Ratings were made every 10 min and summed over the observation period (maximum possible score 18 for each behaviour). For all behavioural measurements, the observer was blind to the treatment conditions.

2.5. Data analysis

Noradrenaline in each dialysate sample is expressed as a percentage of the absolute amount of noradrenaline in the sample collected immediately before drug or vehicle injection. For noradrenaline measurements, statistical differences between groups were assessed by two-way analysis of variance (ANOVA) with repeated measures, followed by a post-hoc Tukey test. Behavioural data were assessed either by two-way ANOVA with repeated measures followed by the Tukey test (activity counts), or the Mann-Whitney U-test (behavioural scores). Probability levels of 5% or less were considered statistically significant.

2.6. Drugs

8-OH-DPAT (8-hydroxy-2-(di-*N*-propylamino)tetralin; Research Biochemicals, SEMAT, St. Albans, UK) was dissolved in 0.9% saline. WAY 100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclo-hexanecarboxamide trihydrochloride; Wyeth Research, UK) and SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol hemimaleate; Schering, Blomfield, USA) were dissolved in water containing 5% (w/v) glucose.

3. Results

3.1. Effect of the 5-HT_{1A} receptor antagonist WAY 100635 on 5-HT behavioural syndrome

8-OH-DPAT (1 mg/kg s.c.) induced components of the 5-HT behavioural syndrome (i.e., head-weaving, forepaw treading, flat body posture) at an intensity which was less than maximal (data not shown). The 5-HT_{1A} receptor antagonist WAY 100635 (0.3 mg/kg s.c., 40 min pretreatment) almost completely abolished the behavioural response to 1 mg/kg s.c. 8-OH-DPAT, as indicated by a marked reduction in both scored behaviours and activity counts (Fig. 1A,B).

Statistical analysis (Mann-Whitney U-test) revealed that each behaviour was reduced by WAY 100635 ($P < 0.01$). Similarly, analysis of the activity count data by two-way ANOVA revealed a significant treatment × time interaction ($F(9,90) = 13.8$, $P < 0.0001$). Activity counts in the WAY 100635/8-OH-DPAT-treated group were different from vehicle/8-OH-DPAT-treated controls at all time points 10–40 min post 8-OH-DPAT ($P < 0.05$, Tukey test).

WAY 100635 (0.3 mg/kg s.c.) alone had no observable behavioural effect (data not shown). The doses of 8-OH-DPAT and WAY 100635 used in this experiment were the starting point for those used in the following microdialysis work.

3.2. Effect of the 5-HT_{1A} receptor antagonist WAY 100635 on the release of noradrenaline induced by 8-OH-DPAT

8-OH-DPAT (1 mg/kg s.c.) increased noradrenaline in hippocampal dialysates of awake rats (Fig. 2). This effect

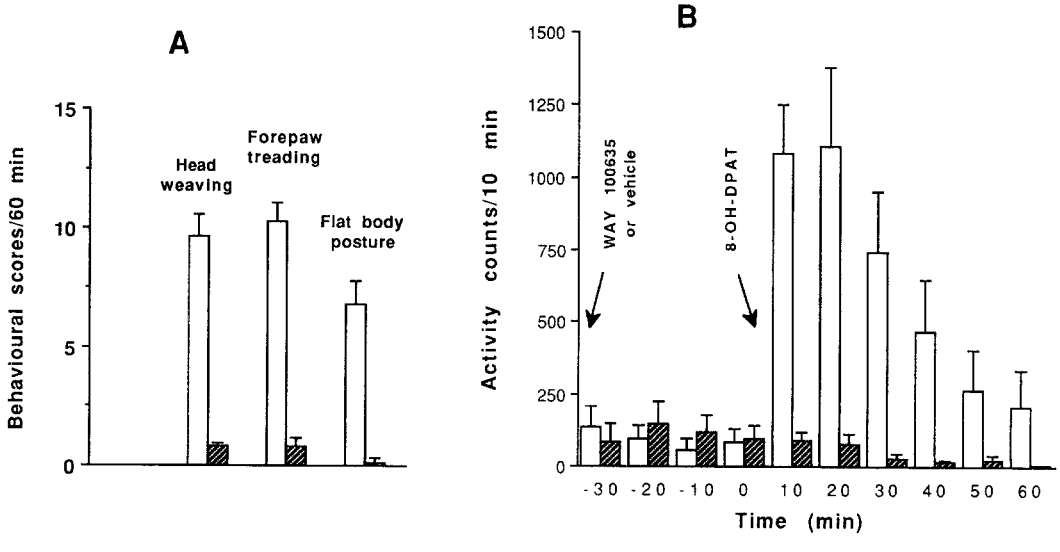

Fig. 1. Effect of WAY 100635 on 8-OH-DPAT-induced behavioural syndrome in rats expressed as (A) individual behavioural components and (B) activity counts. All rats were injected with 8-OH-DPAT (1 mg/kg s.c.) 40 min after vehicle (open columns) or WAY 100635 (0.3 mg/kg s.c.) (hatched columns). Behavioural scores were accumulated over 60 min. Columns represent means ± S.E.M. values of 5–6 determinations. WAY 100635 caused a statistically significant reduction in the 8-OH-DPAT-induced behavioural response (see Results for details).

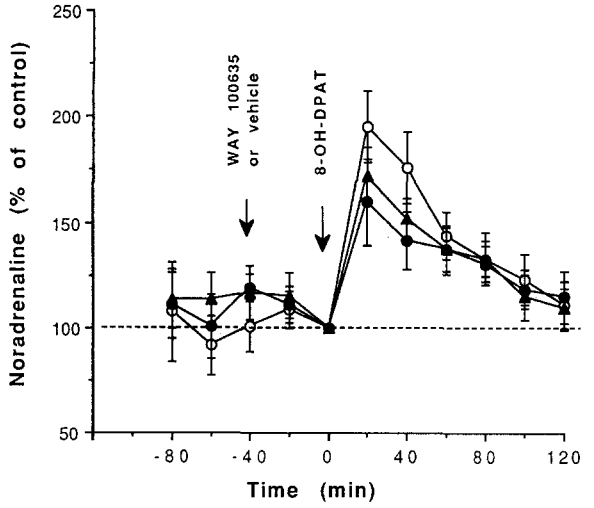

Fig. 2. Effect of different doses of WAY 100635 on the increase in extracellular noradrenaline release induced in the hippocampus of the awake rat by a higher dose of 8-OH-DPAT (1 mg/kg s.c.). All rats received 8-OH-DPAT 40 min after injection of WAY 100635 (0.3 or 1 mg/kg s.c.) or vehicle. Treatments were: (open circles) vehicle/8-OH-DPAT, (closed triangles) 0.3 WAY 100635/8-OH-DPAT or (closed circles) 1.0 WAY 100635/8-OH-DPAT. Mean ± S.E.M. (n) baseline levels of noradrenaline (immediately before the first treatment) were 0.09 ± 0.03 (6), 0.12 ± 0.03 (6) and 0.17 ± 0.02 (5) pmol/sample, respectively. Each point is the mean ± S.E.M. of 5–6 determinations. Statistical analysis (two-way ANOVA) revealed no significant difference between the groups.

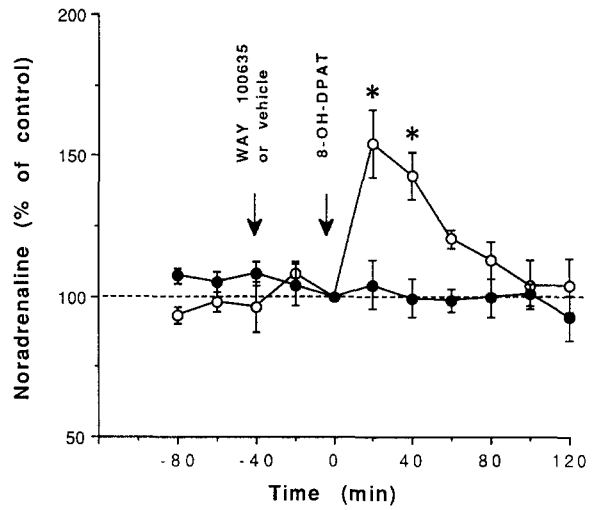

Fig. 3. Effect of WAY 100635 on the increase in extracellular noradrenaline release induced in the hippocampus of the awake rat by a lower dose of 8-OH-DPAT (0.1 mg/kg s.c.). Rats received 8-OH-DPAT 40 min after injection of WAY 100635 (1 mg/kg s.c.) or vehicle. Treatments were (open circles) vehicle/8-OH-DPAT or (closed circles) WAY 100635/8-OH-DPAT. Baseline levels of noradrenaline were 0.15 ± 0.04 (6) and 0.17 ± 0.02 (8) pmol/sample. Each point is a mean ± S.E.M. value of 6–8 determinations. Statistical analysis (two-way ANOVA) indicated that the effect of 8-OH-DPAT was significantly less in rats treated with WAY 100635 (see Results for details); * $P < 0.05$ WAY 100635/8-OH-DPAT versus vehicle/8-OH-DPAT (Tukey test).

was greatest (+95% above basal levels) in the first 20 min sample after 8-OH-DPAT, and lasted for about 1 h. The noradrenaline response to 1 mg/kg s.c. 8-OH-DPAT was not altered by pretreatment with 0.3 mg/kg sc. WAY 100635 (Fig. 2). A higher dose of WAY 100635 (1 mg/kg s.c.) tended to reduce the response to 1 mg/kg s.c. 8-OH-DPAT (Fig. 2), however two-way ANOVA revealed no statistically significant effect.

In a further experiment WAY 100635 was given with a lower dose of 8-OH-DPAT (0.1 mg/kg s.c.) which alone increased noradrenaline by about 50% above baseline (Fig. 3). In rats pretreated with WAY 100635 (1 mg/kg s.c.), the noradrenaline response to 0.1 mg/kg s.c. 8-OH-DPAT was abolished. Statistical analysis of the time course data by two-way ANOVA revealed a significant treatment × time interaction ($F(10,130) = 9.6$, $P < 0.0001$).

Control experiments showed that when administered alone, WAY 100635 (0.3 and 1 mg/kg s.c.) did not alter noradrenaline compared to the effect of vehicle (Fig. 4). Statistical analysis (two-way ANOVA) revealed no significant difference between WAY 100635- and vehicle-treated groups.

3.3. Effect of the dopamine D_1 receptor antagonist SCH 23390 on the release of noradrenaline induced by 8-OH-DPAT

The dopamine D_1 receptor antagonist, SCH 23390 (0.5 mg/kg s.c., 40 min pretreatment), significantly reduced the effect of 8-OH-DPAT (0.1 mg/kg s.c.) on hippocampal noradrenaline when compared to vehicle (5% glucose) injected controls (Fig. 5). Statistical analysis of the time course data by two-way ANOVA revealed a significant interaction between time and treatment ($F(22,132) = 2.7$, $P < 0.0005$). The effect of 8-OH-DPAT (0.1 mg/kg s.c.)

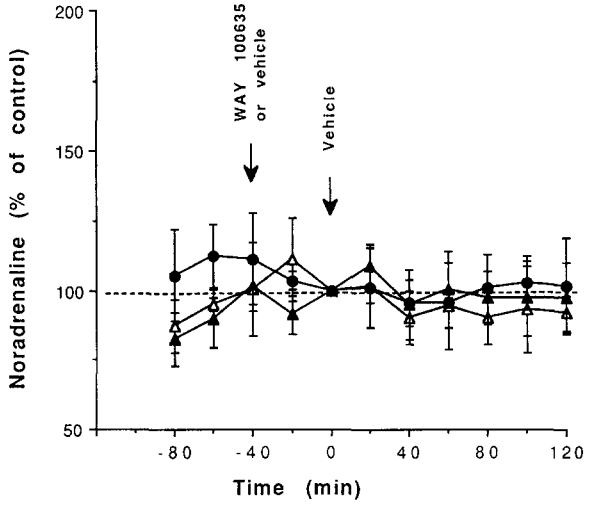

Fig. 4. Effect of WAY 100635 (0.3 and 1.0 mg/kg s.c.) on extracellular noradrenaline in the hippocampus of the awake rat. Treatments were: (open triangles) vehicle/vehicle, (closed triangles) 0.3 WAY 100635/vehicle or (closed circles) 1.0 WAY 100635/vehicle. Baseline levels of noradrenaline were 0.21 ± 0.01 (4), 0.16 ± 0.02 (5) and 0.14 ± 0.01 (5) pmol/sample, respectively. Each point is a mean ± S.E.M. value of 4–5 determinations. Statistical analysis (two-way ANOVA) revealed no significant difference between groups.

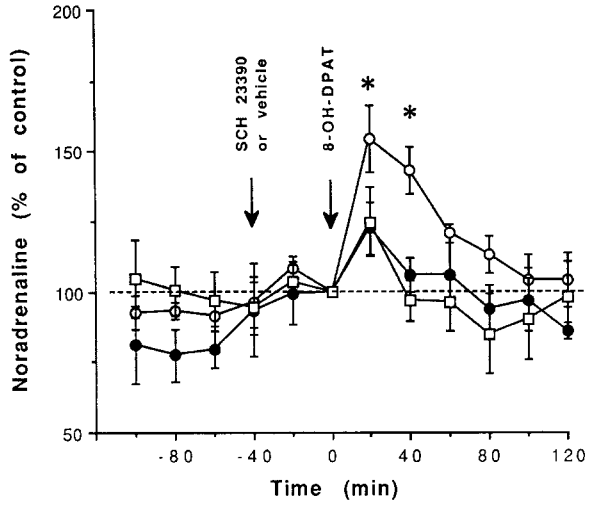

Fig. 5. Effect of SCH 23390 on the increase in extracellular noradrenaline release induced in the hippocampus of the awake rat by 8-OH-DPAT. Rats received 8-OH-DPAT (0.1 mg/kg s.c.) 40 min after injection of SCH 23390 (0.5 mg/kg s.c.) or glucose vehicle. Treatments were (open circles) vehicle/8-OH-DPAT, (closed circles) SCH 23390/8-OH-DPAT or (open squares) SCH 23390/vehicle. Baseline levels of noradrenaline were 0.15 ± 0.04 (6), 0.20 ± 0.03 (5) and 0.13 ± 0.02 (4) pmol/sample, respectively. Each point is a mean ± S.E.M. value of 4–6 determinations. Statistical analysis (two-way ANOVA) indicated that the effect of 8-OH-DPAT was significantly less in rats treated with SCH 23390, and that SCH 23390 alone had no effect compared to vehicle (see Results for details); * $P < 0.05$ SCH 23390/8-OH-DPAT versus vehicle/8-OH-DPAT (Tukey test).

was tested in two rats pretreated with a lower dose of SCH 23390 (0.1 mg/kg s.c.): 8-OH-DPAT did not evoke a release of noradrenaline in either rat (data not shown).

Noradrenaline output was not significantly altered by injection of SCH 23390 (0.5 mg/kg s.c.) alone when compared to vehicle (Fig. 5).

4. Discussion

The present results confirm our earlier observation (Done and Sharp, 1994) that systemic administration of the 5-HT_{1A} receptor agonist 8-OH-DPAT increases extracellular noradrenaline in the hippocampus of awake rats as measured by microdialysis. We also find that 8-OH-DPAT increases extracellular noradrenaline in the frontal cortex (unpublished observation), and others report a similar effect in the hypothalamus (Suzuki et al., 1995) and the ventral tegmental area (Chen and Reith, 1995). A rise in extracellular noradrenaline is also detected following administration of other 5-HT_{1A} ligands, including buspirone, ipsapirone, MDL 73005, NAN-190 (Done and Sharp, 1994; Hajós-Korcsok et al., 1994) and MKC-242 (Suzuki et al., 1995). Together these data suggest that there is a widespread increase in forebrain noradrenergic activity in response to administration of drugs acting at the 5-HT_{1A} receptor.

Although many of the 5-HT_{1A} ligands tested have less than full agonist activity at the 5-HT_{1A} receptor (e.g., MDL 73005 and NAN-190), an agonist rather than antagonist action is likely to account for the noradrenaline effect. Thus, we show in the present study that the selective 5-HT_{1A} receptor antagonist WAY 100635, which does not have intrinsic activity in any in vivo model of 5-HT_{1A} function tested to date (Fletcher et al., 1995), had no effect on noradrenaline when administered alone at doses which blocked the response to 8-OH-DPAT. These results confirm that 5-HT_{1A} receptors mediate the rise in extracellular noradrenaline induced by 8-OH-DPAT. Furthermore, the lack of effect of WAY 100635 indicates that the receptors are not tonically activated.

Suzuki et al. (1995) found that an analogue of WAY 100635, WAY 100135, antagonised the increase in extracellular noradrenaline induced by 8-OH-DPAT and MKC-242. Although one study (Routledge et al., 1993) found that WAY 100135 administered alone increased noradrenaline, Suzuki et al. (1995) reported no effect. Given the clear lack of effect of WAY 100635 reported here (i.e., when administered alone), any increase in noradrenaline induced by WAY 100135 is not likely to be mediated through blockade of 5-HT_{1A} receptors. It cannot be excluded that WAY 100135 increases noradrenaline through a partial 5-HT_{1A} agonist effect.

Partly on the basis of electrophysiological and biochemical evidence that 5-HT neurones tonically inhibit the activity of noradrenergic neurones (e.g., McRae-Degueurce et al., 1985; Reader et al., 1986), we proposed previously that 5-HT_{1A} receptor agonists increase extracellular noradrenaline through activation of somatodendritic 5-HT_{1A} autoreceptors and the resulting inhibition of 5-HT release (Done and Sharp, 1994). However, evidence is accumulating that postsynaptic 5-HT_{1A} receptors, and not somatodendritic 5-HT_{1A} autoreceptors, mediate the increase in noradrenaline induced by 5-HT_{1A} agonists. Thus, neither depletion of brain 5-HT by synthesis inhibition, nor 5-HT denervation, prevent 8-OH-DPAT from increasing extracellular noradrenaline (Chen and Reith, 1995; Suzuki et al., 1995).

There are, however, two findings which indicate that the pharmacology of the 5-HT_{1A} receptor facilitating the release of noradrenaline is unusual for a postsynaptic 5-HT_{1A} receptor. Firstly, in the present study 1 mg/kg 8-OH-DPAT induced both the 5-HT behavioural syndrome (a well-recognised postsynaptic 5-HT_{1A} receptor-mediated response), and a rise in extracellular noradrenaline, and yet only the behavioural response to this dose of 8-OH-DPAT was abolished by WAY 100635. The 5-HT_{1A} receptor antagonist significantly blocked the noradrenaline response only when the dose of 8-OH-DPAT was reduced 10 times. Secondly, the partial 5-HT_{1A} receptor agonists MDL 73005 and NAN-190 increase extracellular noradrenaline to the same extent as 8-OH-DPAT (Done and Sharp, 1994; Hajós-Korcsok et al., 1994) and yet do not elicit the 5-HT

behavioural syndrome (Hjorth and Sharp, 1990; Moser et al., 1990). In fact, the latter drugs show antagonist properties at the postsynaptic 5-HT_{1A} receptor and agonist properties at the 5-HT_{1A} autoreceptor (Gartside et al., 1990; Hjorth and Sharp, 1990).

Together, these results indicate that the 5-HT_{1A} receptors mediating the increase in extracellular noradrenaline are much more sensitive to stimulation than those mediating the 5-HT behavioural syndrome. Indeed, the pharmacology of the 5-HT_{1A} receptor influencing noradrenaline appears to resemble more that of the 5-HT_{1A} autoreceptor which is also highly sensitive to agonists. The latter property is attributed, at least in part to high receptor reserve (Meller et al., 1990). It is possible, therefore, that the 5-HT_{1A} receptor influencing noradrenaline also has high receptor reserve even if it is located postsynaptically.

An interesting result was that the dopamine D_1 receptor antagonist, SCH 23390, also inhibited the increase in noradrenaline induced by 8-OH-DPAT. It seems unlikely that SCH 23390 interacts at the 5-HT_{1A} receptor to block the effect of 8-OH-DPAT since SCH 23390 has low affinity for the 5-HT_{1A} receptor (IC_{50} 2.6 μM; Biscoff et al., 1988) versus D_1 receptor (IC_{50} 0.01 μM; Iorio et al., 1983), and does not inhibit the 5-HT behavioural syndrome at doses (0.04–0.2 mg/kg s.c.) similar to those used here (Pugh et al., 1985). Although SCH 23390 has antagonist properties at 5-HT_2 receptors (Hicks et al., 1984), it is not easy to relate this to the inhibition of the stimulatory effect of 8-OH-DPAT on noradrenaline, especially since 5-HT_2 receptor antagonists increase extracellular noradrenaline when injected alone (Done and Sharp, 1994). Furthermore, evidence that SCH 23390 inhibits in vivo binding of [^{3}H]spiperone to rat cortex with an ID_{50} value of 1.5 mg/kg (Biscoff et al., 1988), suggests that SCH 23390 would not have significant occupancy at 5-HT_2 receptors at the doses (0.5 and 0.1 mg/kg) used in the present study.

Overall, therefore, the evidence favours an involvement of D_1 receptors at some point in the mechanism mediating the facilitation of noradrenaline release by 5-HT_{1A} receptors. In support of this view, there is evidence that 8-OH-DPAT increases dopamine cell-firing and stimulates the release of dopamine in rat cortex (Arborelius et al., 1993a,b).

As with noradrenaline, D_1 receptor antagonists (SCH 23390 and SCH 39166) also block the facilitation of acetylcholine release by 8-OH-DPAT (Consolo et al., 1996). Indeed the ways in which acetylcholine and noradrenaline release are facilitated by the 5-HT_{1A} receptor are similar in other respects: (i) not only 8-OH-DPAT but other 5-HT_{1A} receptor agonists (including the partial agonists ipsapirone and MDL 73005) are effective (Wilkinson et al., 1994); (ii) the effect is blocked by the selective 5-HT_{1A} receptor antagonist, WAY 100635 (Consolo et al., 1996); (iii) the effect is not prevented by 5-HT lesions (Consolo et al., 1996); and (iv) the effect occurs in various brain regions, specifically frontal cortex and hippocampus (Wilkinson et al., 1994; Consolo et al., 1996). From this, one can speculate that the 5-HT_{1A} receptor has a key role in mediating the influence of 5-HT on both noradrenergic and cholinergic pathways. This would provide a route for the modulation by 5-HT of brain functions in which both noradrenaline and acetylcholine have a recognised role (e.g., attention, mood and cognition).

In summary, we find that the release of noradrenaline in hippocampus of the awake rat induced by low doses of 8-OH-DPAT is blocked by pretreatment with the selective 5-HT_{1A} receptor antagonist, WAY 100635. Our data are consistent with the view that noradrenaline is influenced by 5-HT_{1A} receptors (but these appear much more sensitive to stimulation than classical postsynaptic 5-HT_{1A} receptors). The blockade of 8-OH-DPAT-induced release of noradrenaline by SCH 23390 also suggests a role for the dopamine D_1 receptor in the response. The latter result in particular, highlights similarities in the mechanism by which 5-HT_{1A} receptor agonists facilitate the release of noradrenaline and acetylcholine. The facilitatory influence of 5-HT_{1A} receptors on noradrenaline and acetylcholine could have relevance to the role of the 5-HT_{1A} receptor in psychiatric disorders such as depression and anxiety, and the antidepressant and anxiolytic action of 5-HT_{1A} receptor agonists.

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