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Evidence for Specific Interactions Between 5-HT_{1A} and Dopamine D_2 Receptor Mechanisms in the Mediation of Extrapyramidal Motor Functions in the Rat

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WADENBERG, M.-L., L. CORTIZO AND S. AHLENIUS. *Evidence for specific interactions between 5-HT_{1A} and dopamine D_2 receptor mechanisms in the mediation of extrapyramidal motor functions in the rat.* PHARMACOL BIOCHEM BEHAV 47(3) 509–513, 1994.—Administration of the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; 0.1 mg kg^{-1} SC) completely antagonised the catalepsy produced by the dopamine (DA) D_2 receptor antagonist raclopride (16 mg kg^{-1} SC). This effect by 8-OH-DPAT was in turn completely antagonised by treatment with the new 5-HT_{1A} receptor antagonist (*S*)-5-fluoro-8-hydroxy-2-(di-*n*-propylamino)tetralin [(*S*)-UH-301] (3.5 mg kg^{-1} SC), but not by the mixed 5-HT_1 receptor/β-adrenoceptor antagonist (−)pindolol (2.0 mg kg^{-1} SC). The failure by (−)pindolol to antagonise the effects of 8-OH-DPAT on raclopride-induced catalepsy could be due to its β-receptor-blocking properties, since by themselves both (−)pindolol and the selective β-adrenoceptor antagonist betaxolol (4 mg kg^{-1} SC) at least partially antagonised the raclopride-induced catalepsy. The present results provide further support for specific interactions between 5-HT_{1A} and DA D_2 receptor mechanisms in the mediation of extrapyramidal motor functions in the rat.

Catalepsy Dopamine Serotonin Raclopride 8-OH-DPAT Rat

A NUMBER of laboratory studies have demonstrated dopamine (DA)-5-hydroxytryptamine (5-HT) interactions in the mediation of neuroleptic-induced extrapyramidal dysfunction. Thus, the catalepsy produced by inhibition of brain dopaminergic neurotransmission is enhanced by increased synaptic availability of 5-HT (4,10,29), whereas it is antagonised by inhibition of serotonergic neurotransmission (14,22). The antagonism by 5-HT_{1A} receptor agonists, like 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and ipsapirone, of the haloperidol- or raclopride-induced catalepsy (7,27) is a supraspinal phenomenon, and in all probability due to stimulation of inhibitory somato-dendritic 5-HT autoreceptors in brainstem raphe nuclei [(20,28); see (15)].

The pharmacological characterization of the 5-HT_{1A} receptor has been hampered by lack of selective and specific receptor antagonists. The β-blockers (−)pindolol and (−)alprenolol have been found to have 5-HT receptor-blocking properties (9,11,12) and to display high affinity for the 5-HT_{1A} receptor site [(19); see (24)]. Recently, a new 5-HT_{1A} receptor antagonist, (*S*)-UH-301, has been characterized [see (5)]. In the present series of experiments we have examined the effects of both these types of 5-HT_{1A} receptor antagonists on the antagonism by 8-OH-DPAT of raclopride-induced catalepsy. Since β-blockers by themselves may antagonise neuroleptic-induced extrapyramidal motor dysfunctions [*e.g.* (3,30)], the selective β-blocker betaxolol (8) was also used.

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METHOD

Animals

Adult male Sprague-Dawley rats (ALAB, Laboratorietjänst AB, Sollentuna, Sweden) weighing 250–350 g were used. The rats arrived from the breeder at least one week before being used in experiments and were housed under controlled conditions of temperature (21 ± 0.4°C), relative humidity (50–60%), and light-dark cycle (12-h, lights off 0600). Food (R36, Ewos, Södertälje, Sweden) and tap water were available ad lib.

Catalepsy

Animals were placed on an inclined (60°) grid, and excluding the first 30 s, the time the rat remained in the same position was measured for a maximum of 2.5 min. The catalepsy was scored from 0–5 according to the time (square root transformation) the animal remained immobile (min): 0 = 0–0.08, 1 = 0.09–0.35, 2 = 0.36–0.80, 3 = 0.81–1.42, 4 = 1.43–2.24, 5 = ≥2.25 min (i.e., if the rat remained immobile for 0–0.08 min it was scored as 0, etc.) [see (1,16)].

Drugs

The following drugs were used: raclopride tartrate (Astra Arcus AB, Södertälje, Sweden), (±)8-hydroxy-2-(di-*n*-propylamino)tetralin HBr (8-OH-DPAT) (RBI, Natick, MA), (−)pindolol (Sandoz, Basel, Switzerland), (±)betaxolol HCl (Synthelabo, Paris), and (*S*)-5-fluoro-8-hydroxy-2-(di-*n*-propylamino)tetralin HBr [(*S*)-UH-301] (synthesized at the Department of Organic Pharmaceutical Chemistry, University of Uppsala, Uppsala, Sweden). All drugs were dissolved in physiological saline and injected SC in a volume of 2 ml/kg^{-1}. Doses refer to the form of the respective compound given above.

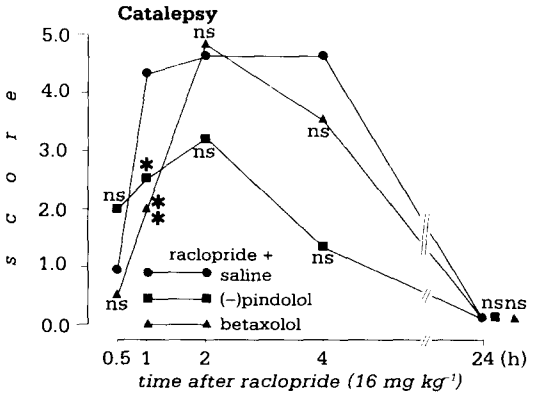

FIG. 1. Effects of (−)pindolol or betaxolol on raclopride-induced catalepsy in rats. (−)Pindolol, 2.0 mg kg^{-1}, or betaxolol, 4.0 mg kg^{-1}, were administered SC 20 min before raclopride. Results are presented as medians based on repeated observations of 22 (raclopride), 10 [(−)pindolol], and 10 (betaxolol) animals in the respective groups. Statistical analysis was performed by means of the Kruskal-Wallis one-way ANOVA by ranks, followed by the Mann-Whitney *U*-test (25) for statistical comparisons with raclopride-treated controls. H_2 = 1.98, NS (0.5 h); H_2 = 7.82, $p < 0.025$ (1 h); H_2 = 2.55, NS (2 h); H_2 = 4.51, NS (4 h); H_2 = 0.45, NS (24 h). $^{ns}p > 0.05$. $^{*}p < 0.05$. $^{**}p < 0.025$.

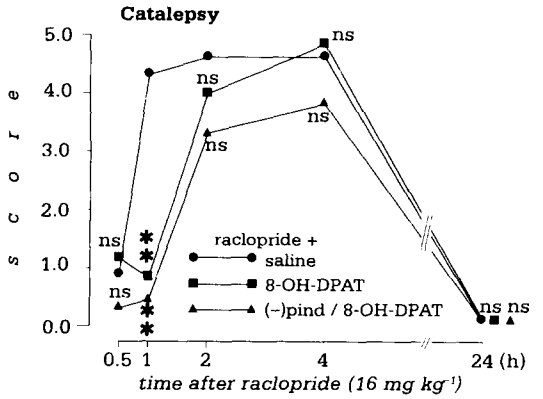

FIG. 2. Effects of 8-OH-DPAT, alone and in combination with (−)pindolol, on raclopride-induced catalepsy in rats. (−)Pindolol, 2.0 mg kg^{-1}, was administered SC 20 min before, and 8-OH-DPAT, 0.1 mg kg^{-1}, was administered SC 10 min after raclopride. Results are presented as medians based on repeated observations of 22 (raclopride), 11 (raclopride/8-OH-DPAT), and 11 [(−)pindolol/8-OH-DPAT] animals in the respective groups. Statistical analysis was performed by means of the Kruskal-Wallis one-way ANOVA by ranks, followed by the Mann-Whitney *U*-test (25) for statistical comparisons with raclopride-treated controls. H_2 = 3.61, NS (0.5 h); H_2 = 23.05, $p < 0.001$ (1 h); H_2 = 4.43, NS (2 h); H_2 = 3.77, NS (4 h); H_2 = 0.50, NS (24 h). $^{ns}p > 0.05$. $^{**}p < 0.01$.

Experimental Procedures and Statistical Evaluation

Separate groups of animals were used for each dose (including controls) of the respective compound. The same animals were followed over time for the time periods indicated in the figures. Statistical evaluation at the respective time intervals was performed by means of the Kruskal-Wallis one-way analysis of variance (ANOVA), followed by the Mann-Whitney *U*-test, in case there was an overall statistical significance in the ANOVA [see (25)].

RESULTS

Effects of Pindolol or Betaxolol on Raclopride-Induced Catalepsy (Fig. 1)

As expected, raclopride (16 mg kg^{-1} SC) produced a complete cataleptic rigidity within 1 h of administration which had a duration of at least 4 h. (It should be noted that the experiments presented in Figs. 1 and 2 were run in series and the raclopride-treated controls are the same in both figures). Pretreatment with either pindolol (2 mg kg^{-1} SC) or betaxolol (4 mg kg^{-1} SC) at least partially antagonised the raclopride-induced catalepsy at the 1-h time interval. No other statistically significant effects were found, although there was a tendency for pindolol to produce an antagonism also at the 2- and 4-h time intervals. No cataleptic rigidity was noted in any of the groups when the animals were observed 24 h after raclopride administration.

Effects of 8-OH-DPAT, Alone and in Combination With Pindolol, on Raclopride-Induced Catalepsy (Fig. 2)

As shown in Fig. 2, treatment with 8-OH-DPAT (0.1 mg kg^{-1} SC) completely antagonised the raclopride-induced catalepsy at the 1-h interval, but not at later time intervals. Pretreatment with pindolol (2 mg kg^{-1} SC), however, did not

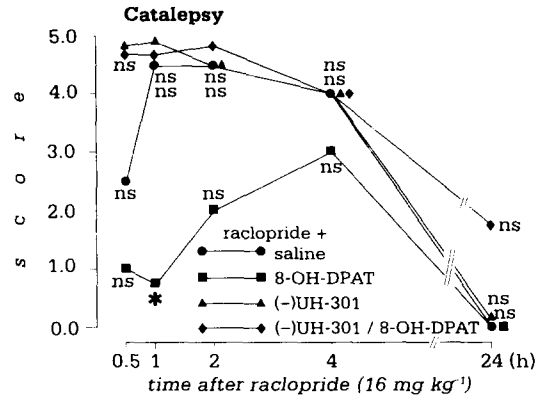

FIG. 3. Effects of (*S*)-UH-301, alone and in combination with 8-OH-DPAT, on raclopride-induced catalepsy in rats. (*S*)-UH-301, 3.5 mg kg^{-1}, and 8-OH-DPAT, 0.1 mg kg^{-1}, were administered SC 5 and 15 min after raclopride, respectively. (For effects of UH-301 by itself see Table 1). Results are presented as medians based on repeated observations of eight animals per group. Statistical analysis was performed by means of the Kruskal-Wallis one-way ANOVA by ranks, followed by the Mann-Whitney *U*-test (25) for statistical comparisons with raclopride-treated controls. $H_3 = 8.74$, $p < 0.05$ (0.5 h); $H_3 = 18.10$, $p < 0.001$ (1 h); $H_3 = 3.71$, NS (2 h); $H_3 = 0.53$, NS (4 h); $H_3 = 4.0$, NS (24 h). $^{ns}p > 0.05$. $^{*}p < 0.05$.

antagonise this effect produced by 8-OH-DPAT. As in the previous experiment, no cataleptic rigidity was seen 24 h after raclopride administration in any of the groups. 8-OH-DPAT by itself did not produce catalepsy at any time interval (data not shown).

Effects of 8-OH-DPAT, Alone and in Combination With (S)-UH-301, on Raclopride-Induced Catalepsy (Fig. 3)

The raclopride-treated controls used in this experiment displayed an onset, efficacy, and duration of raclopride-induced effects similar to those described above (Figs. 1-2). As in the immediately preceding experiment above, 8-OH-DPAT (0.1 mg kg^{-1} SC) completely antagonised the raclopride-induced catalepsy at the 1-h time interval. This effect of 8-OH-DPAT was antagonised by pretreatment with (*S*)-UH-301 (3.5 mg kg^{-1} SC). In fact, the raclopride-treated animals given both these compounds were as cataleptic as the raclopride-treated controls. There were no statistically significant effects by (*S*)-UH-301 on the raclopride-induced catalepsy. Finally, when tested 24 h after raclopride administration, no cataleptic rigidity was noted in any of the groups.

(*S*)-UH-301 by itself did not produce any cataleptic rigidity at the time points (0.5 h, 1 h) when the 8-OH-DPAT-induced effects were antagonised. At later time intervals (2-4 h), however, there was a slight and statistically significant degree of cataleptic rigidity (Table 1). As also shown in Table 1, saline controls did not display any signs of cataleptic rigidity under the present test conditions.

DISCUSSION

In order to obtain maximal catalepsy by the DA D$_2$ receptor antagonist raclopride in the inclined grid test, a dose of 16 mg kg^{-1} is required. This effect is obtained within 1 h, with a duration of between 4-8 h (16,27). The catalepsy thus induced is completely antagonised by administration of the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT in the dose range 0.1-1.6 mg kg^{-1}, but not by doses below 0.05 mg kg^{-1} [(27) and unpublished observations]. In further support for specific interactions between 5-HT$_{1A}$/DA D$_2$ receptor mechanisms in the mediation of extrapyramidal motor functions, this effect of 8-OH-DPAT on raclopride-induced catalepsy was fully antagonised by administration of the 5-HT$_{1A}$ receptor antagonist (*S*)-UH-301 (3.5 mg kg^{-1} SC) in the present study. This dose of (*S*)-UH-301 is required to obtain, at least partially, an antagonism of the suppression of forebrain 5-HT synthesis, produced by 8-OH-DPAT, with a duration of approximately 1 h (5,6). Higher doses may produce suppression of behavior (6,23) that possibly could interfere with the catalepsy observations.

In the present study a weak tendency for cataleptic rigidity was noted 2-4 h after the administration of (*S*)-UH-301, and gross observations of the animals indicated a slight sedation. Recent results of studies of effects of (*S*)-UH-301 in rodents and monkeys suggest, however, sedative-hypnotic rather than neuroleptic properties of this compound (23). Thus, for example, (*S*)-UH-301 in a high dose (10 mg kg^{-1} SC) did not impair performance of rats in a rotarod test, a test situation known to be highly sensitive for detection of extrapyramidal motor impairment produced by DA receptor- blocking agents [e.g., (16)]. It is thus not likely that dopaminergic mechanisms do contribute to the interaction between (*S*)-UH-301 and 8-OH-DPAT in the present study. It should also be noted that at the time point of maximal antagonism (1 h) there was no tendency whatsoever for (*S*)-UH-301 to produce cataleptic rigidity.

Ligand receptor-binding studies, as well as biochemical and behavioral studies, provide strong evidence that (*S*)-UH-301 is a specific 5-HT$_{1A}$ antagonist with little or no intrinsic activity at doses and time intervals relevant for the present study. Thus, for example, in contrast to effects produced by 8-OH-DPAT the administration of (*S*)-UH-301 to rats does

TABLE 1

EFFECTS OF (-)UH-301, 3.5 mg kg^{-1} SC, ON CATALEPTIC RIGIDITY IN THE RAT

	0.5 h	1 h	2 h	4 h	24	(*n*)
NaCl	0.0 ± 0	0.0 ± 0	0.1 ± 0	0.1 ± 0	0.1 ± 0.3	(8)
(-)UH-301	0.3 ± 1^{ns}	0.8 ± 0.8^{ns}	2.0 ± 1.3**	1.3 ± 1**	0.1 ± 0^{ns}	(8)

Following the administration of (-)UH-301 or vehicle, the animals were observed at the various time invervals as shown in the table. Results are presented as medians ± semi-interquartile range, based on repeated observations of eight animals per group. Statistical evaluation was performed by means of the Mann-Whitney *U*-test [see (25)] for comparisons between animals given (-)UH-301 and time-matched saline controls, as indicated in the table. $^{ns}p > 0.05$. $^{**}p < 0.01$.

not result in a compensatory decrease in forebrain 5-HT synthesis, nor does (*S*)-UH-301 antagonise the forskolin-induced stimulation of adenylyl cyclase activity in vitro. This forskolin-induced stimulation of adenylyl cyclase formation, however, is totally inhibited by addition of 8-OH-DPAT to the medium, an effect fully antagonised by the addition of (*S*)-UH-301 (5,17).

It should be noted that both 8-OH-DPAT and (*S*)-UH-301 have a weak DA D_2 agonist-like profile in in vivo pharmacological experiments (2,5). Unpublished observations from this laboratory suggest that (*S*)-UH-301 is somewhat more efficacious in this respect than 8-OH-DPAT. However, doses of 8-OH-DPAT higher than 0.1 mg kg^{-1} are needed to produce such effects, and the weak DA D_2 receptor-stimulating properties of (*S*)-UH-301 should thus not explain its antagonism of 8-OH-DPAT-induced effects in the present study. It should be noted that possible weak intrinsic activity of 8-OH-DPAT and (*S*)-UH-301 at brain DA receptors may show as agonist or antagonist properties depending on test situation, and it can not be excluded that further studies will disclose complex interactions between 8-OH-DPAT and (*S*)-UH-301 on the one hand, and raclopride on the other. For reasons discussed above, however, such effects should not be of importance here.

(−)Pindolol and certain other β-blocking agents have been found to possess 5-HT receptor antagonist properties and display selective affinity for the 5-HT_1 receptor site (see introduction). In the present study, however, (−)pindolol in a dose (2.0 mg kg^{-1}) that effectively antagonises 8-OH-DPAT-induced hypothermia and suppression of locomotor activity in rats (13,21) did not antagonise the effects of 8-OH-DPAT on raclopride-induced catalepsy. In fact, (−)pindolol by itself counteracted the catalepsy produced by raclopride. This effect of (−)pindolol, however, is probably due to its β-receptor-blocking properties, since the selective β-receptor blocker betaxolol (4 mg kg^{-1}) (8) was equally effective in this regard. It should be noted, however, that (−)pindolol, in contrast to (*S*)-UH-301, has some intrinsic activity at brain 5-HT_{1A} receptors (18), and it cannot be excluded that such properties also may contribute to the effects of (−)pindolol in the present study.

In view of the findings that both (−)pindolol and betaxolol antagonised the raclopride-induced catalepsy, it is interesting to note that β-blockers in some studies have been claimed to antagonise acute and late-occuring neuroleptic-induced extrapyramidal motor side effects (see introduction). This contention is further supported by the observation that the DA-β-hydroxylase inhibitor fusaric acid has been shown to antagonise symptoms of tardive dyskinesia (26).

In conclusion: In agreement with previous results from this laboratory, 8-OH-DPAT completely antagonised the catalepsy induced by raclopride. The antagonism by (*S*)-UH-301 of this effect by 8-OH-DPAT provides further support for specific 5-HT_{1A}/DA D_2 receptor interactions in the mediation of extrapyramidal motor functions in the rat.

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