The effect of 5-HT_{1A} receptor agonists on locomotor activity in the guinea-pig

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1 The present study examined the effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), flesinoxan, ipsapirone and buspirone, all agonists at the 5-HT_{1A} receptor, on the locomotor activity of guinea-pigs. The effects of these drugs were contrasted with those of the non-selective 5-HT agonist, 5-methoxy-*N,N*-dimethyl tryptamine (5-MeO-DMT) and the dopamine D₂ antagonist, raclopride.

2 8-OH-DPAT, flesinoxan and 5-MeO-DMT markedly increased the locomotor activity of naive, unhabituated guinea-pigs in a dose-dependent manner. Buspirone also did so, although to a lesser extent and for a shorter time. The doses at which this effect was seen were higher than those normally employed in rats. Ipsapirone and raclopride had no significant effects on locomotor activity.

3 The locomotor activity increasing effect of 1.0 mg kg⁻¹ 8-OH-DPAT was blocked by the selective 5-HT_{1A} antagonist (S)-UH-301 (3.0 and 10.0 mg kg⁻¹), but not by (–)-alprenolol (15.0 mg kg⁻¹). Ipsapirone (30.0 mg kg⁻¹) and raclopride (3.0 mg kg⁻¹) antagonized 8-OH-DPAT-induced locomotor activity but only to a small extent. The 5-HT reuptake inhibitor, zimelidine (10.0 mg kg⁻¹) had no effect.

4 The effect of the 5-HT_{1A} agonists in the guinea-pig contrasts with the effects of 8-OH-DPAT on the locomotor activity of unhabituated rats and mice tested in the same apparatus, but are similar to the effects of 8-OH-DPAT on habituated rats, which show a low baseline of activity.

5 These results support the suggestion that 5-HT_{1A} agonists may have an intrinsic activating effect which may be masked by other effects of the drug (e.g. hypothermia, 5-HT syndrome). The rank ordering of the 5-HT_{1A} agonists also suggests that the degree to which the drugs increase locomotor activity is related to their agonist efficacy at the postsynaptic 5-HT_{1A} receptor.

Keywords: 5-Hydroxytryptamine agonists; 8-OH-DPAT; locomotor activity in guinea-pig

Introduction

Agonists at the 5-hydroxytryptamine_{1A} (5-HT_{1A}) receptor, exemplified by the selective agonist, 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) elicit a characteristic set of behaviours in the naive rat, including aspects of the 5-HT syndrome, a long, flat, body posture and fore-paw treading (Tricklebank *et al.*, 1984), and hypothermia (Goodwin & Green, 1985). Partial agonists (such as the azapirones, buspirone, ipsapirone and gepirone) have a similar profile (Wilkinson & Dourish, 1991). 8-OH-DPAT also has clear effects on locomotor activity, which, however, are somewhat complex. If naive rats are tested soon after injection, overall activity is reduced but the proportion of forward locomotion is increased (Hillegaart *et al.*, 1989; Ericson *et al.*, 1991). However, if rats are continuously monitored for several hours, the initial reduction in activity passes over into an increase in activity (Evenden & Ångeby-Möller, 1990).

Evenden & Ångeby-Möller (1990) found very similar effects in mice to those in rats, on measures of both locomotor activity and rearing. In contrast, Buhot *et al.* (1989) noted that, in the same dose-range, 8-OH-DPAT did not alter exploratory activity in the hamster. Other effects of the drug also show marked species differences. For example, it has not proved easy to obtain signs of the 5-HT syndrome in mice in response to 8-OH-DPAT treatment that are seen in rats, except after intravenous administration of high doses (Yamada *et al.*, 1988). Bill *et al.* (1991) have also reported evidence for a species difference in the 8-OH-DPAT-induced hypothermic response. A species difference has also been noted in the effects of 5-HT_{1A} receptor agonists on responding punished by electric shocks in animal models of anxiety. In rats and monkeys the increase in punished behaviour after 5-HT_{1A} agonist treatment is inconsistent (Barrett & Witkin, 1990; Gleeson & Barrett, 1990), whereas in pigeons there is

an increase comparable to that produced by benzodiazepines (Ahlers *et al.*, 1992).

Recently, interest has revived in the behavioural pharmacology of 5-HT in the guinea-pig, largely due to an apparent difference in the presynaptic receptor mediating 5-HT release (5-HT_{1B} in the rat vs 5-HT_{1D} in the guinea-pig and man; Hoyer & Middlemiss, 1989). However, differences in the effects of 8-OH-DPAT have also been reported. In contrast to its hypothermia-inducing effects in the rat, the drug increased body temperature in the guinea-pig, and differences were noted in the effect of the drug on cortical acetylcholine release and the electrocortigram (Siniscalchi *et al.*, 1990). Ryan (personal communication) has found that 8-OH-DPAT induces wet dog shakes in guinea-pigs but not in rats. As far as locomotor activity is concerned, a brief report by Skingle & Bradbury (1989) demonstrated that 8-OH-DPAT increased locomotor activity in the guinea-pig, in a dose-dependent manner from 0.1 to 1.0 mg kg⁻¹ s.c., just such a treatment that suppresses activity in the rat. The partial agonist, gepirone, had a similar but weaker effect, and also partially blocked the effect of 8-OH-DPAT. These authors concluded that the overt behavioural effect of 8-OH-DPAT in the guinea-pig, including indices of the 5-HT syndrome, were 'quite distinct from the syndrome reported in the rat.'

The present study was designed to provide a direct comparison between the effects of 5-HT_{1A} agonist on locomotor activity in the guinea-pig and rat, by using the same apparatus and experimental design employed by Evenden & Ångeby-Möller (1990). To explore the relationship between agonist efficacy and response, the effects of four 5-HT_{1A} receptor agonists were examined, 8-OH-DPAT, flesinoxan, ipsapirone and buspirone. Of these, 8-OH-DPAT and flesinoxan have highest efficacy (although see Millan *et al.*, 1991), whereas buspirone and ipsapirone are clearly partial agonists (Schoeffer & Hoyer, 1988; Boddeke *et al.*, 1992). These drugs were compared with the non-selective 5-HT

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receptor agonist, 5-methoxy-*N,N*-dimethyl-tryptamine (5-MeO DMT), which is also a full agonist at the 5-HT_{1A} receptor (Dumuis *et al.*, 1988). The 5-HT_{1A} receptor agonists also vary in their selectivity vis-à-vis other neurotransmitter receptors. 8-OH-DPAT is relatively selective for the 5-HT_{1A} receptor, as is flesinoxan (Van Wijngaarden *et al.*, 1990; Schipper *et al.*, 1991). Buspirone has a well-documented affinity for the dopamine D₂ receptor, where it acts as an antagonist, and shares with ipsapirone the active metabolite 1-(2-pyrimidinyl)-piperazine which has α_2 -adrenoceptor antagonist activity (Caccia *et al.*, 1986). The structurally unrelated 8-OH-DPAT and flesinoxan cannot generate this metabolite. Raclopride, a selective D₂ antagonist (Köhler *et al.*, 1985), was included both as a control for the D₂ antagonist activity of buspirone and as an active comparison.

To verify that the effect of 8-OH-DPAT is mediated by 5-HT_{1A} receptors, the 5-HT_{1A} receptor antagonists, (–)-alprenolol and (S)-UH-301 were used in combination with 8-OH-DPAT. Of the two, (S)-UH-301 is more selective (Björk *et al.*, 1991), whereas (–)-alprenolol has affinity for the 5-HT_{1B} site (Middlemiss *et al.*, 1985) as well as acting as a β -adrenoceptor antagonist. Comparisons were made with combinations of 8-OH-DPAT with ipsapirone, raclopride or the 5-HT reuptake inhibitor, zimelidine.

Methods

Animals

Male Dunkin Hartley guinea-pigs were used in the agonist experiments these were aged 3–6 months at the time of use, and weighed 500–1000 g. In the antagonist experiments these were 2–3 months old and weighed 350–500 g. The subjects were housed in groups of 3 or 4, under a 12:12 h cycle (lights on at 06 h 00 min), with free access to food and water. All experiments took place in the light phase of the cycle.

Apparatus

The apparatus consisted of four open field arenas, 70 × 70 cm, equipped with two rows of infra-red photo beams, each consisting of eight cells on the X- and eight on the Y-axis. These were situated 4.0 and 12.5 cm above the floor. The individual photocells were spaced 9.0 cm apart, with a gap of 2.5 cm between the end beams and the side walls of the test apparatus. The apparatus itself was constructed with side-walls and floor of clear plastic, and each was individually housed within an outer chamber, 100 cm square. These chambers were opaque, but open at the top, so that the subjects could hear, but not see, each other. During the experiment the apparatus was illuminated by the normal fluorescent room lighting. A locomotor count was defined as a movement which broke two different beams successively. The data were recorded by an IBM PC-compatible computer using software provided by Kungsbacka Mät- och Reglerteknik, Fjärås, Sweden. A more complete description of the characteristics of the apparatus may be found in Ericson *et al.* (1990).

Procedure

Guinea-pigs were generally tested in groups of three or four. In the agonist studies, each subject was weighed and then injected with one of the test drugs or vehicle according to a pseudo latin-square design. Immediately after injection, it was placed in one of the arenas: one animal to each arena. When all subjects had been treated, the session was started. Each session then continued for 4 h during which time the subjects were not disturbed. At the end of each session, the apparatus was cleaned prior to testing the next group. The antagonist experiment proceeded in a similar manner with two differences. The subjects were initially injected with one

of the antagonist treatments or saline 30 min before receiving a second injection of either 1.0 mg kg^{–1} 8-OH-DPAT or saline. During the interval between injections the subjects remained in their home cage. After the second treatment they were placed in the locomotor apparatus for a period, in this case, of 2 h. Eight guinea-pigs received such treatment except for 3.0 mg kg^{–1} (S)-UH-301 + 8-OH-DPAT (*n* = 9) and zimelidine + 8-OH-DPAT (*n* = 7).

It may be noted that the experiments involving 8-OH-DPAT, buspirone and 5-MeODMT were carried out in late 1989, the experiments involving ipsapirone, flesinoxan and raclopride in mid 1992, and the antagonist experiment in late 1993, that is, over a period of four years. Each agonist was compared to its own vehicle control group. Since the antagonists were given in only single doses (two in the case of (S)-UH-301), these were all compared to a single set of vehicle- and 8-OH-DPAT-treated rats which were tested at the same time interspersed in the pseudo-latin square design.

Drugs

The drugs used were 8-hydroxy-2-(di-*n*-propylamino)tetralin hydrochloride (Research Biochemicals Inc.), flesinoxan hydrochloride (Duphar), buspirone hydrochloride (Sigma Chemical Co.), ipsapirone (Troponwerke), 5-methoxy-*N,N*-dimethyl tryptamine (Sigma Chemical Co.), raclopride tartrate (Astra Arcus), zimelidine (Astra Arcus), (–)-alprenolol hydrogentartrate monohydrate (Astra Hässle) and (S)-UH-301 hydrochloride (S-5-fluoro-8-hydroxy-2-(di-*n*-propylamino)tetralin hydrochloride, Dept of Organic Pharmaceutical Chemistry, University of Uppsala). All drugs were injected s.c. in the flank. Ipsapirone was injected in a volume of 2.0 ml kg^{–1}, the other drugs in a volume of 1.0 ml kg^{–1}. All drugs were dissolved in 0.9% saline, which served as a control.

Measurements and analysis

A locomotor count was recorded when the subject consecutively broke two different beams in the lower series. Locomotor counts were cumulated into 5 min bins. After square root transformation to normalize the distribution, data from these bins were subjected to two-factor analysis of variance Treatment Group by Time Bin (BMDP model 2V). Dunnett's *t* test was used *post hoc* to compare treatment groups with the saline control in each bin. A 5% level of significance was used for the analysis of variance, and a 2% level of significance for the Dunnett's test.

Results

Agonist experiments

The effects of the agonists on the locomotor activity of guinea-pigs may be seen in Figures 1 and 2. 5-MeO DMT increased locomotor activity in the first hour after treatment, but not thereafter ($F_{int}(141,1128) = 3.06$, $P < 0.0001$). Statistically significant increases in activity were obtained with 1.0 mg kg^{–1} in the first 10 min, with 3.0 mg kg^{–1} up to 35 min and with 10.0 mg kg^{–1} up to 55 min (Figure 1a). 8-OH-DPAT had a similar but longer lasting effect ($F_{int}(235,1974) = 4.74$, $P < 0.0001$). No significant increase in locomotor activity was seen with 0.01 and 0.1 mg kg^{–1}. A statistically significant increase in activity was seen with 1.0 mg kg^{–1} up to 70 min post injection, with 3.0 mg kg^{–1} up to 90 min post-injection and with 10.0 mg kg^{–1} up to 145 min post injection (Figure 1b). Flesinoxan also increased locomotor activity ($F_{int}(188,1645) = 3.07$, $P < 0.0001$). The minimum effective dose was 3.0 mg kg^{–1} which had significant effects up to 30 min post-injection. The dose of 10.0 mg kg^{–1} had effects up to 90 min post-injection (Figure 1c). In contrast, buspirone had only a weak effect

($F_{int}(141,1316) = 1.27$, $P < 0.05$). The lowest dose tested, a higher dose by the standards of rat studies, was 10.0 mg kg^{-1} which significantly increased locomotor activity in the first 5 min of testing. The two higher doses, 30.0 and 100.0 mg kg^{-1} significantly increased locomotor activity for a little longer, up to 20 min post-injection (Figure 2a). The weak effects of buspirone were complemented by the lack of effect of ipsapirone ($F_{int}(141,1316) = 0.86$, $P > 0.80$, Figure 2b).

The dopamine D₂ receptor antagonist, raclopride, was also without effect ($F_{int}(188,1645) = 1.1$, $P > 0.10$, Figure 2c).

Antagonist experiments

The effects of the various drug treatments on 8-OH-DPAT-induced hyperactivity in the guinea-pig may be seen in Figure 3. Note that the curves for the saline- and 8-OH-DPAT-

Figure 1 The effects of (a) 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), (b) 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and (c) flesinoxan on horizontal activity in the guinea-pig. In all three panels the horizontal axis shows the time since the start of testing (substance administered at time 0), and the vertical axis the number of locomotor counts after square root (sq rt) transformation. Note that only the first 2 h of the 4 h test are shown in the figure. The doses used were (a) for 5-MeO-DMT: saline (○), 1.0 mg kg^{-1} (●), 3.0 mg kg^{-1} (◆) and 10.0 mg kg^{-1} (■); (b) for 8-OH-DPAT: saline (○), 0.01 mg kg^{-1} (●), 0.1 mg kg^{-1} (▼), 1.0 mg kg^{-1} (■), 3.0 mg kg^{-1} (▲) and 10.0 mg kg^{-1} (+); and (c) for flesinoxan: saline (○), 0.3 mg kg^{-1} (●), 1.0 mg kg^{-1} (▼), 3.0 mg kg^{-1} (■) and 10.0 mg kg^{-1} (▲). The dashed line shows the level of activity required to achieve a significant difference from the vehicle-treated group using Dunnett's *t* test ($P < 0.02$). Symbols appearing above this line illustrate a significant increase in activity compared to saline-treated guinea-pigs. All three drugs significantly increased locomotor activity.

Figure 2 The effects of (a) buspirone, (b) ipsapirone and (c) raclopride on horizontal activity in the guinea-pig. In all three panels the horizontal axis shows the time since the start of testing (substance administered at time 0), and the vertical axis the number of locomotor counts after square root (sq rt) transformation. The doses used were (a) for buspirone: saline (○), 10.0 mg kg^{-1} (●), 30.0 mg kg^{-1} (▼) and 100.0 mg kg^{-1} (■); (b) for ipsapirone: saline (○), 3.0 mg kg^{-1} (●), 10.0 mg kg^{-1} (▼) and 30.0 mg kg^{-1} (■); and (c) for raclopride: saline (○), 0.1 mg kg^{-1} (●), 0.3 mg kg^{-1} (▼), 1.0 mg kg^{-1} (■) and 3.0 mg kg^{-1} (▲). The dashed line shows the level of activity required to achieve a significant difference from the vehicle-treated group using Dunnett's *t* test ($P < 0.02$). Symbols appearing above this line illustrate a significant increase in activity compared to saline-treated guinea-pigs. Buspirone slightly increased locomotor activity soon after injection. The other two drugs had no significant effect.

treated groups in the two panels represent the same data. Dunnett's *t* test was performed after a significant statistical interaction ($F_{int}(161,1288) = 4.95$, $P < 0.0001$), which confirms that there were differences amongst the treatment groups. Zimelidine (10.0 mg kg^{-1}) had little effect on 8-OH-DPAT-induced hyperactivity. A significant increase in activity was noted 50–55 min after 8-OH-DPAT treatment which may represent a slight prolonging of 8-OH-DPATs effect. Ipsapirone (30.0 mg kg^{-1}) and raclopride (3.0 mg kg^{-1}) had very similar effects to each other, in that both reduced the peak activity of the guinea-pigs. The effect of ipsapirone was statistically significant from 5–10 min and that of raclopride from 5–15 min after 8-OH-DPAT treatment. These statistically significant effects formed part of a clear trend (Figure 3a). In addition, there was also a slight increase in the activity of the raclopride + 8-OH-DPAT treated guinea-pigs compared to the guinea-pigs treated with 8-OH-DPAT alone from 55–60 min again suggesting a slight prolongation of the effect of 8-OH-DPAT.

Much clearer effects were obtained with the two 5-HT_{1A} receptor antagonists. However, these were completely opposite in nature. (–)-Alprenolol clearly potentiated the

effects of 8-OH-DPAT, in that the animals with the combined treatment were significantly more active than those treated with 8-OH-DPAT alone from 50–85 min (except 60–65). This difference can be seen in Figure 3b. (–)-Alprenolol had no effect on locomotor activity when given alone at a dose of 15.0 mg kg^{-1} ($F_{int}(47,470) = 0.86$, NS: data not shown). In contrast, (S)-UH-301 blocked the effects of 8-OH-DPAT. A dose of 3.0 mg kg^{-1} partially blocked the increase in activity, with significant effects from 0–35 min, whereas a dose of 10.0 mg kg^{-1} totally blocked the effects of 8-OH-DPAT from 0–55 min after which 8-OH-DPAT itself did not significantly increase activity compared to the saline-treated guinea-pigs (see Figure 3b).

Discussion

In contrast to the effects in mice and rats, 8-OH-DPAT increased locomotor activity in a dose-dependent and straightforward manner. However, the doses required to obtain the greatest effect were around 10 times higher than the doses previously used in this procedure in rodents (Evenden & Ångeby-Möller, 1990). Flesinoxan had a similar effect. This drug also reduces locomotor activity in the rat when monitored in similar apparatus to that used here (Hillegaart *et al.*, 1989). Likewise, relatively high doses of flesinoxan were used in the present study to obtain a significant effect. The partial agonists at the 5-HT_{1A} receptor, buspirone and ipsapirone, had, respectively, little and no effect on the locomotor activity of the guinea-pig. These drugs have also been reported to reduce locomotor activity in the rat (Mittman & Geyer, 1989). The weak effect of buspirone is unlikely to reflect the D₂ antagonist properties of the drug since ipsapirone does not have a significant affinity for the D₂ receptor. Furthermore, the D₂ antagonist, raclopride, did not itself affect guinea-pig locomotor activity, and only weakly blocked 8-OH-DPAT-induced hyperactivity. Although both buspirone and ipsapirone are rapidly metabolized giving a metabolite, 1-PP, which has antagonist activity at the α_2 -adrenoceptor, this is also unlikely to be the reason for their lack of effect, since Skingle & Bradbury (1989) have reported that gepirone, which generates same active metabolite, does increase locomotor activity in the guinea-pig, but to a lesser extent than 8-OH-DPAT.

The 8-OH-DPAT-induced hyperactivity was clearly blocked by the selective 5-HT_{1A} receptor antagonist, (S)-UH-301, but curiously, not by (–)-alprenolol, which has otherwise been reported to block 8-OH-DPAT-induced effects in other tests in rats (Middlemiss *et al.*, 1985; Rényi, 1991). The drug did not itself increase locomotor activity, and the dose used here has been found to block 8-OH-DPAT-induced wet dog shakes in the guinea-pig (Ryan & Pakh, unpublished). Kalkman & Soar (1990) found that β -adrenoceptor antagonists enhanced 8-OH-DPAT hyperlocomotion in rats, and it appears to be this aspect of the pharmacological profile of (–)-alprenolol which predominates in the present experiment. Ipsapirone, which is a partial agonist at the 5-HT_{1A} receptor, did block the effects of 8-OH-DPAT to a certain extent. Previously, Skingle & Bradley (1989) noted that gepirone also partially blocked 8-OH-DPAT-induced hyperactivity in the guinea-pig, and Kalkman & Soar, (1990) found that buspirone blocked 8-OH-DPAT-induced hyperlocomotion in the rat. The effect of 8-OH-DPAT was not prevented by pretreatment with the 5-HT reuptake inhibitor, zimelidine, which suggests that the hyperactivity in the guinea-pig does not depend upon reduced extracellular levels of 5-HT.

Together, these results suggest that to increase locomotor activity in the guinea-pig, a 5-HT_{1A} agonist must have high efficacy at the 5-HT_{1A} receptor, since only drugs that are relatively full agonists had this effect (i.e. 8-OH-DPAT, flesinoxan and 5-MeO DMT). The prototypical selective 5-HT_{1A} receptor antagonist, 8-OH-DPAT has been tested in

Figure 3 The effects of (a) zimelidine, ipsapirone, and raclopride, and (b) (–)-alprenolol and (S)-UH-301 on the 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT)-induced increase in horizontal activity in the guinea-pig. In all three panels the horizontal axis shows the time since the start of testing (8-OH-DPAT administered at time 0), and the vertical axis the number of locomotor counts after square root (sq rt) transformation. The treatments were as follows: (a) saline + saline (○); saline + 1.0 mg kg^{-1} 8-OH-DPAT (□); 10.0 mg kg^{-1} zimelidine + 1.0 mg kg^{-1} 8-OH-DPAT (▲); 30.0 mg kg^{-1} ipsapirone + 1.0 mg kg^{-1} 8-OH-DPAT (■) and 3.0 mg kg^{-1} raclopride + 1.0 mg kg^{-1} 8-OH-DPAT (▲); and (b) saline + saline (○); saline + 1.0 mg kg^{-1} 8-OH-DPAT (□); 15.0 mg kg^{-1} (–)-alprenolol + 1.0 mg kg^{-1} 8-OH-DPAT (▲); 3.0 mg kg^{-1} (S)-UH-301 + 1.0 mg kg^{-1} 8-OH-DPAT (■) and 10.0 mg kg^{-1} (S)-UH-301 + 1.0 mg kg^{-1} 8-OH-DPAT (▲). The dashed line shows the level of activity required to achieve a significant reduction in activity compared to the saline + 8-OH-DPAT-treated group using Dunnett's *t* test ($P < 0.02$). Symbols appearing below this line illustrate a significantly lower activity than this control group.

a range of species. As noted in the Introduction, in addition to the increase in locomotor activity reported here and by Skingle & Bradley (1989) in the guinea pig, the drug has been noted primarily to reduce locomotor activity in the rat and mouse. However, rats and mice do not necessarily appear to be sedated by the drug, since Tricklebank *et al.* (1984) in an observational study, found an increase in 'ambulation' in the rat after 8-OH-DPAT treatment. The drug appeared to have no effect on exploratory activity in the hamster (Buhot *et al.*, 1989). In the domestic pig, 8-OH-DPAT induced ataxia and general sedation (Löschner *et al.*, 1990), with sedation also being reported in the cynomolgus monkey (Mizuta *et al.*, 1990). However, these latter two were observational studies with no quantification of locomotor activity. Flesinoxan has also been reported to induce a feeling of relaxation and drowsiness in man (Ansseau *et al.*, 1992). From this list, the guinea-pig stands out as being the only species so far tested in which locomotor stimulation has clearly been observed.

The effects of 8-OH-DPAT may depend in part upon differences in the behaviour of the species. In the present study there were differences in the way in which guinea-pigs and rats behave in this apparatus. Guinea-pigs are very much less active when treated with saline than are rats. In the study of Evenden & Ångeby-Möller (1990), unhabituated rats made as many as 800 counts in the first 5 min of testing, falling to around 100–200 counts per 5 min up to about 80 min. In the present study, unhabituated guinea-pigs made only around 100 counts in the first 5 min and less than 50 counts per 5 min after around 30 min. In this respect the guinea-pigs more resembled habituated rats, which had been familiarized with the apparatus for 2 h before treatment. These rats were less active than unhabituated rats, and showed a hyperactivity in response to 1.0 mg kg⁻¹ 8-OH-DPAT (Evenden & Ångeby-Möller, 1990). This suggests that obtaining an increase in locomotor-activity after 8-OH-DPAT treatment may

depend in part on having a low baseline level of activity i.e. the effect may be baseline-dependent. This is confirmed by the findings of Björk *et al.* (1992) who tested rats either unhabituated or habituated in cages similar to the home cages. In this study (R)-8-OH-DPAT increased locomotor activity, and this increase was antagonized by (S)-UH-301.

These differences in locomotor activity form only part of the overall profile of differences between rats and guinea-pigs (see Introduction). There are also neuroanatomical differences between the two species (Sijbesma *et al.*, 1991). Furthermore, sub-chronic treatment of rats with 8-OH-DPAT induces a tolerance when hypothermia or induction of the 5-HT syndrome are monitored (Larsson *et al.*, 1990), but a progressively increasing hyperactivity has been seen in a two-way avoidance test (Evenden, 1992). Thus, in some respects, i.e. lack of obvious 5-HT syndrome, lack of hypothermic response and hyperactivity, the guinea-pig more closely resembles the '8-OH-DPAT-tolerant' than the '8-OH-DPAT-naïve' rat.

In conclusion, these results lend support to suggestions that there are important species differences in the response to treatment with 5-HT_{1A} receptor agonists. They indicate that it is necessary to take into account differences in the baseline behaviour between species but leave open the question of the biochemical mechanisms underlying this behaviour, and whether these may also be species specific.

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References

- AHLERS, S.T., WEISSMAN, B.A. & BARRETT, L.E. (1992). Antagonism studies with BMY-7378 and NAN-190: effects on 8-hydroxy-2-(di-n-propylamino)tetralin-induced increases in punished responding of pigeons. *J. Pharmacol. Exp. Ther.*, **260**, 474–481.
- ANNSSEAU, M., LEMBRECHTS, M., PITCHOT, W., GONZALEZ MORENO, A., LEGROS, J.J. & BRADFORD, L.D. (1992). Neuroendocrine responses to intravenous flesinoxan as an index of serotonergic neurotransmission. *Clin. Neuropharmacol.*, **15** (suppl 1B), 114.
- BARRETT, J.E. & WITKIN, J.M. (1990). Buspirone in animal models of anxiety. In *Buspirone: Mechanisms and Clinical Aspects*. ed. Tunnicliff, G., Eison, A.S. & Taylor, D.P. pp. 37–79, New York: Academic Press.
- BILL, D.J., KNIGHT, M., FORSTER, E.A. & FLETCHER, A. (1991). Direct evidence for an important species difference in the mechanism of 8-OH-DPAT-induced hypothermia. *Br. J. Pharmacol.*, **103**, 1857–1864.
- BJÖRK, L., CORNFELD, L.J., NELSON, D.L., HILLVER, S.-E., ANDÉN, N.-E., LEWANDER, T. & HACKSELL, U. (1991). Pharmacology of the novel 5-hydroxytryptamine 1A receptor antagonist (S)-5-fluoro-8-hydroxy-2-(dipropylamino)tetralin: Inhibition of (R)-8-hydroxy-2-(di-n-propylamino)tetralin-induced effects. *J. Pharmacol. Exp. Ther.*, **258**, 58–65.
- BJÖRK, L., FREDRIKSSON, A., HACKSELL, U. & LEWANDER, T. (1992). Effects of (R)-8-OH-DPAT and the enantiomers of UH-301 on motor activities in the rat: antagonism of (R)-8-OH-DPAT-induced effects. *Eur. J. Neuropsychopharmacol.*, **2**, 141–147.
- BODDEKE, H.W.G.M., FARGIN, A., RAYMOND, J.R., SCHOEFFTER, P. & HOYER, D. (1992). Agonist/antagonist interactions with cloned human 5-HT_{1A} receptors: variations in intrinsic activity studied in transfected HeLa cells. *Naunyn Schmied. Arch. Pharmacol.*, **345**, 257–263.
- BUHOT, M.-C., RAGE, P. & SEGU, L. (1989). Changes in exploratory behaviour of hamsters following treatment with 8-hydroxy-2-(di-n-propylamino)tetralin. *Behav. Brain Res.*, **35**, 163–179.
- CACCIA, S., CONTI, I., VIGANO, G. & GARATTINI, S. (1986). 1-(2-Pyrimidinyl)-piperazine as active metabolite of buspirone in man and rat. *Pharmacology*, **33**, 46–51.
- DUMUIS, A., SEBBEN, M. & BOCKEAER, J. (1988). Pharmacology of 5-hydroxy-tryptamine-1A receptors which inhibit cAMP production in hippocampal and cortical neurones in primary culture. *Mol. Pharmacol.*, **33**, 176–186.
- ERICSON, E., SAMUELSSON, J. & AHLENIUS, S. (1991). Photocell measurements of rat motor activity. *J. Pharmacol. Methods*, **34**, 111–122.
- EVENDEN, J.L. (1992). Effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) after repeated administration on a conditioned avoidance response (CAR) in the rat. *Psychopharmacology*, **109**, 134–144.
- EVENDEN, J.L. & ÅNGEBY-MÖLLER, K. (1990). Effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) on locomotor activity and rearing of mice and rats. *Psychopharmacology*, **102**, 485–491.
- GLEESON, S. & BARRETT, J.E. (1990). 5-HT_{1A} agonist effects on punished responding of squirrel monkeys. *Pharmacol. Biochem. Behav.*, **37**, 335–337.
- GOODWIN, G.M. & GREEN, A.R. (1985). A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT₁ and 5-HT₂ receptors. *Br. J. Pharmacol.*, **84**, 743–753.
- HILLEGAART, V., WADENBURG, M.L. & AHLENIUS, S. (1989). Effects of 8-OH-DPAT on motor activity in the rat. *Pharmacol. Biochem. Behav.*, **32**, 797–800.
- HOYER, D. & MIDDELMISS, D.N. (1989). Species difference in the pharmacology of terminal 5-HT autoreceptors in mammalian brain. *Trends Pharmacol. Sci.*, **10**, 130–132.
- KALKMAN, H.O. & SOAR, J. (1990). Determination of the 5-HT receptor subtype involved in 8-OH-DPAT-induced hyperlocomotion: potential difficulties arising from inadequate pharmacological tools. *Eur. J. Pharmacol.*, **191**, 383–390.

- KÖHLER, C., HALL, H., ÖGREN, S.O. & GAWELL, L. (1985). Specific in vitro and in vivo binding of ^3H -raclopride. A potent substituted benzamide drug with high affinity for dopamine D-2 receptors in the rat brain. *Biochem. Pharmacol.*, **34**, 2251–2259.
- LARSSON, L.-G., RÉNYL, L., ROSS, S.B., SVENSSON, B. & ÄNGEBY-MÖLLER, K. (1990). Different effects on the responses of functional pre- and postsynaptic 5-HT_{1A} receptors by repeated treatment of rats with the 5-HT_{1A} receptor agonist 8-OH-DPAT. *Neuropharmacology*, **29**, 85–91.
- LÖSCHER, W., WHITE, U., FREDOW, G., TRABER, J. & GLASER, T. (1990). The behavioural responses to 8-OH-DPAT, ipsapirone and the novel 5-HT_{1A} receptor agonist Bay Vq 7813 in the pig. *Naunyn-Schmied. Arch. Pharmacol.*, **342**, 271–277.
- MIDDLEMISS, D.N., NEILL, J. & TRICKLEBANK, M.D. (1985). Subtypes of the 5-HT receptor involved in hypothermia and forepaw treading induced by 8-OH-DPAT. *Br. J. Pharmacol.*, **85**, 251P.
- MILLAN, M.J., BERVOETS, K. & COLPEART, F.C. (1991). 5-Hydroxytryptamine (5-HT)_{1A} receptors and the tail flick response. 1. 8-hydroxy-2-(di-n-propylamino)tetralin HBr-induced spontaneous tail-flicks in the rat as an in vivo model of 5-HT_{1A} receptor-mediated activity. *J. Pharmacol. Exp. Ther.*, **256**, 973–982.
- MITTMAN, S.M. & GEYER, M.A. (1989). Effects of 5-HT-1A agonists on locomotor and investigatory behaviours in rats differ from those of hallucinogens. *Psychopharmacology*, **98**, 321–329.
- MIZUTA, E., YAMAGUCHI, M. & KUNO, S. (1990). Behavioural effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) in monkeys. *Eur. J. Pharmacol.*, **178**, 125–127.
- RÉNYL, L. (1991). The involvement of the 5-HT₁ and 5-HT₂ receptors and of catecholaminergic systems in different components of the 5-HT syndrome in the rat. *Pol. J. Pharmacol. Pharm.*, **43**, 405–419.
- SCHIPPER, J., TULP, M.TH.M., BERKELMANS, B., MOS, J., VAN DER HEIJDEN, J.A.M. & OLIVIER, B. (1991). Preclinical pharmacology of flesinoxan: a potential anxiolytic and antidepressant drug. *Human Psychopharmacology*, **6**, S53–S61.
- SCHOEFFTER, P. & HOYER, D. (1988). Centrally acting hypotensive agents with affinity for 5-HT_{1A} binding sites inhibit forskolin-stimulated adenylate cyclase activity in calf hippocampus. *Br. J. Pharmacol.*, **95**, 975–985.
- SIJBESMA, H., SCIPPER, J., CORNELISSEN, J.C.H.M. & DE KLOET, E.R. (1991). Species differences in the distribution of central 5-HT₁ binding sites: a comparative autoradiographic study between rat and guinea pig. *Brain Res.*, **555**, 295–304.
- SINISCALCHI, A., BEANI, L. & BIANCHI, C. (1990). Different effects of 8-OH-DPAT, a 5-HT_{1A} receptor agonist on acetylcholine release, electrocortigram and body temperature in guinea pigs and rats. *Eur. J. Pharmacol.*, **175**, 219–223.
- SKINGLE, M. & BRADBURY, A.J. (1989). Behavioural and biochemical effects of 8-OH-DPAT in the guinea pig. Poster presentation at *Serotonin from Cell Biology to Pharmacology and Therapeutics*, Florence, March 29–April 1, 1989.
- TRICKLEBANK, M.D., FORLER, C. & FOZARD, J.R. (1984). The involvement of subtypes of the 5-HT_{1A} receptor and of catecholaminergic systems in the behavioural response to 8-hydroxy-2-(di-n-propylamino)tetralin in the rat. *Eur. J. Pharmacol.*, **106**, 271–282.
- WILKINSON, L.O. & DOURISH, C.T. (1991). Serotonin and animal behaviour. In *Serotonin Receptor Subtypes: Basic and Clinical Aspects* ed. Peroutka, S.J. pp. 147–210. New York: Wiley-Liss Inc.
- VAN WIJNGAARDEN, I., TULP, M.TH.M. & SOUDIJN, W. (1990). The concept of selectivity in 5-HT receptor research. *Eur. J. Pharmacol.*, **188**, 301–312.
- YAMADA, J., SUGIMOTO, Y. & HORISAKA, K. (1988). The behavioural effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) in mice. *Eur. J. Pharmacol.*, **154**, 299–304.

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