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Head and whole-body jerking in guinea pigs are differentially modulated by 5-HT_{1A}, 5-$HT_{1B/1D}$ and 5-HT_{2A} receptor antagonists

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Abstract

The present study examined the role of 5-hydroxytryptamine 5-HT receptor subtypes on 5-hydroxytryptamine- (5-HT-) mediated myoclonus in guinea pigs, evaluating head and whole-body jerking as two distinct behavioural responses. Myoclonus was induced by the 5-HT precursor L-5-hydroxytryptophan (L-5-HTP) and the non-selective 5-$HT_{1A/1B}$/5-HT_2 receptor agonist 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT). The selective 5-HT_{1A} receptor antagonist WAY100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride) inhibited both head and whole-body jerking. The selective 5-$HT_{1B/1D}$ receptor antagonist GR127935 (*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 hemifumarate) only inhibited whole-body jerking, which resulted in unmasked head jerking. Co-administration of GR127935 and the selective 5-HT_{2A} receptor antagonist MDL100.151 ((±)-α-(2,3-dimethoxyphenyl)-1-[-2-(4-fluorphenyl)ethyl]-4-piperidinmethanol) caused a complete inhibition of whole-body as well as head jerking. MDL100.151 had only limited effect on myoclonic jerking when given alone. The inhibitory effects of the 5-HT receptor antagonists on either L-5-HTP- or 5-MeODMT-induced myoclonus were found to be very similar. These data confirm a role for the 5-HT_{1A} and 5-$HT_{1B/1D}$ receptors and suggest a role for 5-HT_{2A} receptors in mediating myoclonus in guinea pigs. Moreover, the study shows that by considering head and whole-body jerking as two pharmacologically distinct behavioural responses, subtype specific 5-HT_{1A}, 5-$HT_{1B/1D}$ and 5-HT_{2A} receptor antagonists can be distinguished.

Keywords: Myoclonus; (Guinea pig); 5-HT_{1A} receptor; 5-$HT_{1B/1D}$ receptor; 5-HT_{2A} receptor

1. Introduction

Myoclonic jerking can be evoked in guinea pigs following administration of 5-hydroxytryptamine (5-HT) precursors and by indole-containing 5-HT receptor agonists. (Klawans et al., 1973; Volkman et al., 1978; Luscombe et al., 1982a; Eison et al., 1993). Klawans et al. (1973) originally described various behavioural alterations after administration of increasing doses of 5-hydroxytryptophan (5-HTP): First extensive grooming appearance appears followed by rapid brief movements of head and neck progressing to discontinuous jerking movements involving the entire body. The final behavioural manifestation consists of continuous rhythmic and symmetric myoclonic body jerks. The frequency and intensity of 5-HTP-induced myoclonic jerking are dose-dependent and correlates with elevation of whole-brain 5-HT concentrations (Klawans et al., 1973). The role of 5-HT has further been confirmed by pharmacological studies. 5-HTP-induced myoclonus is potentiated by selective serotonin uptake inhibitors (Luscombe et al., 1986), blocked by the centrally active decarboxylase inhibitor NSD-1035 (3-hydroxybenzylhydrazine dihydrochloride; Chadwick et al., 1978), and by the non-selective 5-HT receptor antagonists, methysergide, cyproheptadine, metergoline (Chadwick et al., 1978; Volkman et al., 1978; Luscombe et al., 1986). Along with the identification of different 5-HT receptor subtypes there has been an effort in determining the specific 5-HT subtype(s) mediating myoclonus. Luscombe et al. (1984a,b, 1986) have suggested that 5-HT-dependent myoclonus in guinea pigs is mediated through 5-HT_1 receptors whereas others have suggested that co-activation of 5-HT_{1A} and 5-HT_2 receptors may be required for the induction of myoclonus (Eison et al., 1993). Recently, co-activation of 5-HT_{1A} and 5-HT_{1D} receptors has shown to induce myoclonus (Hagan et al., 1995). Moreover, 5-HTP-induced myoclonus has

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shown to be inhibited by selective 5-HT_{1A} or 5-HT_{1D} antagonism (Hagan et al., 1995).

Myoclonic jerking is not to be confounded with other 5-HT-mediated behaviours in the guinea pig. Mundey et al. (1996) observed tremor, flat body posture, hindlimb abduction, head weaving, head jerks and forepaw treading induced by 5-HT_{1A} receptor stimulation. The same group found head twist (or wet dog shaking) to be induced by 5-HT_2 receptor stimulation.

Myoclonic jerking can be quantified by visual observation (Luscombe et al., 1981, 1982a) or by automated methods (Volkman et al., 1978; Hagan et al., 1995). The expression of myoclonus in the guinea pig involves whole-body jerking and isolated head jerks which are considered to be behaviourally distinct (Pranzatelli and Snodgrass, 1987; Eison et al., 1993). By rating head jerking as a part of whole-body jerking or quantifying myoclonic jerking by activity measurements, effects on isolated head jerks may be overlooked. In order to elucidate pharmacological differentiation between head and whole-body jerking as part of the myoclonic syndrome, the present study has examined the effects of WAY100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride) (selective 5-HT_{1A} receptor antagonist) (Forster et al., 1995), GR127935 (*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 hemifumarate) (selective 5-$HT_{1B/1D}$ receptor antagonist) (Skingle et al., 1996) and MDL100.151 ((±)-α-(2,3-dimethoxyphenyl)-1-[-2-(4-fluorophenyl)ethyl]-4-piperidinmethanol) (selective 5-HT_{2A} receptor antagonist, racemate with MDL100.907 as the active enantiomer) (Kehne et al., 1996) on myoclonus induced by L-5-HTP (L-5-hydroxytryptophan) and the non-selective 5-$HT_{1A/1B}$/5-HT_2 receptor agonist 5-MeODMT (5-methoxy-*N*,*N*-dimethyltryptamine) (Tricklebank et al., 1985). The study has been presented in a preliminary form at the 27th meeting in Society for Neuroscience, New Orleans, Nov., 1997 (Nielsen and Skarsfeldt, 1997).

2. Materials and methods

2.1. Animals

Male guinea pigs (SSC:AL, Seruminstituttet, Denmark) weighing 220–350 g were used. The guinea pigs were housed in pairs in Macrolon type III cages and maintained on a 12 h light/dark cycle (light on 06.00 a.m.). They had free access to food and water. Temperature (21 ± 1°C), relative humidity (55 ± 5%) and air exchanges (16 times per h) were automatically controlled. The animals were used in two experiments. The second time the order of treatments was randomised and there was an interval of at

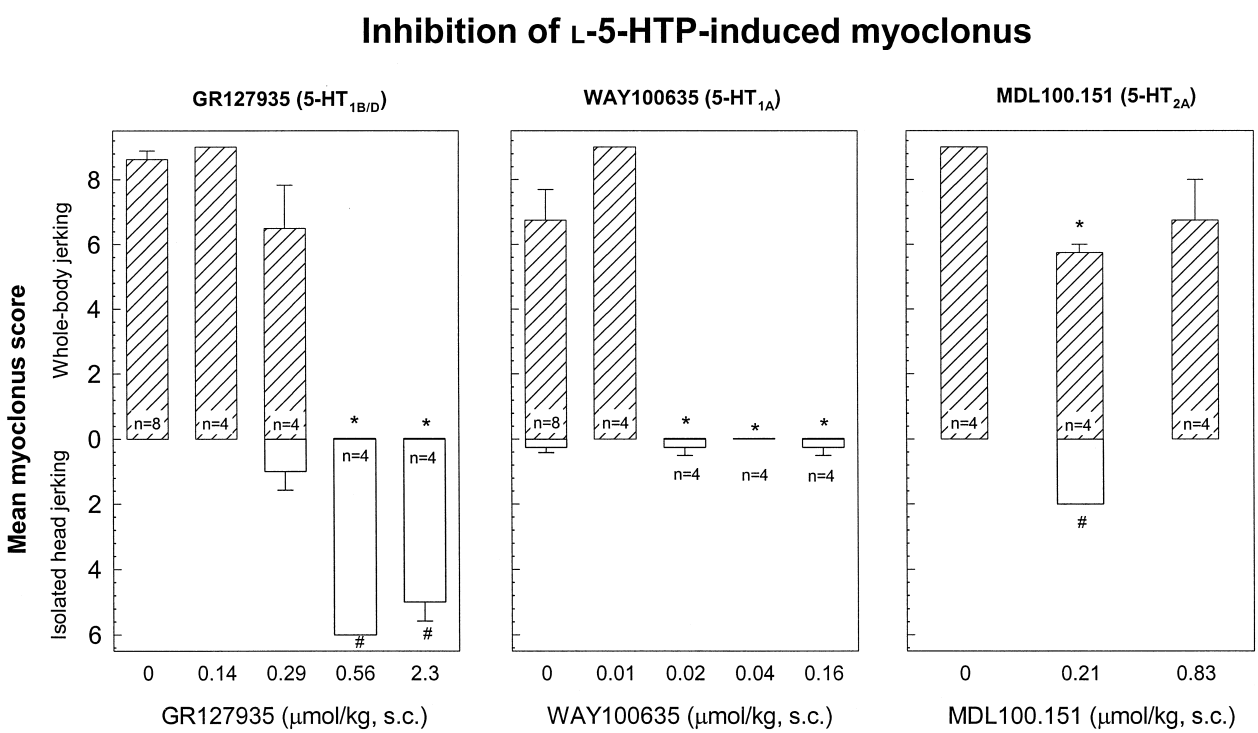

Fig. 1. Inhibition of L-5-HTP-induced myoclonic behaviour by GR127935 (0.14–2.3 μmol/kg s.c.; left), WAY100635 (0.01–0.16 μmol/kg s.c.; middle) and MDL100.151 (0.21 and 0.83 μmol/kg s.c.; right). The antagonists were given 15 min prior to L-5-HTP (454 μmol/kg). Head jerking and whole-body jerking were rated (see Materials and methods) 30, 40 and 50 min after L-5-HTP injection. Values represent the mean myoclonus score (±S.E.M.) of 4–8 animals using box plot; the open bar representing head jerking and the filled bar whole-body jerking. $* P < 0.05$ significant decrease in whole-body jerking compared to vehicle/L-5-HTP control. $\# P < 0.05$ significant occurrence of isolated head jerks compared to vehicle/L-5-HTP control. (Kruskal–Wallis one-way ANOVA on ranks, Dunn's test).

least 3 days between the experiments. From initially experiments we found that the animals did not change in their sensitivity to L-5-HTP and 5-MeODMT the second time of use.

2.2. Behavioural testing

2.2.1. Induction of myoclonus

Before behavioural observations, guinea pigs were injected subcutaneously (s.c.) with drug or vehicle and placed individually in Perspex cages (12×25 cm). Myoclonic behaviour was assessed by rating head jerking as absent (score 0), occasional (score 1) or continuous (score 2) and whole-body jerking as absent (score 0), occasional (score 1), almost continuous (score 2) or continuous rhythmic (score 3), respectively. The rating scales were chosen to cover frequency range of myoclonic jerking and obtain reproducible rating.

Myoclonic behaviour were rated 30, 40 and 50 min after injection of L-5-HTP (454 μmol/kg, s.c. (116 mg/kg)) and 10, 15 and 20 min after injection of 5-MeODMT (23 μmol/kg, s.c. (5 mg/kg)). The doses were chosen on basis on previous experiments to obtain reliable responding of myoclonic behaviour. Major part of the study was performed with full time courses. The antagonists affected the maximum response and did not course a shift in time course. Therefore, the three observation times covering peak intensity were chosen to illustrate effects on myoclonic behaviour.

2.2.2. Inhibition of myoclonus

5-HT receptor antagonists were given 15 min prior to L-5-HTP and 30 min prior to 5-MeODMT. In combination studies the antagonists were given simultaneously.

2.3. Statistical analysis

The scores of the three observation times were added for each animal., Head jerking and whole-body jerking were analysed separately. The maximum obtainable score per animal for whole-body jerking and head jerking was 9 and 6, respectively. Data were expressed as the mean scores for at least 4 animals at each dose. Comparisons between groups were made by means of Kruskal–Wallis One Way Analysis of Variance on Ranks followed by post hoc comparisons based on Dunn's test on unequal sample sizes (SigmaStat version 2.0). $P < 0.05$ was considered as significant.

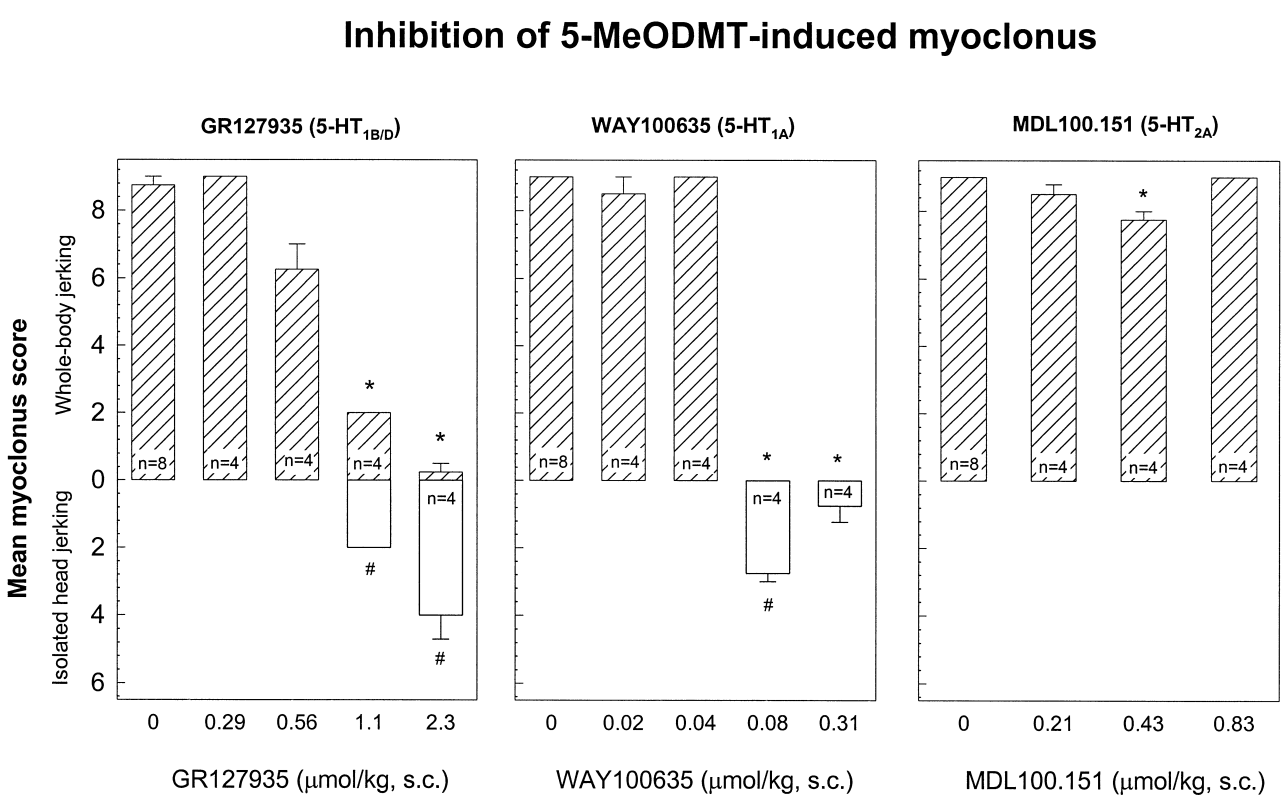

Fig. 2. Inhibition of 5-MeODMT-induced myoclonic behaviour by GR127935 (0.29–2.3 μmol/kg s.c.; left), WAY100635 (0.02–0.31 μmol/kg s.c.; middle) and MDL100.151 (0.21–0.83 μmol/kg s.c.; right). The antagonists were given 30 min prior to 5-MeODMT (23 μmol/kg). Head jerking and whole-body jerking were rated (see Materials and methods) 10, 15 and 20 min after 5-MeODMT injection. Values represent the mean (±S.E.M.) myoclonus score of 4–8 animals using box plot; the open bar representing head jerking and the filled bar whole-body jerking. $*P < 0.05$ significant decrease in whole-body jerking compared to vehicle/5-MeODMT control. $\#P < 0.05$ significant occurrence of isolated head jerks compared to vehicle/5-MeODMT control. (Kruskal–Wallis one-way ANOVA on ranks, Dunn's test).

2.4. Drugs

L-5-HTP (L-5-hydroxytryptophan, $2H_2O$; molecular weight (mw) 256; Sigma, USA) and WAY100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride; mw 513; synthesized at Department of Medicinal Chemistry, H. Lundbeck A/S, Denmark) were dissolved in saline. The following drugs were dissolved by addition of minimum amounts of dilute acid (phosphoric acid, tartaric acid or methanesul fonic acid): MDL 100.151((±)-α-(2,3-dimethoxyphenyl)-1-[-2-(4-fluorphenyl)ethyl]-4-piperidinmethanol; mw 374; H. Lundbeck A/S), 5-MeODMT (5-methoxy-*N*,*N*-dimethyltryptamine; mw 218; Sigma) and GR127935 (*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 hemifumarate; mw 556; H. Lundbeck A/S). The injection volumes were 5 ml/kg body weight.

3. Results

3.1. Inhibition of L-5-HTP-induced myoclonus

The inhibitory effects of 5-HT receptor antagonists on L-5-HTP (454 μmol/kg, s.c.) induced myoclonus are shown in Fig. 1. The 5-$HT_{1B/1D}$ receptor antagonist, GR127935 (0.14–2.3 μmol/kg, s.c. (0.08–1.3 mg/kg)) induced a dose-dependent inhibition of whole-body jerking but did not inhibit unmasked head jerking. At 0.56 and 2.3 μmol/kg (0.31 and 1.3 mg/kg) GR127935 abolished whole-body jerking and caused a significant occurrence of isolated head jerks. WAY100635 (5-HT_{1A} receptor antagonist) inhibited the myoclonic behaviour in an all or none manner, the lowest dose (0.01 μmol/kg, s.c. (0.005 mg/kg)) being ineffective, and the higher doses (0.02–0.16 μmol/kg, s.c. (0.01–0.08 mg/kg)) completely abolishing myoclonus. The 5-HT_{2A} receptor antagonist, MDL100.151 (0.21 and 0.83 μmol/kg, s.c. (0.08 and 0.31 mg/kg)) did cause a modest decrease in myoclonic behaviour, with a maximum effect of 36% inhibition of whole-body jerking.

3.2. Inhibition of 5-MeODMT-induced myoclonus

Fig. 2 shows the inhibitory effects of the antagonists on 5-MeODMT (23 μmol/kg, s.c.) induced myoclonus. GR127935 significantly inhibited whole-body jerking and caused a significant occurrence of isolated head jerks at the doses 1.1 and 2.3 μmol/kg, s.c. (0.63 and 1.3 mg/kg). WAY100635 (0.08 and 0.31 μmol/kg, s.c. (0.04 and 0.16 mg/kg)) abolished whole-body jerking. Isolated head jerks significantly occurred at one dose 0.08 μmol/kg, s.c, but not at the higher dose 0.31 μmol/kg of WAY100635. MDL100.151 caused a slightly decrease in whole-body jerking at 0.43 μmol/kg, s.c. (0.16 mg/kg) but the higher dose level (0.83 μmol/kg, s.c.) was ineffective.

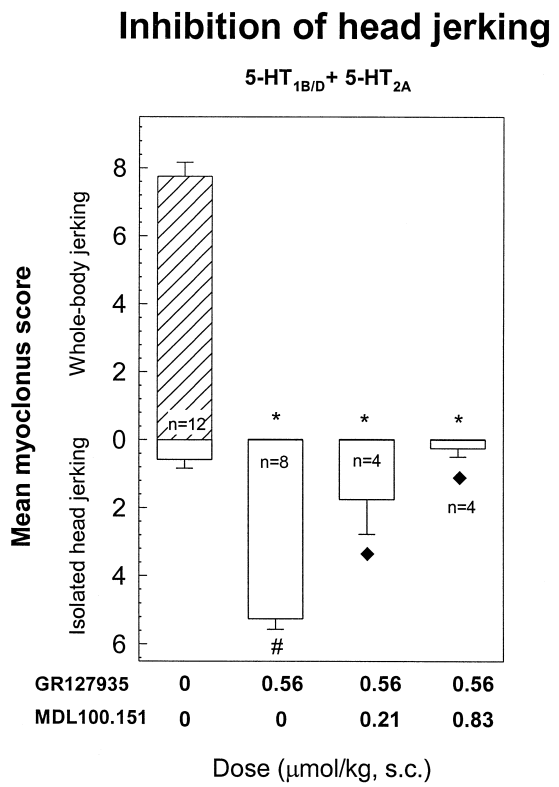

Fig. 3. Inhibition of 5-L-HTP-induced myoclonic behaviour by GR127935 (0.56 μmol/kg s.c.) given alone or combined with MDL100.151 (0.21 and 0.83 μmol/kg s.c.). The antagonists were given alone or simultaneously 15 min prior to L-5-HTP (454 μmol/kg). Head jerking and whole-body jerking were rated (see Materials and methods) 30, 40 and 50 min after L-5-HTP injection. Values represent the mean (±S.E.M.) myoclonus score of 4–12 animals using box plot; the open bar representing head jerking and the filled bar whole-body jerking. $* P < 0.05$ significant decrease in whole-body jerking compared to vehicle/L-5-HTP control. $\# P < 0.05$ significant occurrence of isolated head jerks compared to vehicle/L-5-HTP control. ◆ $P < 0.05$ significant decrease in isolated head jerks compared to L-5-HTP/GR127935. (Kruskal–Wallis one-way ANOVA on ranks, Dunn's test).

3.3. Inhibition of head jerking

When given alone GR127935 (0.56 μmol/kg, s.c.) inhibited L-5-HTP induced whole-body jerking but did not inhibit unmasked head jerking (Fig. 3). Head jerking occurred in the absence of whole-body jerking. The head jerking was abolished by co-administration of GR127935 (0.56 μmol/kg, s.c.) and MDL100.151 (0.21 and 0.83 μmol/kg, s.c.) in a dose-dependent manner. In the previous experiment (Fig. 1) MDL100.151 given alone only caused a modest decrease in myoclonic behaviour.

4. Discussion

In the present study myoclonus was induced by 5-L-HTP and the 5-MeODMT and the behaviour was subdivided into head and whole-body jerking, respectively. WAY100635 inhibited whole-body jerking as well as un-

masked head jerks. GR127935 inhibited whole-body jerking leaving unmasked head jerking unaffected. MDL100.151 given alone did not inhibit whole-body jerking but inhibited head jerks unmasked by GR127935.

Since Klawans et al. (1973) gave a thorough description of the phenomenon of myoclonus in guinea pigs several methods for quantifying this behaviour has been reported. Luscombe et al. (1981) described an observer rating system which assesses the frequency and intensity of jerking in which rating includes head as well as whole-body jerking. Other methods are based on an automated system (Volkman et al., 1978; Hagan et al., 1995). Lloyd et al. (1996) described an automated system detecting number of jerks as well as the amplitude. As stated by Lloyd et al. (1996) an automated method overcomes the shortcomings of observer based methods which among other things are open to subjective bias and operator variability. Nevertheless, the present study illustrates the advantage of an observer rating evaluating effects on head and whole-body jerking separately.

In most studies 5-HT precursors are used to investigate the ability of 5-HT receptor antagonists to inhibit myoclonus (Klawans et al., 1973; Chadwick et al., 1978; Volkman et al., 1978; Luscombe et al., 1981, 1982b, 1986; Hagan et al., 1995; Lloyd et al., 1996). In the present study we compared the ability of subtype specific 5-HT receptor antagonists to prevent myoclonus induced by a 5-HT precursor and a non-selective 5-$HT_{1A/B}$/5-HT_2 receptor agonist. From our observations L-5-HTP and 5-MeODMT differ in their way of inducing myoclonus (unpublished observations). L-5-HTP typically induced head jerking followed by full blown whole-body jerking with a peak effect occurring around 30 min. 5-MeODMT gradually induced whole-body jerking without prior occurrence of head jerks and reached a peak effect already after 10 min. However, head jerks were unmasked when 5-MeODMT-induced whole-body jerking were inhibited by 5-$HT_{1B/1D}$ or 5-HT_{1A} receptor antagonists. This indicates that both head and whole-body jerking are involved in L-5-HTP- and 5-MeODMT-induced myoclonus. The rapid onset of 5-MeODMT-induced myoclonus is advantageous regarding its usefulness as a screening model. Furthermore, we found the effects of 5-HT receptor antagonists on either L-5-HTP- or 5-MeODMT-induced myoclonus to be very similar.

In addition to head and whole-body jerking we observed flat body posture, tremor and head twist (or head shakes) after 5-HTP and 5-MeODMT administration. Though, these behaviours occurred to a less extent and far from consistent and it may be that they are superseded by myoclonus. We found head and whole-body jerking to be the far most quantifiable and reducible behaviours induced by L-5-HTP and 5-MeODMT.

Previous studies have suggested that both 5-HT_{1A} and 5-HT_{1D} receptors play an important role in 5-HTP-mediated myoclonus as WAY100635 and GR127935, respectively, inhibit both the number and amplitude of jerks (Hagan et al., 1995). This is confirmed by the present study as both WAY100635 and GR127935 dose-dependently inhibited myoclonus with respect to whole-body jerking. However, they differ with respect to head jerking as this behavioural response is inhibited by WAY100635 but not GR127935. This indicates that involvement of 5-$HT_{1B/1D}$ receptors in expression of head jerking is unlikely to be of importance. The involvement of 5-HT_{1A} receptors in expression of head jerking is further supported by Mundey et al. (1996) who found that low doses of a 5-HT_{1A} receptor agonist (8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT)) induces head jerking and, at high doses, whole-body jerking.

5-HT_2 receptors seem also to play a mediating role in myoclonic behaviour, but to which extent is debatable (Eison et al., 1993; Hagan et al., 1995). Eison et al. (1993) found that co-activation of 5-HT_{1A} and 5-HT_2 receptors may be required for expression of whole-body myoclonus, whereas Hagan et al. (1995) found that co-activation of 5-HT_{1A} and 5-HT_{1D} receptors was sufficient to elicit the full myoclonic response. However, the latter group found that ritanserin (5-$HT_{2A/2C}$ receptor antagonist) antagonised 5-HTP-induced myoclonus and suggested an additional role for 5-HT_2 receptors. Interaction between 5-HT_{1A} and 5-HT_2 receptors has also been found in rats using forepaw treading and head twitches as 5-HT-mediated behaviours (Arnt and Hyttel, 1989). In the present study we examined the effect of MDL100.151 (selective 5-HT_{2A} receptor antagonist) on myoclonus in guinea pigs. In a dose range sufficient to exert 5-HT_2 receptor antagonistic effect (inhibition of DOI (1-(2,5-di-methoxy-4-iodophenyl)-2-aminopropane) discrimination (Arnt, 1996)), we observed limited effect on whole-body jerking. 5-HT_2 receptor stimulation has shown to induce head twitches (or wet dog shakes) in rats (Niemegeers et al., 1983) as well as in guinea pigs (Skingle et al., 1991). Even though, head jerking and head twitches are behaviourally distinct it lead to the idea of co-administering GR127935 and MDL100.151. Administered alone GR127935 only inhibited the L-5-HTP-induced whole-body jerking but additional treatment with MDL100.151 completely abolished myoclonic behaviour. This suggests that 5-HT_{2A} receptors play an important role in mediating head jerking but not whole-body jerking.

In summary, the results confirm a role for the 5-HT_{1A} and 5-$HT_{1B/1D}$ receptors and in addition suggest a role for 5-HT_{2A} receptors in mediating myoclonus. Moreover, the study implies that head and whole-body jerking are behaviourally and pharmacologically distinct responses that offer the possibility of discriminating subtype-specific 5-HT receptor antagonists.

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