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The Preferential Dopamine Autoreceptor Antagonist (+)-UH232 Antagonizes the Positive Reinforcing Effects of Cocaine and *d*-Amphetamine in the ICSS Paradigm

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KLING-PETERSEN, T., E. LJUNG AND K. SVENSSON. *The preferential dopamine autoreceptor antagonist (+)-UH232 antagonizes the positive reinforcing effects of cocaine and* d-*amphetamine in the ICSS paradigm.* PHARMACOL BIOCHEM BEHAV **49**(2) 345–351, 1994.—The dopamine autoreceptor and D_3 preferring antagonist [*cis*-(+)-5-methoxy-1-methyl-2-(di-n-propylamino)tetralin] (+)-UH232, exerts weak stimulatory effects when tested in locomotor activity experiments using habituated animals. (+)-UH232 also blocks *d*-amphetamine-, cocaine-, and apomorphine-induced hyperactivity, but fails to induce catalepsy. Thus, the behavioral effects of (+)-UH232 appear to be dependent upon the baseline activity of the animal. The antagonistic properties of (+)-UH232 were studied in the intracranial self-stimulation (ICSS) technique in the rat. (+)-UH232 and haloperidol produced inhibitory effects over a wide dose range. Cocaine, GBR12909 and *d*-amphetamine clearly lowered ICSS thresholds, indicating stimulatory effects. (+)-UH232 antagonized the stimulatory effects of cocaine, GBR12909, and *d*-amphetamine, whereas haloperidol, at a dose producing an inhibition similar to (+)-UH232, was significantly weaker in antagonizing cocaine- or *d*-amphetamine-induced stimulation. This difference between (+)-UH232 and haloperidol with respect to stimulant-blocking ability, support the concept that the effects of (+)-UH232 are not representative of either classical DA agonists or DA antagonists.

(+)-UH232 Copcaine *d*-Amphetamine ICSS Paradigm DA Autoreceptor Antagonist GBR 12909

DOPAMINE (DA) is one of the brain neurotransmitters often mentioned to play a central role in mediating brain stimulation reward (15,16,25,27,30,49) [for a recent review see (21)]. In support of this is the neurochemical evidence that DA is released in the nucleus accumbens during intracranial self-stimulatory (ICSS) behavior (29,33). In addition, self-stimulation thresholds are dose dependently increased after administration of a selective DA receptor antagonist (8,10,14). Furthermore, an overwhelming amount of reports indicates the reward-enhancing effects of indirect DA agonists such as *d*-amphetamine, nomifensine and cocaine [e.g., (12,28, 31,41)].

These results imply that direct acting DA agonists, such as apomorphine or quinpirole, should enhance ICSS behavior, an assumption that has proven hard to ascertain. Some researchers report experiments where apomorphine inhibits ICSS behavior (2,22), whereas others have found the opposite (5,23). The directly acting DA D_2/D_3 receptor agonist, quinpirole (0.0625–4.0 mg/kg) also failed to facilitate ICSS and produced a weak, but statistically significant increase in reward threshold [unpublished results, this laboratory, but see (31)]. The differences in results could be explained by the fact that many direct-acting DA agonists express a higher preference for the presynaptic receptors compared to the postsynaptic DA receptors, thus, resulting in behavioral inhibition. Another possibility is that a agonist induces a higher tonic activation of the DA system and this masks the enhanced DA signal (2,3,22,23). In contrast, indirect agonists such as cocaine or *d*-amphetamine mainly enhances the neurotransmission of neurons actively firing, thereby selectively facilitating DA activity in neurons possibly involved in brain reward.

The preferential DA autoreceptor antagonist (+)-UH232

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[*cis*-(+)-5-methoxy-1-methyl-2-(di-n-propylamino)tetralin] represents a new class of weak behavioral stimulants (18,46). (+)-UH232 and its monopropyl analog (+)-AJ76 increase the synthesis rate and turnover of DA in brain limbic and striatal regions that, in turn, results in increased extracellular levels of DA (6). In behavioral studies, (+)-UH232 produces a mild stimulation over a fairly wide dose range with only weak hypomotility and no catalepsy observed even after very high doses. The degree of stimulation produced by (+)-UH232 is highly dependent upon the baseline activity of the animal. In rats with a comparable high degree of activity (e.g., animals exploring a new environment), (+)-UH232 induces a weak stimulation, whereas a pronounced stimulation is observed in animals that are strongly habituated to the locomotor activity boxes (46). However, in animals displaying hyperactivity induced by cocaine or *d*-amphetamine, (+)-UH232 blocks this stimulation down to, but not below, saline control levels (34,47). This suggests that these compounds have a behavioral normalizing profile.

In models designed to test for positive reinforcing effects, varying results have been obtained. Both (+)-UH232 and (+)-AJ76 induced conditioned place preference over a wide dose range (35,48). However, (+)-AJ76 was not self-administered by rats and blocked the self-administration of cocaine in the same species (35). Furthermore, it has also been shown that (+)-AJ76 only partially substituted for cocaine in drug discrimination tests, while (+)-UH232 was inactive (7). Finally, (+)-AJ76 was found to be inhibitory in the ICSS paradigm (19). Taken together, these results would suggest that (+)-UH232 and (+)-AJ76 have low, if any, abuse potential.

The aim of the present study was to examine the effects of (+)-UH232 alone and in combination with *d*-amphetamine, cocaine, and GBR12909 in the ICSS paradigm. In addition, the properties of (+)-UH232 were compared to those of the classical neuroleptic haloperidol.

METHOD

Animals and Surgery

The experiments were performed on male Sprague-Dawley rats (B&K Universal AB, Sollentuna, Sweden and Mφllegaard A/S, Denmark) that, at the time of surgery, weighed between 270 and 400 g. Animals were implanted with a twisted bipolar electrode (Model no 303/2, Plastic One, Roanoke, USA) aimed at the median forebrain bundle. A mixture of ketamine (100 mg/kg) and xylazine (5 mg/kg) were injected IP to induce surgical anaesthesia. With the skull held horizontal between bregma and lambda, the stereotactic coordinates were the following: bregma +4.3, midline ±1.7, and surface of the skull −8.7 (4). Two or three stainless steel screws were fixed to the skull prior to placement of the electrode and screws and electrode was then fixed together using cranioplastic cement (Perm Reline Repair Resin, Akron, OH). The animals were kept in individual boxes with food and water available ad lib. The colony room was maintained on a 12 L : 12 D cycle with lights on 1800 h. The animals were allowed at least 1 week postoperative recovery before training began. All experiments were approved by the local animal ethical committee.

Drugs

The following drugs were used: *d*-amphetamine sulphate (Apoteksbolaget AB, Sweden), cocaine hydrochloride (Sigma, St Louis, MO), GBR12909 (Novo, Bagsvaerd, Denmark), haloperidol (Janssen, Bersee, Belgium) and (+)-UH232 [*cis*-(+)-5-methoxy-1-methyl-2-(di-n-propylamino)tetralin] (synthesized at The Upjohn Company, Kalamazoo, MI by Dr. Mark A. Krook). All compounds, except haloperidol, were dissolved in saline and administered in a volume of 5 ml/kg body weight. Haloperidol was dissolved in a drop of acetic acid and diluted with 5.5% glucose solution. (+)-UH232 and *d*-amphetamine were administered subcutaneously in the neck region and all other compounds were administered intraperitoneally. All compounds were administered 15 min before testing began.

Experimental Apparatus

The experiments were performed in commercially available cages (size 50 × 28 × 30 cm) consisting of two aluminia walls and two Plexiglas walls and a grid floor (E10-10 Coulbourn Inst. Lehigh Valley, PA). Each cage was equipped with a lever (E21-03 Coulbourn Inst.) placed 6 cm above the floor and positioned in the middle of one of the side walls. Each test cage was placed inside a light- and sound-attenuating chamber equipped with a weak house light and a fan, helping to mask out external noises.

Once inside the test cage, a lead, connected to a commutator, was screwed to the electrode. The commutator (model No. SL2C, Plastic One) allowed the animal to move freely around in the cage. The lead from the commutator was connected to the stimulator (E13-51, Coulbourn Inst.) and the applied electrical stimulation was monitored using a standard laboratory oscilloscope. Control of stimulators and operant boxes was accomplished using an Apple Macintosh computer equipped with an interface card (National Inst., Austin, TX). All software was written in our laboratory using Object Oriented Programming (LabVIEW, National Inst.) (20).

The stimulation following each lever press consisted of 0.3 s train of cathodal rectangular pulses of a 0.3 ms duration. The frequency was set to 100 Hz.

The rate/intensity curve was generated by presenting the animal with a descending series of current intensities starting at an intensity two to three data points higher than expected (i.e., control) maximal response. Each intensity was presented for 3 min and the number of lever presses per minute was recorded. The first minute of each intensity was regarded as warm-up time and subsequently discarded. The current intensity was then decreased with 0.05 log units until the animal stopped responding. Starting current intensity was usually between 250–500 μA.

Control experiments were run until stable EC_{50} values were generated. This usually took between 6–10 control sessions. Testing of drugs usually took place two times a week, Tuesday and Friday, with each experiment preceded 24 h earlier by a control (vehicle) experiment. In addition to recording the EC_{50} for each experiment, the upper asymptote (usually between 170–230 lever presses/minute) and the slope of the curve was recorded to establish any motor disturbances [for examples of typical curves see (19)].

Analysis of Rate/Intensity Curves

The rate/intensity curve for each experiment was subjected to a modified Probit conversion according to the technique of Litchfield and Wilcoxon (24) and an EC_{50} (effective current) value for each experiment was calculated. EC_{50} was defined as the current intensity necessary to maintain 50% of maximal response rate (19). Once all EC_{50} values (control and experimental) had been collected, control $EC9_{50}$ values were sub-

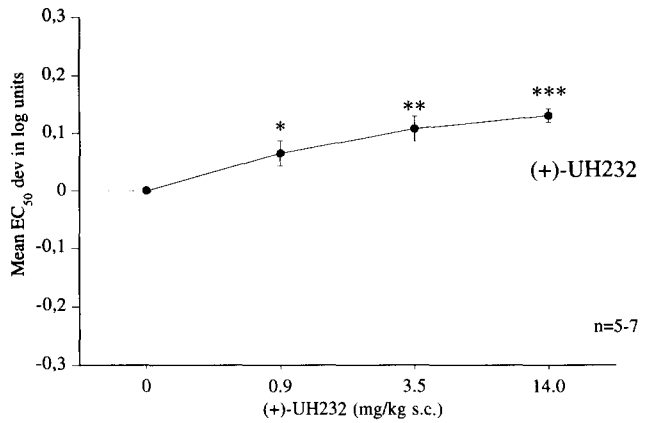

FIG. 1. Effects of (+)-UH232 in the ICSS paradigm. The dose-dependent inhibition of ICSS behavior is shown as an increase in the mean EC_{50} deviation. (+)-UH232 was administered subcutaneously 15 min before testing began. Mean ± SEM (n = 5–7). Statistics: ANOVA followed by Fisher's PLSD (*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ vs. saline-treated controls).

tracted from their corresponding drug data point enabling all data points to be compared statistically. For an in depth description of the methodology see (20).

Statistical Analysis

The recalculated data points (negative numbers if a left shift occurred and vice versa) were then subjected to an ANOVA followed by a Fisher's PLSD post hoc test to establish statistically significant differences. Probability levels (p) less than 0.05 were considered statistically significant.

Verification of Electrode Sites

Histological verification, using a methodology previously described (19,20), revealed that the tips of the electrodes were inside the median forebrain bundle in all animals used in the present series of experiments.

RESULTS

(+)-UH232 dose dependently (0.9–14.0 mg/kg) increased the ICSS threshold (EC_{50} values, Fig. 1) as did haloperidol (0.005–0.16 mg/kg, Fig. 2). In contrast, cocaine (1.0–16.0 mg/kg, Fig. 3), *d*-amphetamine (0.25–4.0 mg/kg, Fig. 4), and GBR12909 (4.0–16.0 mg/kg Fig. 5) all facilitated ICSS behavior. The facilitation was most pronounced for *d*-amphetamine (4.0 mg/kg). (+)-UH232 did not affect the upper asymptote in doses up to 14.0 mg/kg. The two highest doses of haloperidol produced, however, a marked decrease (20–30%) in upper asymptote (data not shown). In contrast, the two lowest doses of *d*-amphetamine and all doses of cocaine tested showed a slight increase in upper asymptote, whereas GBR12909 was inactive in this respect (data not shown).

(+)-UH232 (3.5 and 14 mg/kg) completely blocked the stimulatory effects of cocaine (4.0–16.0 mg/kg, Fig. 3) as well as *d*-amphetamine (0.25–4.0 mg/kg, Fig. 4) with exception of the combination of *d*-amphetamine (4.0 mg/kg) and (+)-UH232 (3.5 mg/kg). (+)-UH232 (14.0 mg/kg) also antagonized the stimulatory effects of all tested doses of GBR12909 (Fig. 5).

For a comparison, cocaine (1.0–16.0 mg/kg) and *d*-amphetamine (0.25–4.0 mg/kg) were examined in combination with haloperidol (0.04 mg/kg). The dose of haloperidol was chosen as a dose producing a similar degree of EC_{50} increase, i.e., inhibitory response, comparable to the two doses (3.5 and 14 mg/kg) of (+)-UH232. Haloperidol (0.04 mg/kg), on the other hand, was capable of antagonizing only the 4.0 mg/kg dose of cocaine and was inactive against the other doses (Fig. 3). The same dose of haloperidol was inactive in antagonizing the facilitatory effects of *d*-amphetamine (Fig. 4).

A comparison of the effects of (+)-UH232 and haloperidol on the facilitation produced by cocaine, showed that (+)-UH232 (3.5 and 14.0 mg/kg) significantly antagonized all doses tested of cocaine. Statistical comparison between the (+)-UH232 and the haloperidol interactions with cocaine revealed a significant difference between the combination of (+)-UH232 (3.5 mg/kg) and cocaine (1.0 and 16.0 mg/kg) and haloperidol (0.04 mg/kg) at the same doses. However, with the cocaine dose of 4.0 mg/kg, no statistical difference was seen. Comparison of (+)-UH232 (14.0 mg/kg) and haloperidol (0.04 mg/kg) in combination with cocaine revealed a significant difference against all doses tested.

When comparing the effects of (+)-UH232 and haloperidol on the facilitation produced by *d*-amphetamine, we found that (+)-UH232 (14.0 mg/kg) significantly antagonized all doses tested of *d*-amphetamine. The lower dose of (+)-UH232 (3.5 mg/kg) significantly blocked the two highest doses of *d*-amphetamine (1.0 and 4.0 mg/kg). Haloperidol (0.04 mg/kg), on the other hand, was inactive against all doses tested of *d*-amphetamine. Comparison of (+)-UH232 (14.0 mg/kg) and haloperidol (0.04 mg/kg) in combination with *d*-amphetamine revealed a significant difference against all doses of *d*-amphetamine, whereas (+)-UH232 (3.5 mg/kg) in comparison with haloperidol (0.04 mg/kg) only differed at the highest dose of *d*-amphetamine (4.0 mg/kg).

DISCUSSION

The dose-dependent increase in EC_{50} produced by (+)-UH232 is interpreted as an inhibition of ICSS reward. This

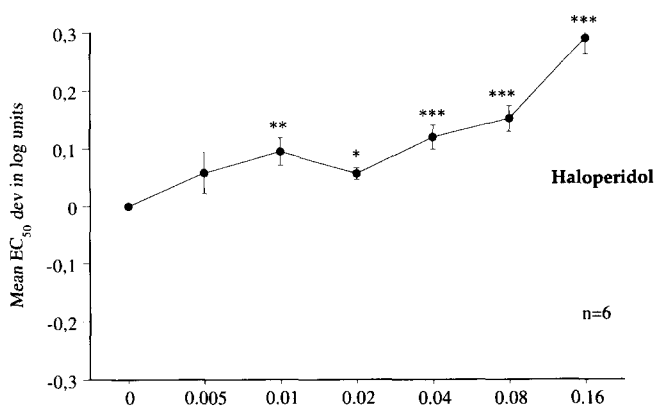

FIG. 2. Effects of haloperidol in the ICSS paradigm. The dose-dependent inhibition of ICSS behavior is shown as an increase in the mean EC_{50} deviation. Haloperidol was administered intraperitoneally 15 min before testing began. Mean ± SEM, (n = 6). Statistics: ANOVA followed by Fisher's PLSD (*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ vs. saline-treated controls).

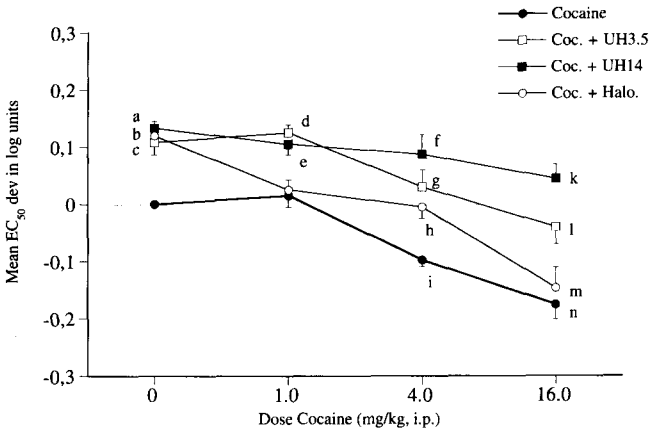

FIG. 3. Effects of cocaine, combinations of cocaine, and haloperidol or combinations of cocaine and (+)-UH232 3.5 mg/kg (UH3.5) or 14.0 mg/kg (UH14) in the ICSS paradigm. The effect on ICSS thresholds is expressed as a decrease in the mean EC_{50} deviation. Cocaine and haloperidol were administered intraperitoneally 15 or 14 min, respectively, before testing began. (+)-UH232 was administered subcutaneously 1 min after the administration of cocaine. Mean ± SEM. Statistics: ANOVA followed by Fisher's PLSD. (a) (+)-UH232, 14.0 mg/kg, vs. saline treated control, $n = 7, p < 0.001$. (b) Haloperidol, 0.04 mg/kg, vs. control, $n = 7, p < 0.001$. (c) (+)-UH232, 3.5 mg/kg, vs. control, $n = 5, p < 0.01$. (d) (+)-UH232, 3.5 mg/kg plus cocaine 1.0 mg/kg vs. control, $p < 0.05$; vs. cocaine 1.0 mg/kg, $p < 0.01$; vs. cocaine 1.0 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.05$. (e) (+)-UH232 14.0mg/kg plus cocaine 1.0 mg/kg vs. control, $p < 0.01$; vs. cocaine 1.0 mg/kg,$p < 0.01$; vs. cocaine 1.0 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.05$. (f) (+)-UH232, 14.0 mg/kg plus cocaine 4.0 mg/kg vs. control, $p < 0.05$; vs. cocaine 4.0 mg/kg, $p < 0.001$; vs. cocaine 4.0 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.05$. (g) (+)-UH232, 3.5 mg/kg plus with cocaine 4.0 mg/kg vs. cocaine 4.0 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.001$. (h) Haloperidol 0.04 mg/kg plus with cocaine 4.0 mg/kg vs. cocaine 1.0 mg/kg, $p < 0.01$. (i) Cocaine 4.0 mg/kg, vs. control, $n = 11, p < 0.001$. (k) (+)-UH232, 14.0 mg/kg plus with cocaine 16.0 mg/kg vs. cocaine 16.0 mg/kg, $p < 0.001$; vs. cocaine 16.0 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.01$. (l) (+)-UH232, 3.5 mg/kg plus with cocaine 16.0 mg/kg vs. cocaine 16.0 mg/kg, $p < 0.01$; vs. cocaine 16.0 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.05$. (m) Haloperidol 0.04 mg/kg plus cocaine 16.0 mg/kg. vs. control, $n = 7, p < 0.01$. (n) Cocaine 16.0 mg/kg, vs. control, $n = 10, p < 0.001$.

effect is in line with earlier observations for (+)-AJ76 (the mono-propyl analog of (+)-UH232 (19). None of the administered doses produced any effect on the upper asymptote (typically between 130–200 lever presses/minute) of the rate/intensity curves indicating that the drug did not affect the animal's motor performance. This is in clear contrast to haloperidol that produced more pronounced motor inhibitory effects in the high dose range [cf., (11,40)]. At the highest dose of haloperidol, the animals showed a marked reduction in response rate resulting in an asymptote level 20–30% lower than controls. This should, however, not affect the EC_{50} value because it has been suggested that low to moderate motor debilitation does not affect reward thresholds (26). Thus, our data support earlier observations that there is a marked difference in behavioral profile between (+)-UH232 and the classical neuroleptic haloperidol [cf., (46)].

According to the hypothesis mentioned in the introduction, the fact that (+)-UH232 does not act as a weak stimulant in the ICSS paradigm could possibly be explained by its baseline dependency and behavioral normalizing profile. The stimulatory effects only become apparent in cases of a low baseline activity, such as in rats habituated to their environment. It is likely, that in the present study, the applied electrical stimulation rapidly increases the DA release in the synapse thereby allowing (+)-UH232's inhibitory effects to be more noticeable. It can also be speculated that the animals, as a result of ICSS training, show a high baseline activity, already before the start of an experiment, due to conditioned expectancy of reward.

d-Amphetamine, cocaine, and the selective DA reuptake inhibitor GBR12909, all produced a dose-dependent decrease

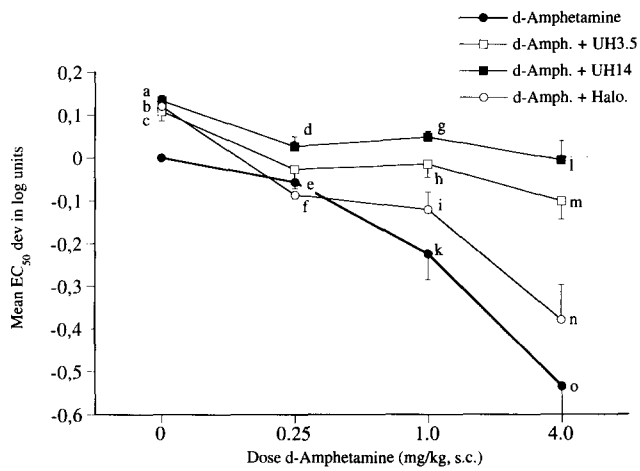

FIG. 4. Effects of *d*-amphetamine, combinations of *d*-amphetamine, and (+)-UH232 3.5 mg/kg, (UH3.5) or 14.0 mg/kg (UH14) and combinations of *d*-amphetamine and haloperidol 0.04 mg/kg, in the ICSS paradigm. The effects on ICSS thresholds are shown as an increase in the mean EC_{50} deviation. *d*-Amphetamine was administered subcutaneously 15 min before testing began. Haloperidol were administered intraperitoneally 1 min after the administration of *d*-amphetamine. (+)-UH232 was administered subcutaneously 1 min after the administration of *d*-amphetamine. Mean ± SEM. Statistics: ANOVA followed by Fisher's PLSD. (a) (+)-UH232, 14.0 mg/kg, vs. saline treated control, $n = 7, p < 0.001$. (b) Haloperidol, 0.04 mg/kg, vs. control, $n = 7, p < 0.001$. (c) (+)-UH232, 3.5 mg/kg, vs. control, $n = 5, p < 0.01$. (d) (+)-UH232, 14.0 mg/kg plus *d*-amphetamine 0.25 mg vs. *d*-amphetamine 0.25 mg/kg, $p < 0.05$; vs. *d*-amphetamine 0.25 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.01$. (e) *d*-Amphetamine 0.25 mg/kg, vs. control, $n = 6, p < 0.01$. (f) Haloperidol 0.04 mg/kg plus *d*-amphetamine 0.25 mg/kg vs. control, $n = 7, p < 0.01$. (g) (+)-UH232, 14.0 mg/kg in combination with *d*-amphetamine 1.0 mg vs. control, $n = 5, p < 0.01$; vs. *d*-amphetamine 1.0 mg/kg, $p < 0.001$; vs. *d*-amphetamine 1.0 mg/kg in combination with haloperidol 0.04 mg/kg, $p < 0.05$. (h) (+)-UH232, 3.5 mg/kg plus *d*-amphetamine 1.0 mg vs. *d*-amphetamine 1.0 mg/kg, $p < 0.01$. (i) Haloperidol 0.04 mg/kg plus *d*-amphetamine 1.0 mg/kg vs. control, $n = 7, p < 0.05$. (k) *d*-Amphetamine 1.0 mg/kg, vs. control, $n = 6, p < 0.01$. (l) (+)-UH232, 14.0 mg/kg plus *d*-amphetamine 4.0 mg vs. *d*-amphetamine 4.0 mg/kg, $p < 0.001$; vs. *d*-amphetamine 4.0 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.01$. (m) (+)-UH232, 3.5 mg/kg plus *d*-amphetamine 4.0 mg/kg vs. control, $n = 5, p < 0.05$; vs. *d*-amphetamine 4.0 mg/kg, $p < 0.001$; vs. *d*-amphetamine 4.0 mg/kg plus haloperidol 0.04 mg/kg, $p < 0.05$. (n) Haloperidol 0.04 mg/kg plus *d*-amphetamine 4.0 mg/kg vs. control, $n = 6, p < 0.001$. (o) *d*-Amphetamine 4.0 mg/kg, vs. control, $n = 6, p < 0.001$.

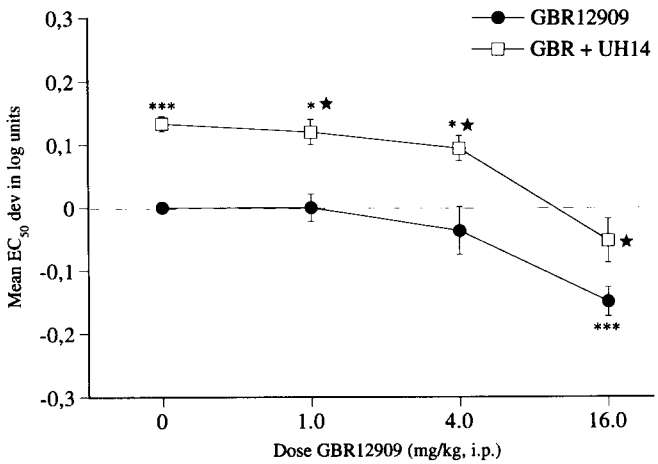

FIG. 5. Effects of GBR12909 (1.0–4.0 mg/kg) and the combination of GBR12909 and (+)-UH232 (14.0 mg/kg) in the ICSS paradigm. The dose-dependent facilitation of ICSS behavior is shown as an increase in the mean EC_{50} deviation. GBR12909 was administered intraperitoneally 15 min before testing began and (+)-UH232 1 min after the administration of GBR12909. Mean ± SEM. Statistics: ANOVA followed by Fisher's PLSD $*p < 0.05$, $***p < 0.001$ vs. saline-treated controls (n = 6–8). $\star p < 0.05$ vs. GBR12909-treated animals (n = 5–6).

in EC_{50} values indicating stimulatory actions. The ICSS facilitating effects are consistent with results obtained by others [e.g., (9,13,33,37,38)]. In the present study, *d*-amphetamine seemed to be more efficacious than cocaine or GBR12909, in facilitating ICSS behavior. The comparatively weak effect of GBR12909 in the ICSS model is surprising because it is supposed to be a more specific DA reuptake blocker than cocaine which also blocks reuptake of other monoamines (1,38). Although GBR12909 has been reported to be up to 700% more potent than cocaine in blocking DA reuptake, it possesses lower efficacy, thereby being a partial agonist (39). This may be of importance for the observed results.

When combined with cocaine, GBR12909, or *d*-amphetamine, (+)-UH232 clearly inhibited the dose-dependent facilitation of ICSS produced by these compounds. This is likely to be the result of a postsynaptic antagonism by (+)-UH232. Despite the similarity between (+)-UH232 and haloperidol's capacity to produce an increase in reward thresholds in the ICSS paradigm, their ability to block the facilitatory effects of the indirect DA agonists are less similar. This can be demonstrated by comparing the blocking efficacy as a function of increasing synaptic levels of DA. The synaptic level of DA is linear to the concentration of cocaine (32) and *d*-amphetamine (42), and the same should be equally true for GBR12909.

As can be seen from Fig. 5, (+)-UH232 produces roughly the same degree of inhibition regardless of the dose of GBR12909. This is illustrated by the dose-response curve being shifted upwards in a parallel fashion. The same is true for the low dose of (+)-UH232 in the cocaine experiments (Fig. 3). However, when cocaine was combined with the highest dose of (+)-UH232 (Fig. 3), a trend developed towards an increase in blocking efficacy. In contrast, a dose of haloperidol that per se produced an ICSS inhibition similar to that of 14 mg/kg of (+)-UH232, was clearly weaker in blocking the stimulatory effects of cocaine (Fig. 3).

The blocking efficacy of (+)-UH232 seemed to increase with increasing doses of *d*-amphetamine. Again, the degree of antagonism was more pronounced with the highest dose of (+)-UH232 as compared to the lower dose (Fig. 4). Furthermore, (+)-UH232 seems to be more efficacious in antagonizing *d*-amphetamine than cocaine in the ICSS paradigm. Haloperidol, at the dose tested, was unable to antagonize *d*-amphetamine in the same manner as did (+)-UH232 (Fig. 4) and, instead, appeared to be almost inactive against the facilitatory effects of *d*-amphetamine.

The explanation for the apparent difference between (+)-UH232 and haloperidol, with respect to antagonism of classical stimulants in the ICSS model, is not obvious. A possible interaction between (+)-UH232 and the indirect agonists at the reuptake complex cannot be ruled out, although it seems unlikely because it is known that (+)-UH232 has a poor affinity for the reuptake transporter in vitro (unpublished data).

A slightly more probable theory is that (+)-UH232 has a higher preference than haloperidol for a subgroup of postsynaptic DA receptors. In view of this, one might speculate that (+)-UH232's, albeit weak (about 4 times), preference for the D_3 (K_i 9.2 nM) vs. the D_2 (K_i 40 nM) receptor is of importance (43). Furthermore, the D_3 receptor has also been shown to have a high abundance in limbic brain areas, often suggested to be of importance in reward mechanisms (44). Also, one cannot rule out the possibility that D_2 and D_3 receptors have opposing functions that are of importance for the reward mechanism as opposed to locomotor activity or other behavioral outputs from the limbic system. The development of more selective tools is of crucial importance for the clarification of the functional roles of the D_2/D_3 receptors.

There have been several attempts to develop pharmacological methods for the treatment cocaine abuse. These include treatment with neuroleptics, bromocriptine, methylphenidate, and tricyclic antidepressants (17). Most of the DA receptor antagonists available today are, despite their acute effects on cocaine or amphetamine behavioral facilitation, limited in their use because they would tend to enhance the withdrawal effects. To minimize the negative effects of drug withdrawal, several studies using bromocriptine, methylphenidate, and tricyclic antidepressants have been performed. These have not demonstrated clinical effectiveness or have caused unacceptable side effects (17).

Other attempts using animal models of abuse include the use of a more selective DA reuptake blocker, GBR12909, which has a pharmacokinetic profile enabling it to effectively block the receptor site occupied by cocaine and due to slow release from the receptor producing a prolonged cocaine opposing effect (39). Even though GBR12909's own reuptake blocking effect does not produce a behavioral activation as efficacious as cocaine (38), GBR12909 should still have an abuse potential. This seems likely because GBR12909 is self-administered by rats (36) and rhesus monkeys (39).

In conclusion, although being inhibitory in the ICSS paradigm, (+)-UH232 does not induce catalepsy, strong hypomotility, or other signs of "anhedonia." In the present study, we have shown that (+)-UH232 effectively blocks the ICSS facilitatory effects of *d*-amphetamine, cocaine, and GBR12909. This is in line with earlier studies showing that (+)-UH232 can antagonize *d*-amphetamine (46)- and cocaine (34)-induced hyperactivity.

In contrast to classical DA antagonists, (+)-UH232 has earlier been shown to possess behavioral stimulatory properties in locomotor activity and sleep studies (45,46). It also induces conditioned place preference in the rat (48). (+)-UH232 does not, however, substitute for cocaine in drug dis-

crimination experiments (7) which, together with the present data, indicate low, if any abuse potential.

Taken together, while (+)-UH232 under certain circumstances produces behavioral stimulation per se, it blocks the action of classical stimulants. This unusual profile suggests that (+)-UH232 may be useful in the treatment of drug abuse without inducing the anhedonia experienced with classical DA antagonists. Interestingly, in a preliminary clinical trial using healthy volunteers, (+)-UH232 showed both weak activating and sedative effects. Further studies along these lines seem warranted.

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