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The corticosterone-enhancing effects of the 5-HT_{1A} receptor antagonist, (S)-UH301, are not mediated by the 5-HT_{1A} receptor

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Abstract

We tried to antagonize the endocrine and behavioural changes induced by the selective 5-HT_{1A} receptor agonist, flesinoxan, with the putative 5-HT_{1A} receptor antagonist, (S)-UH301 ((*S*)-5-fluoro-8-hydroxy-2-(di-*n*-propylamino)tetralin). The interaction of (S)-UH301 (3 and 10 mg/kg s.c.) with flesinoxan (3 mg/kg s.c.) showed no antagonistic effects of (S)-UH301 on flesinoxan-induced corticosterone secretion. In fact, like flesinoxan (1 and 3 mg/kg s.c.), (S)-UH301 (3 and 10 mg/kg s.c.) itself dose dependently increased plasma corticosterone levels. Unlike flesinoxan, (S)-UH301 did not induce hyperglycemia, lower lip retraction and flat body posture. Moreover, flesinoxan-induced hyperglycemia and behavioural changes were effectively antagonized by (S)-UH301, showing potent 5-HT_{1A} receptor antagonistic effects of (S)-UH301. Therefore we conclude that (S)-UH301 is a potent 5-HT_{1A} receptor antagonist and that the (S)-UH301-induced corticosterone secretion is mediated by a non-5-HT_{1A} receptor mechanism.

Keywords: 5-HT_{1A} receptor; Corticosterone; Glucose; 5-HT (5-hydroxytryptamine, serotonin); Behavioral syndrome; (S)-UH301; Flesinoxan

1. Introduction

Among the various serotonin (5-HT) receptor subtypes currently recognized, the 5-HT_{1A} receptor has received considerable attention because of its involvement in many physiological processes, for example the regulation of mood, temperature, motor behaviour, cardiovascular function and (neuro)endocrine secretion (Dourish et al., 1987). Several 5-HT_{1A} receptor agonists have been shown to activate both the hypothalamic-pituitary-adrenal and the sympathoadrenal axis (Chaouloff, 1993). 8-Hydroxy-2-(di-*n*-propyl-amino)tetralin-hydrobromide (8-OH-DPAT), the prototypic 5-HT_{1A} receptor agonist, increased plasma adrenocorticotropin hormone (ACTH) (Calogero et al., 1988; Gilbert et al., 1988) and corticosterone levels in the rat (Calogero et al., 1988; Koenig et al., 1987), as well as plasma adrenaline (Bagdy et al., 1989) and glucose levels (Chaouloff et al., 1990a). Partial 5-HT_{1A} receptor agonists such as buspirone and ipsapirone also induced rises in plasma ACTH (Gilbert et al., 1988), corticosterone (Matheson et al., 1988), adrenaline and noradrenaline levels (Chaouloff et al., 1990b; De Boer et al., 1991). Several studies have been performed to characterize the 5-HT_{1A} involvement in these responses (Calogero et al., 1990; Chaouloff and Jeanrenaud, 1987), but the lack of highly selective 5-HT_{1A} receptor antagonists has hampered these investigations. Development of specific 5-HT_{1A} receptor antagonists devoid of agonistic activity, such as (S)-UH301 (Hacksell et al., 1993) and WAY-100,135 (Fletcher et al., 1993a,b) has made it possible to define the functional consequences of 5-HT_{1A} receptor activation more closely.

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So far, only a few studies have been done in which the effects of 5-HT_{1A} receptor antagonists on plasma corticosterone and glucose levels were investigated. WAY-100,135 antagonized the increases in plasma corticosterone (Lejeune et al., 1993) and glucose levels (Critchley et al., 1994b) induced by 5-HT_{1A} receptor agonists. (S)-UH301, a recently developed 8-OH-DPAT analogue (Hillver et al., 1990), blocked the 8-OH-DPAT-induced rises in plasma corticosterone levels (Kelder and Ross, 1992). (S)-UH301 also appeared to antagonize various effects induced by 8-OH-DPAT in rats, such as lower lip retraction and hyperphagia (Moreau et al., 1992) and reduction in 5-HT biosynthesis (Björk et al., 1991b), without having an agonistic action itself. Therefore, this drug is considered as a 'silent' and potent 5-HT_{1A} receptor antagonist.

We investigated the antagonistic effects of (S)-UH301 on endocrine and behavioural changes induced by the potent and selective 5-HT_{1A} receptor agonist, flesinoxan. Flesinoxan is presently under investigation for generalized anxiety disorder and depression and preliminary studies already have shown promising results (Ansseau et al., 1993; Deakin, 1993; Graf et al., 1993,). We measured the effects of these drugs on plasma corticosterone and glucose concentrations in rats. To our surprise (S)-UH301 itself induced corticosterone release and seemed not able to block the flesinoxan-induced corticosterone secretion. To get a better insight into the antagonistic properties of (S)-UH301 we therefore also studied the antagonizing effects of (S)-UH301 on flesinoxan-induced lower lip retraction and flat body posture, which are known to be mediated by 5-HT_{1A} receptors (Berendsen et al., 1989).

2. Materials and methods

2.1. Animals

Male Wistar rats (Harlan-CPB, Zeist, Netherlands) weighing approximately 300 g on arrival in the laboratory, were housed individually in either clear Plexiglass cages (25 × 25 × 30 cm, cannulation experiments) or standard Macrolon cages (behavioural observation test) under non-reversed 12 h light–12 h dark cycle conditions (lights on from 7:00 a.m. to 7:00 p.m.). The animals were housed at constant room temperature (21 ± 2°C) and relative humidity (55 ± 5%) with free access to water and standard food (Hope Farms), unless stated otherwise.

2.2. Surgery and blood sampling

Rats used in the blood sampling tests were equipped with cannulas in the jugular vein according to the technique described by De Boer et al. (1991), using Hypnorm (5–10 mg/kg fluanisone and 0.15–0.30 mg/kg fentanylcitrate) and Dormicum (5 mg/kg midazolam-hydrochloride) as anesthetic after premedication with atropine (1 mg/kg). This technique allows frequent blood sampling in freely moving animals, without disturbing them behaviourally or physiologically. The animals were allowed to recover for at least 1 week prior to the start of experiments. During this period, the animals were handled daily and accustomed to the blood sampling procedure. Before the start of an experiment, bedding material was cleaned and food was removed from the cages. Subsequently, the rats were connected to polyethylene blood sampling tubing and given at least a 1-hour rest before testing was started. During the experiment blood samples of 0.35 ml were withdrawn. Immediately after each blood sample an equal volume of saline was transfused through the cannula. At the end of an experiment the jugular vein cannula was filled with 0.9% NaCl containing 500 IU heparin/ml and 60% polyvinylpyrrolidone (Merck) and closed with a small polyethylene plug.

2.3. Chemical determinations

Blood was collected in ice-cooled tubes containing 0.21 M EDTA (50 μl/ml blood). Plasma was separated by centrifugation (3000 rpm for 10 min at 4°C) and stored at −20°C until assayed. Plasma corticosterone concentrations were measured in duplicate using a standard radioimmunoassay, with an antiserum raised against corticosterone-21-hemisuccinate bovine serum albumin as described earlier (Van Oers et al. 1992). Plasma glucose levels were measured in duplicate using a commercially available enzymatic UV test with hexokinase (Hoffman-LaRoche, Diagnostica, Mijdrecht, Netherlands).

2.4. Behavioural observation

Male rats, weighing approximately 225 g were used for a behavioural observation test, after 1 week of adaptation to the laboratory. Directly after subcutaneous drug injections the rats were placed individually in transparent Plexiglass cages (25 × 25 × 30 cm) without bedding material. Lower lip retraction and flat body posture were scored at 5, 15, 30, 45 and 60 min after injection, using the following scores for lower lip retraction: 0 = incisors not or hardly visible, 1 = incisors partly visible, 2 = completely visible lower incisors. Flat body posture was scored as either 0 = absent or 1 = present.

2.5. Drugs

(*S*)-5-Fluoro-8-hydroxy-2-(di-*n*-propylamino)-tetralin hydrobromide ((S)-UH301) and flesinoxan-hydrochloride (*R*(+)-*N*-[2[4-(2,3-dihydro-2-2-hydroxy-

methyl-1,4-benzodioxin-5-yl)-1-piperazinyl]ethyl]-4-fluorobenzoamide), synthetized by Solvay Duphar, Weesp, were dissolved in saline (vehicle). Drug ((S)-UH301: pH 4.6 and flesinoxan: pH 4.2, respectively) and vehicle (adjusted to pH 4.3 using hydrochloric acid) solutions were administered subcutaneously in the left and the right flank, in a volume of 2 ml/kg.

2.6. Experiments

Four separate experiments were performed. In the first, a dose-response study of flesinoxan-induced rises in plasma corticosterone and glucose levels was performed, using a dose of 0, 1 or 3 mg/kg s.c. ($n = 7$ per dose). Blood samples were taken at $t = 0$, 15, 30, 45, 60, 90 and 120 min respectively. The animals were tested only once, with conditions randomized over 4 test days. In the second experiment a dose-response study of (S)-UH301 (0, 3 and 1 mg/kg s.c.) was performed, using the same set-up as in the first experiment, with five to six rats per dose. In the third experiment we repeated the dose-response study of (S)-UH301 (0, 3 and 10 mg/kg) and also investigated the interactions of (S)-UH301 (0, 3 and 10 mg/kg s.c.) with flesinoxan (3 mg/kg s.c.) on plasma corticosterone and glucose levels. Blood samples were collected at $t = 0$, 15, 30, 45 and 60 min. Two injections were given immediately after the $t = 0$ min sample, according to a design with six experimental conditions (vehicle/vehicle, 3 mg/kg (S)-UH301/vehicle, 10 mg/kg (S)-UH301/vehicle, vehicle/3 mg/kg flesinoxan, 3 mg/kg (S)-UH301/3 mg/kg flesinoxan and 10 mg/kg (S)-UH301/3 mg/kg flesinoxan). All animals were tested twice, with at least a 1-week interval between two tests, using a randomized design (6 test days) to control for possible carry-over effects. Each condition was tested in six to seven rats. The interaction effects of (S)-UH301 (0, 3 and 10 mg/kg s.c.) with flesinoxan (3 mg/kg s.c.)

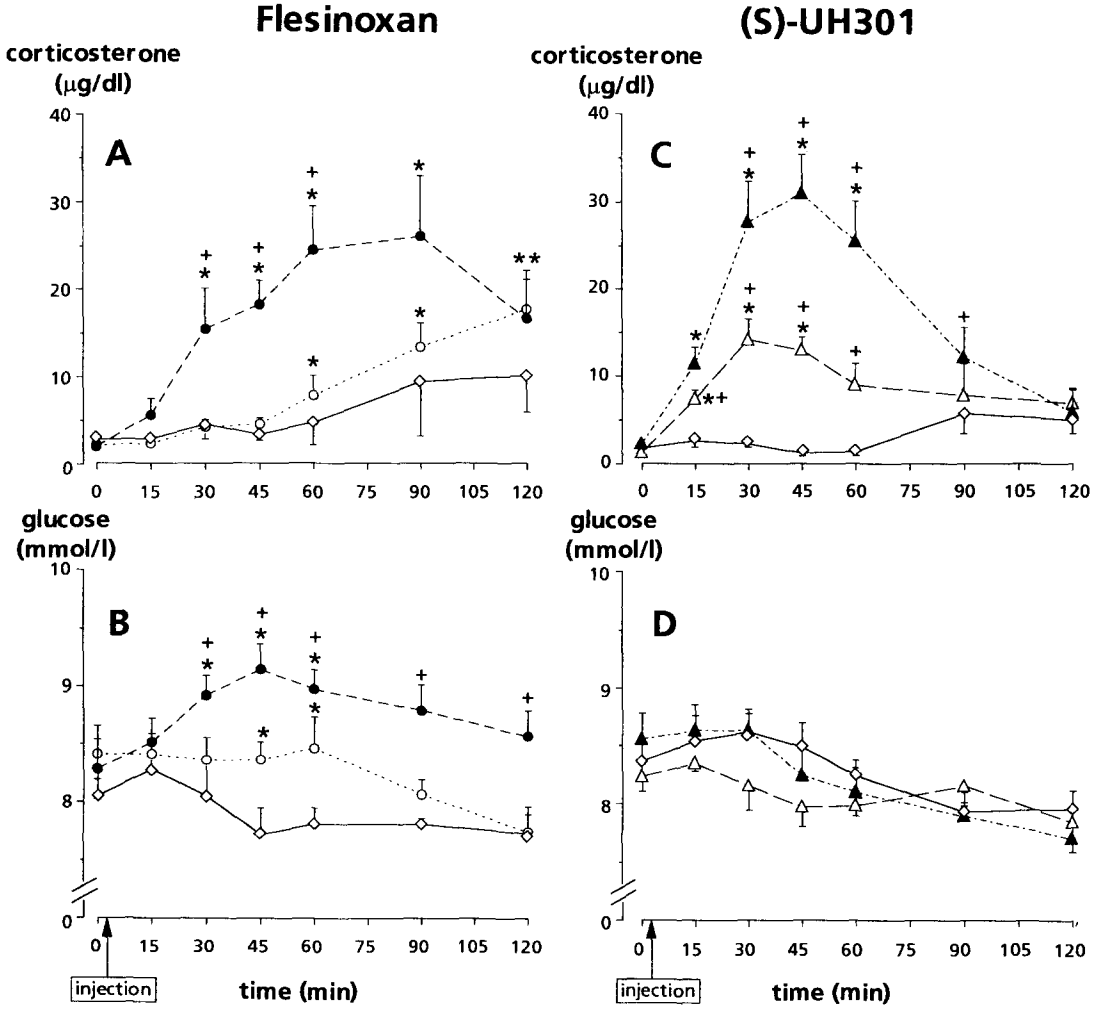

Fig. 1. Time course of plasma corticosterone and glucose levels after subcutaneous administration of flesinoxan (A,B: ◇ = 0 mg/kg, ○ = 1 mg/kg, ● = 3 mg/kg) or (S)-UH301 (C,D: ◇ = 0 mg/kg, △ = 3 mg/kg, ▲ = 10 mg/kg). Each time point represents the mean (S.E.M.) from five to seven rats. * $P < 0.05$ as compared to corresponding vehicle value (Duncan's multiple range test); + $P < 0.05$ as compared to $t = 0$ min (paired Student's t-test).

on lower lip retraction and flat body posture as well as the effects of (S)-UH301 and flesinoxan with vehicle were studied in the fourth experiment. At $t = 0$ min the rats received two subcutaneous injections, using the same six conditions as described for experiment 3. Observations were made at 5, 15, 30, 45 and 60 min after treatment. In this experiment we used non-cannulated male rats ($n = 10$ per condition), which were tested once, with conditions randomized over 4 test days. All experiments were performed between 8:30 a.m. and 12:15 p.m.

2.7. Statistics

For plasma corticosterone and glucose levels statistical comparisons were made using a three-way analysis of variance (ANOVA) with sampling time as a repeated within-subject factor and with the (S)-UH301 and flesinoxan treatments as between-subject factors. In the case of significant effects separate ANOVAs were performed. Further analyses were performed using a paired Student's t-test (within-group comparisons) or Duncan's multiple range test (between-group comparisons) to determine the source of the detected significance in the ANOVAs. For comparisons of the behavioural observations the Kruskal-Wallis test was used, and if significant, was followed by the Mann-Whitney U-test. Analyses were made of behavioural sum scores obtained by adding the five separate scores in time (5, 15, 30, 45 and 60 min post-treatment) for each rat, as well as on scores per time point. The sum scores were used to determine overall treatment effects. The criterion of significance was set at $P < 0.05$ for all tests.

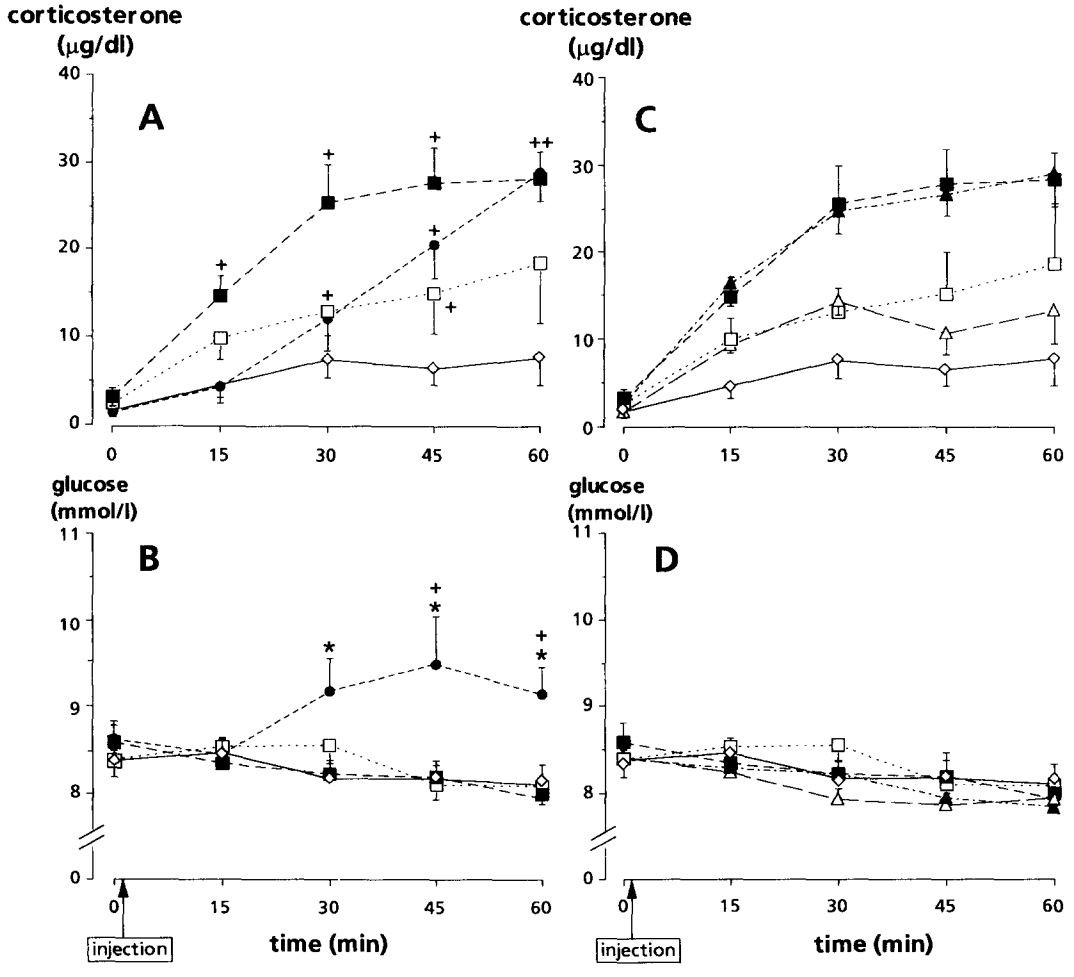

Fig. 2. Effects of (S)-UH301 (0, 3 mg/kg or 10 mg/kg s.c.) on the time course of plasma corticosterone (A,C) and glucose levels (B,D) after combined administration of either vehicle (2 ml/kg s.c.) or flesinoxan (3 mg/kg s.c.). vehicle/vehicle (◇), 3 mg/kg S(−)UH301/vehicle (△), 10 mg/kg (S)-UH301/vehicle (▲), vehicle/flesinoxan (●), 3 mg/kg (S)-UH301/flesinoxan (□), 10 mg/kg (S) UH301/flesinoxan (■). Each time point represents the mean (S.E.M.) from six to seven rats. * $P < 0.05$ as compared to corresponding vehicle value (Duncan's multiple range test); + $P < 0.05$ as compared to $t = 0$ min (paired Student's t-test).

3. Results

Injection of flesinoxan significantly and dose dependently increased both plasma corticosterone (Fig. 1A, $F(16,2) = 6.45$, $P = 0.009$) and plasma glucose concentrations (Fig. 1B, $F(17,2) = 6.97$, $P = 0.006$) as compared to the control, vehicle-treated group. The 1 mg/kg dose slightly enhanced plasma corticosterone concentrations 60–120 min after injection and plasma glucose levels 45–60 min after drug administration. After 3 mg/kg s.c. flesinoxan, plasma corticosterone and glucose concentrations were significantly enhanced from 30 min, whereas maximal increases were found 45 min (glucose) and 60–90 min (corticosterone) after injection. The 3 mg/kg dose of flesinoxan was chosen for subsequent antagonist studies with (S)-UH301.

(S)-UH301 (3 and 10 mg/kg s.c.) induced a dose-dependent rise in plasma corticosterone levels (Fig. 1C, $F(13,2) = 25.8$, $P < 0.0001$). Significant differences from vehicle values were already detected 15 min after injection of either dose of the drug. Maximal plasma corticosterone concentrations were reached after approximately 30–60 min. After 90 min, the corticosterone levels were no longer different from their baseline values. (S)-UH301 had no effect on plasma glucose levels (Fig. 1D, $F(13,2) = 0.79$, $P = 0.743$). These effects of flesinoxan (exp. 1) and (S)-UH301 (exp. 2) on plasma corticosterone and glucose concentrations were replicated in experiment 3.

Combined injections of (S)-UH301 (3 or 10 mg/kg s.c.) with flesinoxan (3 mg/kg s.c.) resulted in increased plasma corticosterone levels in all three treatment groups (vehicle/flesinoxan, 3 mg/kg (S)-UH301/flesinoxan, 10 mg/kg (S)-UH301/flesinoxan) as compared to the vehicle/vehicle-treated group (Fig. 2A). The corticosterone-enhancing effects of the three treatments did not differ significantly (main effect 'treatment' $F(15,2) = 2.37$, $P = 0.13$) and antagonistic effects of (S)-UH301 were not evident. Fig. 2C shows that combined administration of either dose of (S)-UH301 (3 or 10 mg/kg s.c.) with flesinoxan (3 mg/kg s.c.) induced plasma corticosterone increases which were largely similar to the corticosterone-enhancing effects induced by administration of these (S)-UH301 doses with vehicle ($F(21,1) = 0.21$, $P = 0.65$). Both doses of (S)-UH301 effectively antagonized the flesinoxan-induced hyperglycemia (Fig. 2B, $F(14,2) = 4.16$, $P = 0.038$) and, similarly to what was found in experiment 2 (Fig. 1B), did not themselves affect plasma glucose concentrations (Fig. 2D, $F(16,2) = 0.46$, $P = 0.693$).

Administration of 3 mg/kg flesinoxan markedly induced lower lip retraction (Fig. 3A, $Z = 3.82$, $P = 0.0001$) and flat body posture (Fig. 3B, $Z = 4.14$, $P < 0.0001$) as compared to control vehicle-treated rats. Five min after drug injection, lower lip retraction was

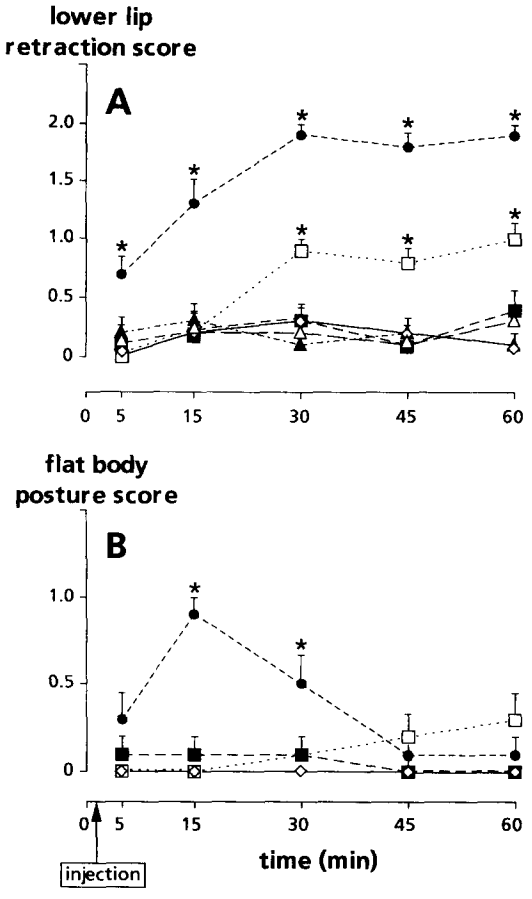

Fig. 3. Effects of (S)-UH301 (0, 3 or 10 mg/kg s.c.) on lower lip retraction (A) and flat body posture (B) after combined injections of either vehicle (2 ml/kg s.c.) or flesinoxan (3 mg/kg s.c.); vehicle/vehicle (◇), 3 mg/kg S(-)UH301/vehicle (△), 10 mg/kg (S)-UH301/vehicle (▲), vehicle/flesinoxan (●), 3 mg/kg (S)-UH301/flesinoxan (□), 10 mg/kg (S)-UH301/flesionxan (■). Each point represents the mean (S.E.M.) from a group of ten rats. * $P < 0.05$ as compared to vehicle/vehicle group (Mann Whitney U-test). Effects of the 3 mg/kg (S)-UH301/vehicle and 10 mg/kg (S) UH301/vehicle groups on flat body posture are not shown, as they coincide with the vehicle/vehicle group.

clearly present and remained until 60 min after injection, whereas the presence of flat body posture was detected 15 min after injection and had disappeared 45 min after drug treatment. (S)-UH301 itself had no effect on lower lip retraction ($H = 0.25$, $P = 0.88$) and flat body posture ($H = 0.19$, $P = 0.91$) and dose dependently antagonized the flesinoxan-induced effects at all observation time points (lower lip retraction: $H = 19.9$, $P < 0.0001$, flat body posture: $H = 15.6$, $P < 0.0004$).

4. Discussion

Flesinoxan, a potent and selective 5-HT_{1A} receptor agonist, significantly elevated both plasma corticosterone and glucose levels, which was consistent with

previously reported effects of flesinoxan and other 5-HT_{1A} receptor agonists (Chaouloff et al., 1990; Critchley et al., 1994b; De Boer et al., 1991; Kelder and Ross, 1992; Przegalinski et al., 1989; Wozniak et al., 1991). Surprisingly, (S)-UH301, which is supposed to be a 'silent' 5-HT_{1A} receptor antagonist, also significantly increased plasma corticosterone concentrations, whereas plasma glucose levels were not affected by this drug. Kelder and Ross (1992), reported no significant effects of (S)-UH301 on plasma corticosterone concentrations, but mentioned 'a tendency to increase corticosterone secretion' after subcutaneous injection of 3 mg/kg (S)-UH301. We used the same doses and route of administration as Kelder and Ross did, but sampled several times after injection. We found a maximal increase in plasma corticosterone levels 60 min after drug administration and observed that corticosterone levels had returned to their baseline values after 90 min. Kelder and Ross measured 75 min post-injection, which may have been too late to detect the significant rises in plasma corticosterone levels, that we found.

Combined injection of (S)-UH301 and flesinoxan resulted in increased plasma corticosterone levels, not clearly indicating antagonistic effects of (S)-UH301, presumably due to the corticosterone-enhancing properties of (S)-UH301 itself as well as to the different time patterns of corticosterone enhancement after (S)-UH301 or flesinoxan administration. Administration of (S)-UH301 combined with flesinoxan induced a similar increase in plasma corticosterone levels following the same time pattern as administration of (S)-UH301 with vehicle, indicating that the corticosterone response to flesinoxan and (S)-UH301 is not additive and that the corticosterone rise induced by (S)-UH301 is not affected by flesinoxan. This strongly suggests that the flesinoxan-induced, 5-HT_{1A} receptor-mediated, corticosterone secretion is antagonized by (S)-UH301 and that the remaining increase in plasma corticosterone levels is induced by another mechanism activated by (S)-UH301. Kelder and Ross (1992) reported that (S)-UH301 effectively antagonized the 8-OH-DPAT-induced corticosterone secretion. These results could be consistent with our findings, considering the above mentioned fact that Kelder and Ross sampled 75 min post-injection, when the corticosterone-enhancing effects of (S)-UH301 itself may already have declined. (±)-WAY100,135, another 5-HT_{1A} receptor antagonist, has been shown to antagonize both 8-OH-DPAT-induced hyperglycemia (Critchley et al., 1994b) and corticosterone secretion induced by S14671, a 5-HT_{1A} receptor agonist (Lejeune et al., 1993). At the highest dose tested (10 mg/kg s.c.), (±)-WAY100,135 slightly enhanced plasma corticosterone levels, but still fully antagonized the S14671-induced corticosterone secretion (Lejeune et al., 1993). The strong and dose-dependent corticosterone-enhancing effects of (S)-UH301 found in this study were markedly different from the slight corticosterone rise induced by (±)-WAY100,135. It is not very likely that the corticosterone-enhancing effects of (S)-UH301 can be attributed to partial 5-HT_{1A} receptor agonistic effects of the drug. The capability of (S)-UH301 to fully antagonize flesinoxan-induced hyperglycemia as well as flesinoxan-induced lower lip retraction and flat body posture, without inducing any agonistic effects itself, does not support the concept of (S)-UH301 being a partial 5-HT_{1A} receptor agonist. However, to exclude this possibility completely, it should be tested whether the corticosterone enhancing effects of (S)-UH301 can be blocked by WAY-100,635, a selective 5-HT_{1A} antagonist which seems devoid of corticosterone-enhancing effects (Critchley et al., 1994a). Studies in which other models of 5-HT_{1A} receptor activity were investigated also showed (S)-UH301 to be a potent 5-HT_{1A} receptor antagonist (Björk et al., 1991a,b; Johansson et al., 1991; Nomikos et al., 1992). On the other hand, (S)-UH301 has been reported to possess anticonvulsant, hypophagic and anxiolytic properties (Moreau et al., 1992) and to reduce motor activity (Björk et al., 1992). Although it is quite possible that these effects of (S)-UH301 are induced by its 5-HT_{1A} antagonistic properties on tonically active 5-HT_{1A} receptor systems, involvement of other receptors should not be ruled out. Apart from the high affinity for 5-HT_{1A} receptors ($K_i = 52$ nM; Hillver et al., 1990), (S)-UH301 also exhibits some affinity for dopamine D_2 receptors ($K_i = 400$ nM; Hillver et al., 1990). It could be suggested that the corticosterone-enhancing effects of (S)-UH301 are modulated by the D_2 receptor, as both dopamine agonists and antagonists have been reported to enhance plasma corticosterone levels (Boaventura et al., 1984). However, as the affinity of (S)-UH301 to the D_2 receptor is rather low, it should not be excluded that the corticosterone enhancing effects of (S)-UH301 are mediated via another, non-5HT_{1A} and non-D_2 receptor mechanism. We are currently investigating the corticosterone-enhancing properties of (S)-UH301 more closely.

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