ELSEVIER

European Journal of Pharmacology 294 (1995) 743–751

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# The role of 5-$HT_{1D}$ and 5-$HT_{1A}$ receptors in mediating 5-hydroxytryptophan induced myoclonic jerks in guinea pigs

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Received 1 June 1995; revised 11 September 1995; accepted 29 September 1995

**Abstract**

Systemic administration of 5-hydroxytryptophan (5-HTP) to guinea pigs causes species-specific, rhythmic, whole body jerks (myoclonic jerks), the frequency and amplitude of which were measured in an automated apparatus. The brain penetrant 5-$HT_{1D}$ receptor agonist 3-(2-dimethylaminoethyl)-4-chloro-5-propoxyindole hemifumarate (SKF 99101H) (3–30 mg/kg i.p.) and the selective 5-$HT_{1A}$ receptor agonist (±)8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (0.3–3 mg/kg s.c.) dose dependently potentiated the frequency and intensity of myoclonic jerks caused by 5-HTP (100 mg/kg). Cotreatment of guinea pigs with 8-OH-DPAT (3 mg/kg s.c.) and SKF 99101H (30 mg/kg i.p.), which were inactive when given alone, gave a marked myoclonic jerk response. Conversely, the myoclonic jerk response to higher doses of 5-HTP (150 mg/kg i.p.) was dose dependently blocked by the 5-$HT_{1D}$ receptor antagonist GR 127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1′-biphenyl]4-carboxamide oxalate) ($ED_{50}$ 0.32 mg/kg i.p.) and the selective 5-$HT_{1A}$ receptor antagonist WAY 100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride) ($ED_{50}$ 0.33 mg/kg i.p.). The response to 5-HTP (150 mg/kg i.p.) was also blocked by ritanserin (0.01–0.3 mg/kg i.p). Our data therefore confirm previous reports concerning the effects of 5-$HT_{2A/2C}$ receptor blockade on 5-HTP induced myoclonic jerks and suggest that both 5-$HT_{1D}$ and 5-$HT_{1A}$ receptors play an important role in mediating this behavioural response.

*Keywords:* Myoclonic jerk; 8-OH-DPAT ((±)-8-hydroxy-2-(di-*n*-propylamino)tetralin); SKF 99101H; GR 127935; WAY 100635; 5-$HT_{1D}$ receptor; 5-$HT_{1A}$ receptor; 5-Hydroxytryptophan; (Guinea-pig)

## 1. Introduction

Behavioural responses to 5-hydroxytryptophan (5-HTP) vary between species. Guinea pigs respond with piloerection, defaecation and highly rhythmic myoclonus, which takes the form of intense whole body jerks (1–2/s) involving all the major muscle groups (myoclonic jerks) (Klawans et al., 1973). Both the frequency and amplitude of this response are dependent upon the dose of 5-HTP administered.

Convincing evidence implicates 5-HT in the mediation of 5-HTP induced myoclonic jerks. The frequency of the response is increased by selective serotonin uptake blockers (Luscombe et al., 1986) and the response to 5-HTP correlates well with hind-brain 5-HT levels (Luscombe et al., 1983). Furthermore, the behaviour is blocked by pretreatment with the centrally active decarboxylase inhibitor NSD-1035 (Chadwick et al., 1978) and by the non-selective 5-HT receptor antagonists methysergide, cyproheptadine, metergoline and cinanserin (Chadwick et al., 1978; Luscombe et al., 1986; Volkman et al., 1978). Dopamine receptor agonists inhibit myoclonic jerking (Volkman et al., 1978; Weiner et al., 1979; Carvey et al., 1986) and some authors report that low doses of haloperidol cause a mild potentiation (Weiner et al., 1979; Carvey et al., 1986). In contrast, the myoclonic response to 5-HTP is unaffected by adrenergic, muscarinic and opiate receptor antagonists (Carvey et al., 1986; Chadwick et al., 1978). Decerebration experiments indicate that myoclonic jerks are mediated by pathways in the lower brainstem and spinal column (Chadwick et al., 1978).

In addition to 5-HTP, 5-HT receptor agonists, particularly those containing an indole moiety (Luscombe

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*SSDI* 0014-2999(95)00627-3

et al., 1982, 1984a, b; Volkman et al., 1978) also cause myoclonic jerks and it has been suggested that these effects are mediated via 5-$HT_1$ receptors in the brainstem (Luscombe et al., 1984a, b). Since those early studies 5-$HT_1$ receptors have been shown to consist of six subtypes (5-$HT_{1A}$–5-$HT_{1F}$) of which the 5-$HT_{1D}$ receptor is further subdivided into 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ (Weinshank et al., 1992; Hartig et al., 1993). 5-$HT_{1D\beta}$ receptors are specific to man and guinea pigs and have as their homologue the 5-$HT_{1B}$ receptor in rats (Humphrey et al., 1993).

We have investigated the role of 5-$HT_{1A}$ and 5-$HT_{1D}$ receptors in mediating myoclonic jerk responses to 5-HTP. For studies of the role of 5-$HT_{1A}$ receptors the selective 5-$HT_{1A}$ receptor agonist (±)8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (Hjorth et al., 1982; Middlemiss and Fozard, 1983) and antagonist WAY 100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride) (Cliffe, 1993) were used. For the studies on the role of 5-$HT_{1D}$ receptors, the selective 5-$HT_{1D}$ receptor antagonist GR 127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1′-biphenyl]-4-carboxamide oxalate) (Skingle et al., 1993) and the selective, brain penetrant 5-$HT_{1D}$ receptor agonist SKF 99101H (3-(2-dimethylaminoethyl)-4-chloro-5-propoxyindole hemifumarate) were tested. The pharmacological profile of SKF 99101H obtained in radioligand binding assays is summarised in Table 1 (Dr. A.T. Brown unpublished data). The compound is 100-fold selective for guinea-pig 5-$HT1_D$ receptors and human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors over other 5-HT receptors tested (5-$HT_{1E,2A,2C,3,4}$), except for the rat 5-$HT_{1A}$ receptor where selectivity was 10-fold. It has no appreciable affinity for human dopamine receptors.

## 2. Materials and methods

### 2.1. Animals

Male Dunkin Hartley guinea pigs (Harlan Porcellus UK) weighing between 250 and 500 g were used. Animals were housed in groups of five or six, in a temperature controlled environment (20 ± 1°C) and maintained on a 12 h light/dark cycle (lights on 7:00–19:00) for at least 5 days prior to use with ad libitum access to food and water. Experiments were carried out in compliance with the Animals (Scientific Procedures) Act 1986 and conformed to SmithKline Beecham ethical guidelines.

### 2.2. Apparatus

Guinea pigs were placed in the individual chambers of a purpose built apparatus designed to automatically measure the frequency and amplitude of myoclonic jerks. The apparatus is described in detail elsewhere (Lloyd et al., in press). Briefly, it consists of ten independent test chambers. Each chamber consists of a perspex box (23 × 15 × 25 cm), with a slide-off, ventilated lid, placed over a spring-mounted steel bar floor which is free to move in response to animal movement. Each base is connected to an accelerometer which measures the acceleration of the floor in response to movement. Signals are analysed on-line using dedicated software to detect the occurence of myoclonic jerks, using an algorithm derived empirically from high-resolution recordings of prototypical myoclonic jerks and validated against observer based recording methods. Analysis of each jerk yields a measure of peak amplitude (arbitrary units) and the time of its occurence. These data are then accumulated into an EXCEL spreadsheet for statistical analysis.

### 2.3. Procedure

5-HTP was administered intraperitoneally (i.p.) and the animals placed into the test chambers immediately (time 0). Doses were chosen on the basis of previous experiments; 5-HTP (100 mg/kg i.p.) is sufficiently above the dose threshold (approximately 80 mg/kg) to give reliable responding whereas the higher dose (150 mg/kg i.p.) causes a submaximal response. In studies with agonists, these were injected at the same time as 5-HTP. In the experiment in which 8-OH-DPAT was combined with SKF 99101H these two compounds were also given simultaneously. WAY 100635, GR

Table 1
Receptor binding affinity values ($pK_i$) for SK99101H in radioligand receptor binding assays

| Receptor assay | Tissue | Ligand | $pK_i$ |
|---|---|---|---|
| 5-$HT_{1A}$ | Rat cortex | [$^3$H]8-OH-DPAT | 7.43 |
| 5-$HT_{1D\alpha}$ | Human 5-$HT_{1D\alpha}$ receptors expressed in CHO cells | [$^3$H]5-HT | 8.72 |
| 5-$HT_{1D\beta}$ | Human 5-$HT_{1D\beta}$ receptors expressed in CHO cells | [$^3$H]5-HT | 8.70 |
| 5-$HT_{1D}$ | Guinea pig cortex | [$^3$H]5-HT | 8.55 |
| 5-$HT_{1E}$ | Human 5-$HT_{1E}$ receptors expressed in CHO cells | [$^3$H]5-HT | 6.56 |
| 5-$HT_{2A}$ | Human 5-$HT_{2A}$ receptors expressed in HEK293 cells | [$^3$H]Ketanserin | 5.79 |
| 5-$HT_{2C}$ | Human 5-$HT_{2c}$ receptors expressed in HEK293 cells | [$^3$H]Mesulergine | 6.38 |
| 5-$HT_3$ | Rat hippocampus | [$^3$H]Granisetron | > 5.00 |
| $D_2$ | Human $D_2$ receptors expressed in CHO cells | [$^{125}$I]Iodosulpiride | 5.39 |
| $D_3$ | Human $D_3$ receptors expressed in CHO cells | [$^{125}$I]Iodosulpiride | 5.28 |

127935, granisetron and ritanserin were injected intraperitoneally 15 min prior to 5-HTP.

### 2.4. Drugs

The following drugs were used and were all prepared within the Medicinal Chemistry Department at SmithKline Beecham Research Laboratories: granisetron HCL, GR 127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1′-biphenyl]-4-carboxamide oxalate), SKF 99101H (3-(2-dimethylaminoethyl)-4-chloro-5-propoxyindole hemifumarate) and WAY 100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)-cyclohexanecarboxamide trihydrochloride). 5-Hydroxytryptophan, was obtained from Sigma. (±)8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and ritanserin were obtained from RBI.

Drugs were dissolved in water with the exception of SKF 99101H which was suspended in 1% methyl cellulose. 5-HTP was gently heated at a concentration of 20 mg/ml. For each treatment the control group received the relevant vehicle. All drugs were administered at a dose volume of 5 ml/kg body weight except for 5-HTP (150 mg/kg) which was administered as 7.5 ml/kg.

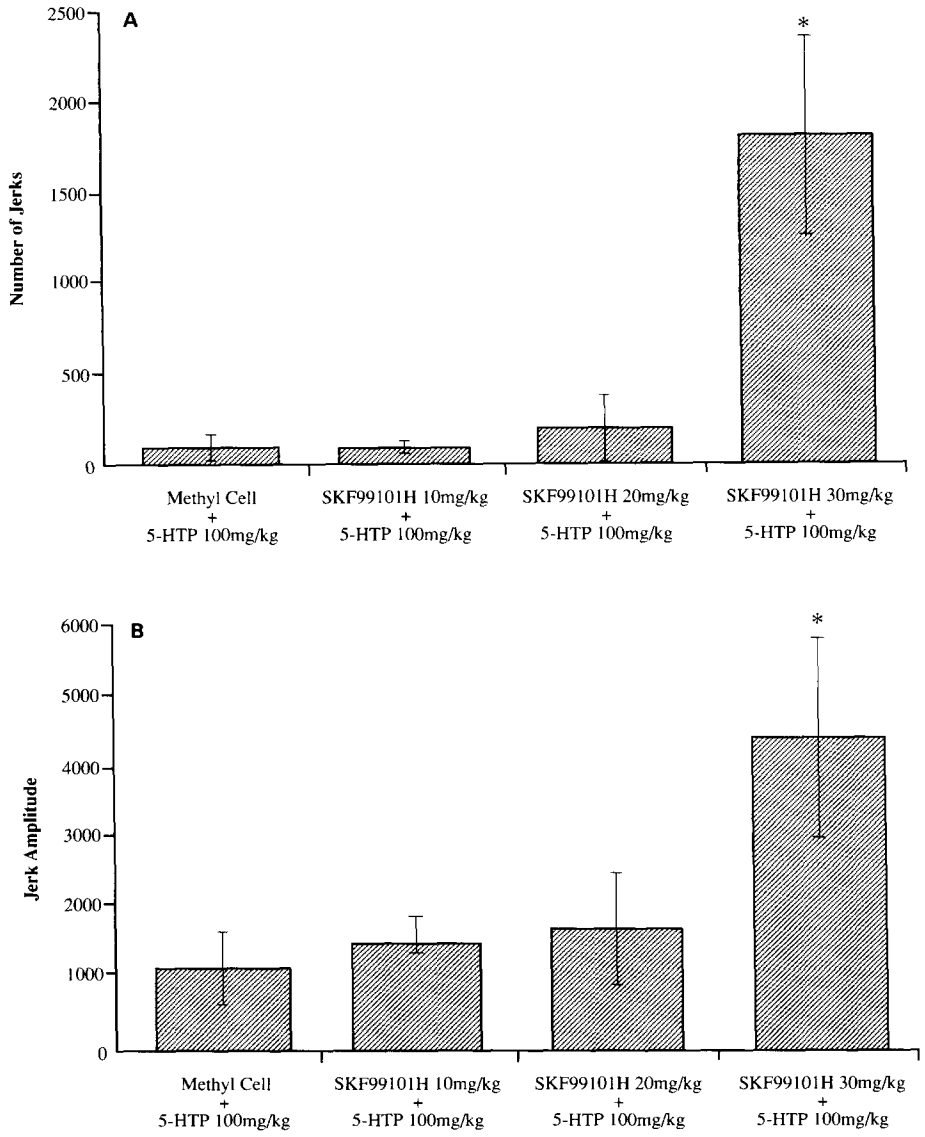


Fig. 1. The effect of SKF 99101H on the mean number (A) and mean amplitude, in arbitrary units (B) (±S.E.M), of myoclonic jerks recorded over 120 min. SKF 99101H (10.0, 20.0, 30.0 mg/kg i.p.) or vehicle were administered 15 min before 5-HTP (100 mg/kg i.p.) which was injected at time 0. Asterisks denote significant increase in myoclonic jerks relative to vehicle/5-HTP controls (1-way ANOVA followed by Dunnett's *t*-test, * $P < 0.05$ ** $P < 0.01$). $n = 6$ per group.

Doses are quoted as mg/kg of the salt forms of each drug.

### 2.5. Statistical analysis

Myoclonic jerks were monitored continously for 2 h in each experiment but for the purpose of analysis observations were accumulated into 5 min bins and from each 5 min bin the number and average amplitude of responses were recorded. The total number of myoclonic jerks and the average amplitudes were assessed using a one way analysis of variance (ANOVA) with post-hoc analysis carried out using Dunnett's *t*-test. $ED_{50}$'s and 95% confidence limits, where appropriate, were calculated using a linear fit procedure in RS1 (Draper and Smith, 1966).

## 3. Results

### 3.1. Agonists selective for 5-$HT_{1A}$ and 5-$HT_{1D}$ receptors

The administration of SKF 99101H alone did not cause myoclonic jerks (see below) but did cause a

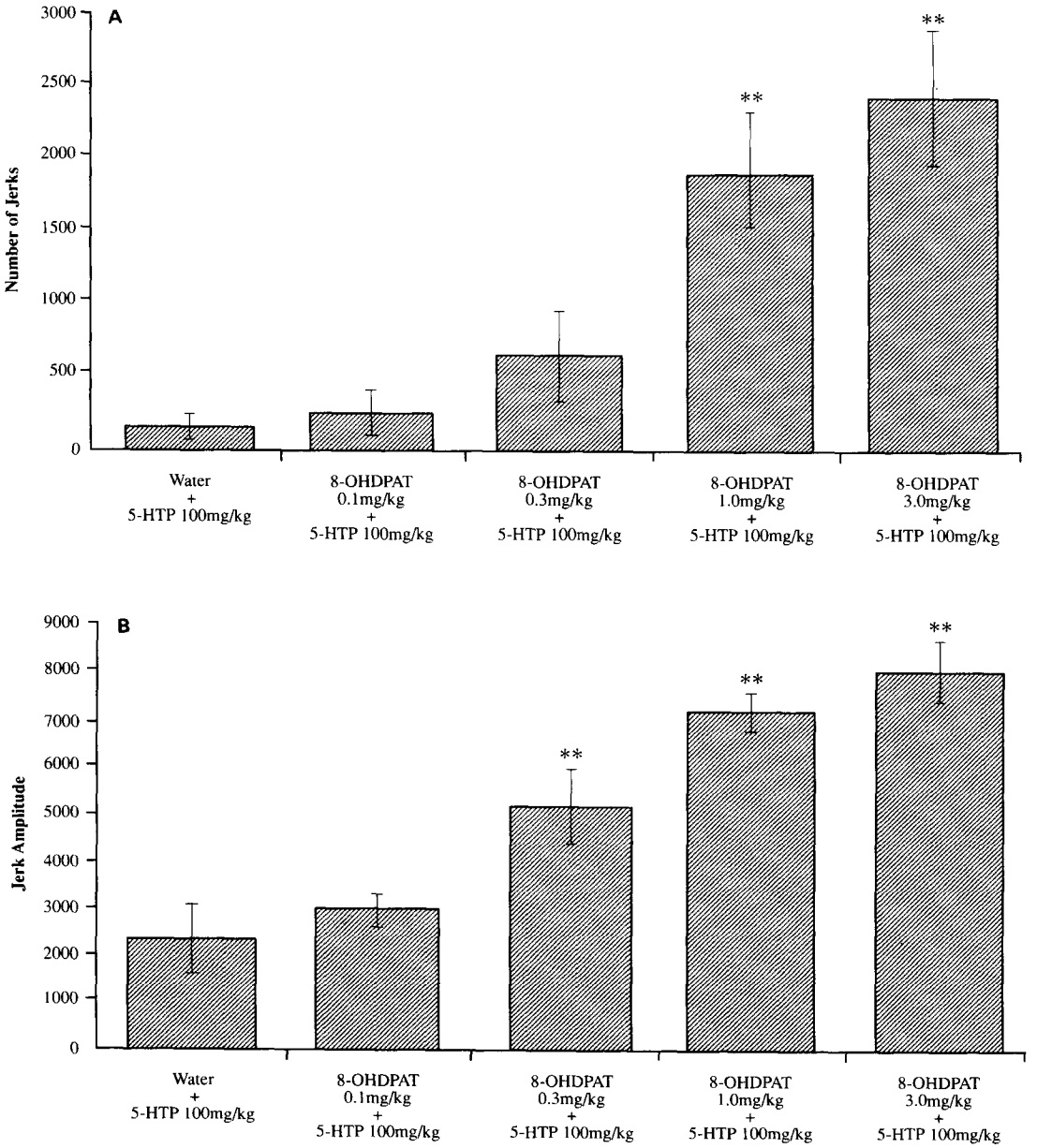


Fig. 2. The effect of 8-OH-DPAT on the mean number (A) and mean amplitude, in arbitrary units (B) (±S.E.M), of myoclonic jerks recorded over 120 min. 8-OH-DPAT (0.1–3 mg/kg s.c.) or vehicle were administered immediately prior to 5-HTP (100 mg/kg i.p.) at time 0. Asterisks denote significant increase in myoclonic jerks relative to vehicle/5-HTP controls (1-way ANOVA followed by Dunnett's *t*-test, ** $P < 0.01$). $n = 6$ per group.

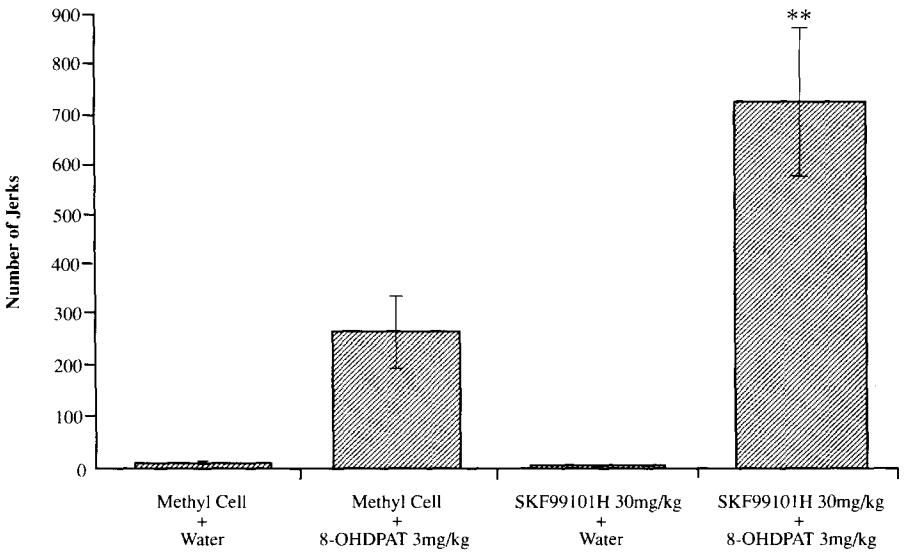


Fig. 3. The effect of combined treatment with SKF 99101H (30 mg/kg i.p.) and 8-OH-DPAT (3 mg/kg s.c.) on the mean number (±S.E.M) of myoclonic jerks recorded over 120 min. Both drugs were administered at time 0. Asterisks denote significant increase in myoclonic jerks relative to vehicle/5-HTP controls (1-way ANOVA followed by Dunnett's $t$-test, ** $P < 0.01$). $n = 6$ per group.

significant increase in both the number $F(3,24) = 8.4$ $P < 0.001$ (Fig. 1) and amplitude $F(3,24) = 3.49$ $P < 0.05$ of myoclonic jerks when combined with 5-HTP (100 mg/kg). Both the total number of myoclonic jerks ($P < 0.01$) and their amplitudes ($P < 0.05$) were significantly increased only after the highest dose (30 mg/kg).

8-OH-DPAT also caused a highly significant, dose dependent, potentiation of the number $F(4,25) = 10.71$ $P < 0.001$ and the amplitude $F(4,25) = 19.73$ $P < 0.001$ (Fig. 2) of myoclonic jerk responses to a low dose of 5-HTP (100 mg/kg i.p.). Post-hoc analysis revealed significant increases in the number of responses in the groups treated with 1.0 ($P < 0.01$) and 3.0 mg/kg ($P < 0.01$) of 8-OH-DPAT. Amplitude was significantly greater following 0.3, 1.0 and 3 mg/kg (all $P < 0.01$).

When SKF 99101H (30 mg/kg i.p.) and 8-OH-DPAT

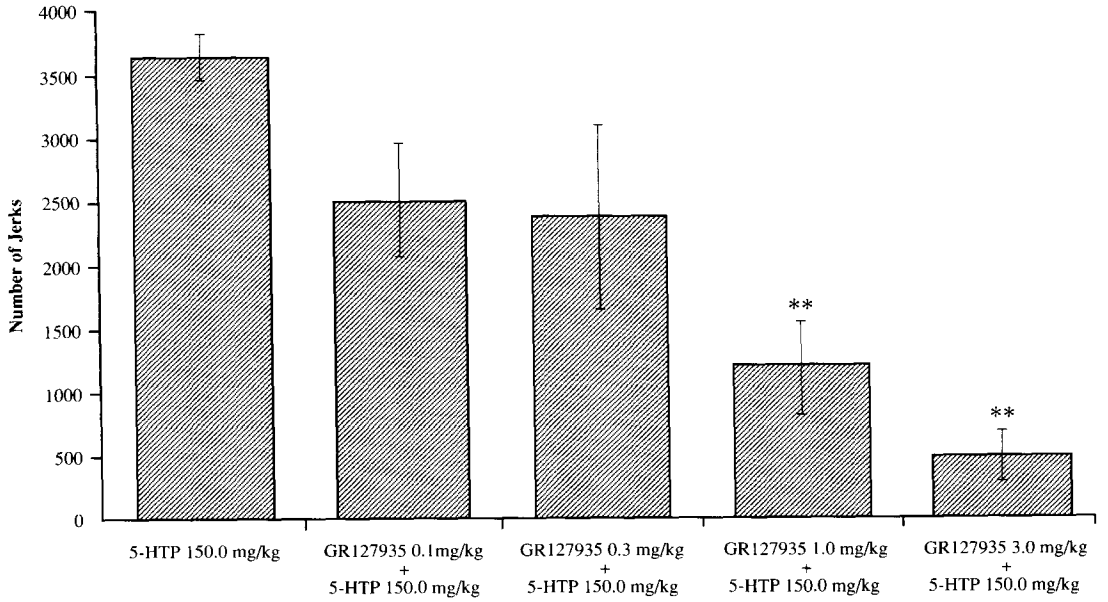


Fig. 4. The effect of GR 127935 (0.1–3 mg/kg i.p.) on the mean number (±S.E.M) of myoclonic jerks induced by 5-HTP (150 mg/kg i.p.), recorded over 120 min. GR 127935 was injected 15 min prior to 5-HTP at time 0. Asterisks denote significant decrease in myoclonic jerks relative to vehicle controls (1-way ANOVA followed by Dunnett's $t$-test, ** $P < 0.01$). $n = 6$ per group.

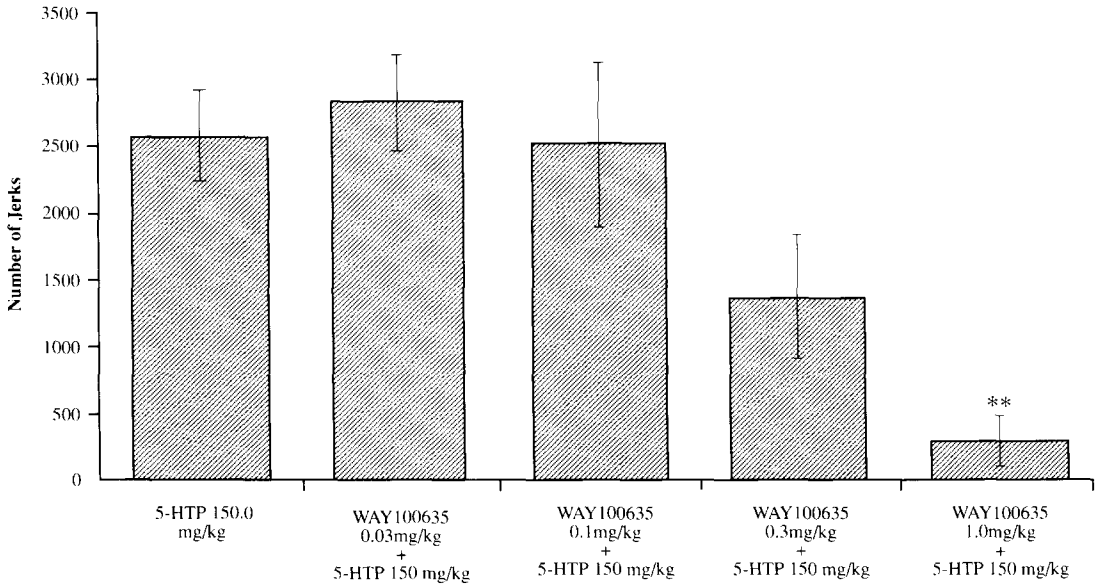


Fig. 5. The effect of WAY 100635 (0.03–1 mg/kg i.p.) on mean number (±S.E.M) of myoclonic jerks induced by 5-HTP (150 mg/kg i.p.), recorded over 120 min. WAY 100635 was injected 15 min prior to 5-HTP at time 0. Asterisks denote significant decrease in myoclonic jerks relative to vehicle/5-HTP controls (1-way ANOVA followed by Dunnett's *t*-test, ** $P < 0.01$). $n = 6$ per group.

(3 mg/kg s.c.) were administered together, in the absence of 5-HTP, analysis of the total number of jerks $F(3,24) = 17.45$ $P < 0.001$ (Fig. 3), and average jerk amplitude $F(3,24) = 29.75$ $P < 0.001$, revealed highly significant treatment effects. Neither compound alone caused a significantly greater number of myoclonic jerks than vehicle treatment but the two agonists combined induced a significant increase in the number of myoclonic jerks ($P < 0.01$). Observations indicated that 8-OH-DPAT (3 mg/kg s.c.) caused some degree of hyperactivity. To confirm that the potentiated responding was not an artifact caused by the hyperactivity response to 8-OH-DPAT each animal was monitored visually for 1 min at 30, 60 and 90 min after the start of the experiment. Analysis of these data confirmed a highly significant treatment effect (Kruskall-Wallis $\chi^2 = 20.7$, df = 3, $P < 0.001$). The number of observer-rated myoclonic jerks was low in animals treated with vehicle-vehicle (0), vehicle/8-OH-DPAT (4.8 ± 1.6), and vehicle/ SKF 99101H (0) but significantly higher in the group treated with 8-OH-DPAT and SKF 99101H (19.2 ± 6.4).

### 3.2. Effects of 5-$HT_{1D}$ receptor antagonism

Following administration of 5-HTP (150 mg/kg i.p.) the number of myoclonic jerks during the 2 h observation periods varied between approximately 2500 and 3600. Both the number of responses and their amplitude were higher than after the lower dose of 5-HTP (100 mg/kg i.p.). The 5-$HT_{1D}$ receptor antagonist GR 127935 caused a dose dependent inhibition in the number of myoclonic jerks $F(4,25) = 8.89$ $P < 0.001$ (Fig. 4). Significant reductions were observed after 1 and 3 mg/kg ($P < 0.01$) and the $ED_{50}$ was 0.32 mg/kg i.p. (95% confidence limits; 0.09–0.65). Dose dependent reduction in the amplitude of myoclonic jerks was also found $F(4,25) = 14.11$ $P < 0.001$. All four doses significantly reduced jerk amplitude ($P < 0.01$).

### 3.3. Effects of 5-$HT_{1A}$ receptor antagonism

Pretreatment with WAY 100635 significantly reduced both the number $F(4,25) = 6.31$ $P < 0.001$ (Fig.

Table 2
The effects of ritanserin and granisetron on 5-HTP (150 mg/kg i.p.) induced myoclonic jerks during a 2 h observation period

| Drug | Dose | | | | | | |
|---|---|---|---|---|---|---|---|
| | Vehicle | 0.01 mg/kg | 0.03 mg/kg | 0.1 mg/kg | 0.3 mg/kg | 1 mg/kg | 3.0 mg/kg |
| Ritanserin | 1919 ± 253 | 2525 ± 613 | 2342 ± 452 | 1013 ± 471 | 256 ± 249 [a] | NT | NT |
| Granisetron | 2450 ± 929 | NT | NT | 4358 ± 169 | 3444 ± 736 | 3642 ± 759 | 3107 ± 728 |

Data are totals ± S.E.M. [a] $P < 0.05$; NT, not tested.

5) and amplitude $F(4,25) = 2.96$ $P < 0.05$ of responses. Reduced numbers of myoclonic jerks were observed between 0.1 and 1.0 mg/kg of WAY 100635, with the highest dose causing significant inhibition ($P < 0.01$). The $ED_{50}$ for inhibition with WAY 100635 was 0.33 mg/kg. Similarly, jerk amplitude was dose dependently inhibited in the same dose range with a significant reduction at the highest dose ($P < 0.05$)

### 3.4. Effects of ritanserin and granisetron on myoclonic jerks

Ritanserin significantly reduced both the number $F(4,25) = 4.89$ $P < 0.005$ (see Table 2) and amplitude $F(4,25) = 3.84$ $P < 0.05$ (data not shown) of the responses to 5-HTP (150 mg/kg). In both cases only the highest dose tested reached significance ($P < 0.05$). Granisetron had no significant effect on either the number (see Table 2) or the amplitude of responses (data not shown).

## 4. Discussion

Systemic injections of the novel, brain penetrant 5-$HT_{1D}$ receptor agonist SKF 99101H caused a significant potentiation of both the frequency and amplitude of myoclonic jerks caused by 5-HTP (100 mg/kg). The compound alone was inactive. In radioligand binding assays SKF 99101H has affinity for the 5-$HT_{1D}$ receptor in guinea-pig tissue and cloned human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors which is at least 100-fold higher than its affinity at either the 5-$HT_{2A/2C}$ or 5-$HT_3$ receptors and 10-fold higher than at the rat 5-$HT_{1A}$ receptor (Table 1). These data suggest that it is stimulation of the 5-$HT_{1D}$ receptor which mediates potentiation of the effects of 5-HTP. This conclusion is supported by the antagonist study with GR 127935, a selective 5-$HT_{1D}$ receptor antagonist (Skingle et al., 1994a), which blocked the myoclonic jerks caused by 150 mg/kg of 5-HTP but was inactive when administered alone (data not shown). As GR 127935 inhibited 5-HTP induced myoclonic jerks it was not tested against the potentiating effect of SKF 99101H. The available antagonists do not distinguish between 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptor subtypes and so the relative contribution of each cannot yet be determined.

5-$HT_{1A}$ receptors also play a mediating role. The selective 5-$HT_{1A}$ receptor agonist 8-OH-DPAT caused a highly significant and dose dependent potentiation of the number and amplitude of myoclonic jerks caused by 5-HTP (100 mg/kg), but was virtually inactive when given alone, confirming published data (Eison et al., 1993). Conversely, the selective 5-$HT_{1A}$ receptor antagonist WAY 100635 inhibited 5-HTP induced myoclonic jerks. The importance of both 5-$HT_{1A}$ and 5-$HT_{1D}$ receptors is further underlined by the synergistic interaction between the two agonists, 8-OH-DPAT and SKF 99101H, when given in the absence of 5-HTP. Co-stimulation of these receptors is therefore sufficient to elicit the full myoclonic response.

Previous studies have suggested that activation of 5-$HT_2$ receptors is necessary to induce myoclonic jerks and that simultaneous activation of 5-$HT_2$ and 5-$HT_{1A}$ receptors by non-specific agonists such as 5-methoxy-*N*,*N*,-dimethyltyptamine (5-MeODMT) (Eison et al., 1993) accounts for the potency of these compounds. Our data suggest that 5-$HT_2$ receptor activation is not a pre-requisite. It is, nevertheless, clear that in addition to 5-$HT_{1A}$ and 5-$HT_{1D}$ receptors, 5-$HT_2$ receptors also play a role in mediating myoclonic jerks. Ritanserin inhibited the 5-HTP induced response, supporting the suggestion by others (Chadwick et al., 1978; Eison et al., 1993; Luscombe et al., 1986; Volkman et al., 1978) for a role for 5-$HT_{2A}$, 5-$HT_{2B}$ or 5-$HT_{2C}$ receptors. The lack of activity with granisetron excludes a role for 5-$HT_3$ receptors.

Decerebration studies (Chadwick et al., 1978) indicate that the myoclonic jerk response to 5-HTP is mediated below the midcollicular level. 5-$HT_{1D}$ and 5-$HT_{1A}$ receptors at the level of the hind brain or spinal cord are therefore likely to be involved in its mediation. However, as both 5-$HT_{1A}$ (Chalmers and Watson, 1991; Miquel et al., 1991; Pompeiano et al., 1992) and 5-$HT_{1D}$ (Bruinvels et al., 1994) receptors are widely distributed throughout the forebrain in rodents the anatomical location through which these receptors modulate the myoclonic jerk response remains to be determined. Some locations can however be excluded. Both receptor subtypes and their species homologues are known to play an inhibitory role in the autoregulation of 5-HT neuronal function (Engel et al., 1986; Schlicker et al., 1989) but, in this case, it seems unlikely that it is through either somatodendritic or terminal autoreceptors that inhibition of myoclonic jerks is mediated. Stimulation of 5-$HT_{1A}$ receptors inhibits raphe cell firing in slice preparations of guinea pig dorsal raphe nucleus (Craven et al., 1994) and stimulation of 5-$HT_{1D}$ and 5-$HT_{1A}$ receptors in vivo (Hjorth, 1993; Routledge et al., 1993; Skingle et al., 1994b) and in vitro (Starkey and Skingle, 1994; Davidson and Stamford, 1995) has been shown to reduce 5-HT release. Yet myoclonic jerk responses caused by 5-HTP are thought to be associated with excess 5-HT (Luscombe et al., 1983; Perry and Fuller, 1993). The potentiation of 5-HTP induced myoclonic jerks seen with the selective 5-$HT_{1D}$ and 5-$HT_{1A}$ receptor agonists is therefore opposite to that which would be predicted if the compounds were exerting their effects through either terminal 5-$HT_{1D}$ or somatodendritic 5-$HT_{1A}$ receptors.

Myoclonic jerks in guinea pigs constitute a species-specific example of a highly repetitive behavioural se-

quence associated with 5-HT overstimulation. Evidence from electrophysiological, behavioural and neurochemical studies implicate central 5-HT in the regulation of tonic and repetitive motor behaviour in a wide range of species (Jacobs and Fornal, 1993; Wallis, 1994). Previous data, from studies of 5-HT agonists injected into the substantia nigra, have suggested that stimulation of 5-$HT_{1D}$ receptors can increase locomotor activity by activating nigrostriatal dopaminergic neurons (Higgins et al., 1991). Furthermore, high levels of 5-$HT_{1D}$ receptors in areas such as substantia nigra reticulata and globus pallidus in human and guinea-pig brain (Bruinvels et al., 1994; Waeber and Palacios, 1989; Waeber et al., 1990) is suggestive of a role in motor control. The 5-HT receptors involved in modulating the control of repetitive motor sequences have been studied in several species and, although the pharmacology is incomplete, the data implicate 5-$HT_{2A/2C}$ and 5-$HT_1$ receptor subtypes (Wallis, 1994). Our data suggest that both 5-$HT_{1D}$ and 5-$HT_{1A}$ receptors play an important role in mediating the effects of 5-HT in controlling repetitive motor sequences in the guinea pig. These findings may have clinical implications for the treatment of some myoclonic disorders in man, for which novel 5-HT receptor selective agonists and antagonists may provide new avenues for treatment (Pranzatelli and Snodgrass, 1985; Brown, 1995; Pranzatelli, 1994).

In summary, our data confirm the role of 5-$HT_{2A/2C}$ receptors and support the evidence for a role for the 5-$HT_{1A}$ receptor in mediating myoclonic jerks. 5-$HT_{1D}$ receptor activation in guinea pigs has previously been shown to cause hypothermia (Skingle et al., 1994a; Hatcher et al., 1995) and the present data suggest that these receptors may also play a role in motor control.

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