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Antagonism by the 5-$HT_{2A/C}$ receptor agonist DOI of raclopride-induced catalepsy in the rat

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Abstract

It has been shown that the administration of 5-hydroxytryptamine (5-HT)$_{1A}$ receptor agonists will antagonize the catalepsy induced by dopamine D_1 or D_2 receptor blocking agents. In the present study, administration of the 5-$HT_{2A/C}$ receptor agonist, 1-(2,5-dimethoxy-4-iodo)-2-aminopropane (DOI) (1 mg kg^{-1} s.c.), counteracted the catalepsy produced by the dopamine D_2 receptor antagonist, raclopride (16 mg kg^{-1} s.c.), but not by the dopamine D_1 receptor antagonist, (*R*)-(+)-8-chloro-2,3,4,5-tetra-hydro-3-methyl-5-phenyl-1*H*-3-benzazepine (SCH 23390) (0.2 mg kg^{-1} s.c.). The effects of DOI on raclopride-induced catalepsy were fully antagonized by pretreatment with the 5-$HT_{2A/C}$ receptor antagonist, ritanserin (2 mg kg^{-1} s.c.). The 5-HT precursor, 5-hydroxytryptophan (5-HTP) (6.25–25.0 mg kg^{-1} i.p.), in combination with the peripheral 5-HTP decarboxylase inhibitor, benserazide (25 mg kg^{-1} i.p.), and the selective serotonin reuptake inhibitor, zimeldine (10 mg kg^{-1} s.c.), enhanced the catalepsy produced by a low dose of raclopride (4 mg kg^{-1} s.c.). It is concluded that stimulation of (postsynaptic) 5-HT_2 receptors results in antagonism of the catalepsy induced by treatment with a dopamine D_2, but not a D_1, receptor antagonist. The fact that 5-HTP, in the presence of benserazide and zimeldine, enhanced raclopride-induced catalepsy suggests the possibility of postsynaptic 5-HT receptors acting in opposition to the 5-HT_1 and 5-HT_2 receptors, as regards extrapyramidal motor functions in the rat.

Keywords: Catalepsy; Dopamine; 5-HT (5-hydroxytryptamine, serotonin); Receptor; (Rat)

1. Introduction

It has been shown that treatment with 5-hydroxytryptamine (5-HT) receptor agonists, selective for the 5-HT_{1A} receptor subtype, can antagonize neuroleptic-induced catalepsy in rats (Invernizzi et al., 1988; McMillen et al., 1988; Broekkamp et al., 1988; Hicks, 1990). It was recently shown that this applies to catalepsy induced by either of the selective dopamine D_1 and D_2 receptor antagonists SCH 23390 (Iorio et al., 1983) and raclopride (Köhler et al., 1985), respectively (Wadenberg and Ahlenius, 1991; Wadenberg, 1992). Results from studies where the selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (Hjorth et al., 1982), was applied locally, suggest that the midbrain raphe is an important target for effects of 5-HT_{1A} receptor agonists on neuroleptic-induced catalepsy (Invernizzi et al., 1988). These findings were confirmed and extended in a recent series of experiments, indicating a preferential involvement of 5-HT_{1A} autoreceptors in the median raphe nucleus (Wadenberg et al., 1993; Wadenberg and Hillegaart, 1995).

It should be noted, however, that stimulation of brain 5-HT_2 receptors by means of the selective agonist, 1-(2,5-dimethoxy-4-iodo)-2-aminopropane (DOI) (Glennon et al., 1988), has been shown to antagonize neuroleptic-induced catalepsy in rats (Hicks, 1990; Elliott et al., 1990). In apparent contrast to these observations and to the above-mentioned findings with 5-HT_{1A} receptor agonists, selective 5-HT neuronal reuptake inhibitors can produce catalepsy in combination with drug-induced impairment of dopaminergic neuro-

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transmission (Fuenmayor and Vogt, 1979; Waldmeier and Delini-Stula, 1979). In fact, the new generation selective serotonin reuptake inhibitors are known to precipitate parkinsonian symptoms in vulnerable individuals (Meltzer et al., 1979; Ketai, 1993; Ames et al., 1993).

The objective of the present study was to examine the effects of DOI on catalepsy induced by the selective dopamine D_1 and D_2 receptor antagonists, SCH 23390 and raclopride. Furthermore, the effect of unselective stimulation of brain 5-HT receptors induced by the 5-HT precursor, 5-hydroxytryptophan (5-HTP), on the onset and magnitude of raclopride-induced catalepsy was studied. In the latter study, all animals given 5-HTP were pretreated with the selective 5-HT reuptake inhibitor, zimeldine (Ross et al., 1976), and the inhibitor of peripheral 5-HTP decarboxylase, benserazide (Bartholini et al., 1967).

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats, 250–300 g (B&K Universal, Sollentuna, Sweden), were used. The rats arrived from the breeder at least one week before being used in experiments, and were housed under constant conditions of temperature (21.0 ± 0.4°C), relative humidity (50–60%) and light-dark cycle (12:12 h, lights off 06.00 h). Food (R36, Ewos, Södertälje, Sweden) and tap water were available ad libitum.

2.2. Catalepsy

The 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 ≥ 2.25 min it was scored as 5, etc. (cf. Ahlenius and Hillegaart, 1986).

2.3. Drugs

The following drugs were used: raclopride tartrate (Astra, Södertälje, Sweden), (*R*)-(+)-8-chloro-2,3,4,5-tetra-hydro-3-methyl-5-phenyl-1*H*-3-benzazepine (SCH 23390 HCl) (RBI, Natick, MA, USA), 1-(2,5-dimethoxy-4-iodo)-2-aminopropane (DOI) (RBI), ritanserin (Janssen, Beerse, Belgium), zimeldine HCl (Astra), benserazide HCl (Roche, Basel, Switzerland), 5-hydroxytryptophan (5-HTP) HCl (Sigma, St. Louis, MO, USA). Ritanserin was dissolved in a minimal amount of glacial acetic acid and was made up to volume with glucose. All other drugs were dissolved in physiological saline. Injections were made by the subcutaneous or the intraperitoneal route in a volume of 2 ml kg^{-1}. Doses refer to the form of the respective compound given above.

2.4. Statistics

Statistical evaluation was performed by means of the Kruskal-Wallis one-way analysis of variance (ANOVA) by ranks, followed by the Mann-Whitney *U*-test (Siegel and Castellan Jr., 1988) for comparisons with raclopride- or SCH 23390-treated controls.

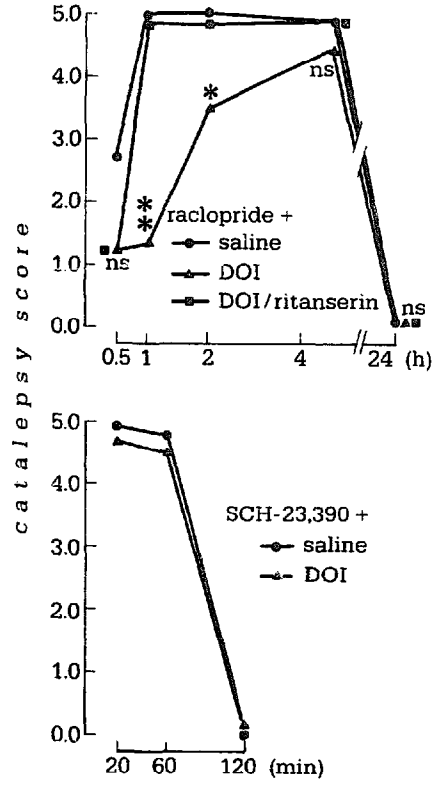

Fig. 1. Effects of DOI on raclopride- or SCH 23390-induced catalepsy in the rat. Raclopride (16 mg kg^{-1} s.c.) and SCH 23390 (0.2 mg kg^{-1} s.c.) were administered 30 and 20 min, respectively, before the first observation. DOI (1 mg kg^{-1} s.c.) was administered 10 min after raclopride and 5 min after SCH 23390. Ritanserin (2 mg kg^{-1} s.c.) was given 10 min before raclopride. Results are presented as medians based on observations of 6–12 animals per group (time-course of action was followed by repeated observations of the respective treatment group). Statistical analysis was performed by means of the Kruskal-Wallis one-way ANOVA by ranks, followed by the Mann-Whitney *U*-test (Siegel and Castellan Jr., 1988) for comparisons between animals given raclopride or SCH 23390 alone, and animals given raclopride or SCH 23390 in combination with DOI or DOI + ritanserin, at the different time intervals. $^{ns}P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$.

3. Results

3.1. Antagonism by DOI of raclopride-induced catalepsy

Raclopride (16 mg kg^{-1} s.c., −30 min) produced maximal catalepsy 1 h after administration with a duration of at least 4 h. Co-treatment with DOI (1 mg kg^{-1} s.c., −20 min) produced a statistically significant antagonism of the raclopride-induced catalepsy at the 1- and at the 2-h time intervals. This effect of DOI was completely antagonized by pretreatment with ritanserin (2 mg kg^{-1} s.c., −40 min) (Fig. 1, top). The animals were fully recovered when observed 24 h after raclopride treatment.

3.2. Effects of DOI on SCH 23390-induced catalepsy

SCH 23390 (0.2 mg kg^{-1} s.c., −20 min) produced maximal catalepsy 20 min after administration, and the effect had a duration of less than 2 h. Co-administration of DOI (1 mg kg^{-1} s.c., −15 min) had no effect on the SCH 23390-induced catalepsy (Fig. 1, bottom).

DOI (1 mg kg^{-1} s.c., −20 min), by itself, had no effect in the catalepsy model (data not shown), and unpublished observations from this laboratory have shown that ritanserin, in doses as high as 5 mg kg^{-1} s.c., does not produce catalepsy.

3.3. Effects of 5-HTP on raclopride-induced catalepsy

5-HTP (6.25 mg kg^{-1} i.p., −30 min), in combination with zimeldine (10 mg kg^{-1} s.c., −60 min) and benserazide (25 mg kg^{-1} i.p., −60 min) produced a faster onset of the raclopride (4 mg kg^{-1} s.c., −30 min) -induced catalepsy. There was also a tendency to an enhanced intensity of the effect of raclopride in animals thus treated, although this could not be verified statistically (Fig. 2). Also higher doses of 5-HTP (12.5 and 25 mg kg^{-1} i.p.) were given in combination with zimeldine and benserazide with the same result (data not shown). Pretreatment with zimeldine and benserazide alone resulted in a faster onset of the raclopride-induced catalepsy.

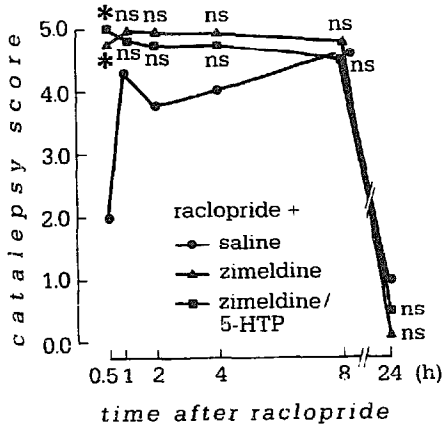

Fig. 2. Effects of 5-HTP, in combination with zimeldine and benserazide, on raclopride-induced catalepsy in the rat. Raclopride (4 mg kg^{-1} s.c.) and 5-HTP (6.25 mg kg^{-1} i.p.) were administered 30 min, whereas zimeldine (10 mg kg^{-1} s.c.) and benserazide (25 mg kg^{-1} i.p.) were administered 60 min before the first observation. Results are presented as medians based on observations of 8 animals per group. Statistical analysis as in Fig. 1. $^{ns}P > 0.05$, $^{*}P < 0.05$.

4. Discussion

The selective 5-HT_2 receptor agonist, DOI, was found to be as effective as the selective 5-HT_{1A} agonist, 8-OH-DPAT (see Introduction), in its ability to antagonize the catalepsy induced by dopamine D_2 receptor blockade. This effect of DOI was completely antagonized by pretreatment with the selective 5-$HT_{2A/C}$ receptor antagonist, ritanserin (see Humphrey et al., 1993), in support of an anticataleptic effect of DOI mediated via this serotonin receptor subtype. There is a relatively high density of 5-HT_2 receptors in the dopamine-rich neostriatum in the rat as well as in the human brain, providing a possible site for the interactions between DOI and raclopride observed in the present study. 5-HT_2 receptors, however, have a wider distribution in the forebrain, including limbic forebrain and neocortex (Hoyer et al., 1986; Pazos et al., 1987), and it cannot be excluded that extra-striatal interactions with dopaminergic mechanisms may be responsible directly or indirectly for the observed effects of DOI on raclopride-induced catalepsy.

As mentioned in the Introduction, there is strong evidence for stimulation of median raphe 5-HT_{1A} autoreceptors being responsible for the antagonism by 8-OH-DPAT of raclopride-induced catalepsy. In contrast, the 5-$HT_{2A/C}$ receptors appear to have a postsynaptic location (Leysen et al., 1983). Thus, stimulation of postsynaptic 5-$HT_{2A/C}$ receptors on target neurons of serotonergic projections to the forebrain should be responsible for effects produced by DOI in the present and previous studies (Hicks, 1990; Elliott et al., 1990).

In the present study DOI did not antagonize the catalepsy induced by the selective dopamine D_1 receptor antagonist, SCH 23390. In view of differences in the distribution of dopamine D_1 and D_2 receptors, pre- and postsynaptically, in the basal ganglia (Boyson et al., 1986), this observation suggests the possibility of a different functional coupling between serotonergic and dopaminergic mechanisms, depending on dopamine receptor subtype. It should be noted, how-

ever, that SCH 23390 itself has affinity for the 5-HT_2 receptor site, presumably as an antagonist (Hicks et al., 1984; Bishoff et al., 1986).

The selective 5-HT neuronal reuptake inhibitor, zimeldine, alone and in combination with 5-HTP produced a faster onset of the raclopride-induced catalepsy and also tended to enhance the intensity of the catalepsy. These effects seem to be postsynaptically mediated, since the co-treatment with 5-HTP did not alter the effect of zimeldine alone. The present findings receive support from earlier studies with the selective serotonin reuptake inhibitors citalopram and fluoxetine (Waldmeier and Delini-Stula, 1979). In general agreement with these observations, midbrain raphe lesions or treatment with the tryptophan hydroxylase inhibitor, *p*-chlorophenylalanine, have been shown to counteract haloperidol- or chlorpromazine-induced catalepsy (Kostowski et al., 1972; Gumulka et al., 1973). These findings suggest that a general increase in the availability of synaptic 5-HT can enhance neuroleptic-induced catalepsy, whereas decreased synaptic 5-HT will ameliorate the catalepsy thus induced. In all probability these alterations result in increased and decreased postsynaptic 5-HT receptor stimulation. The fact that raphe lesions and *p*-chlorophenylalanine both counteract neuroleptic-induced catalepsy is in agreement with the finding that stimulation of median raphe 5-HT_{1A} autoreceptors is equally effective in this regard (Invernizzi et al., 1988; Wadenberg and Hillegaart, 1995). The present results suggest that postsynaptic 5-HT_2 receptor stimulation also constitutes a possibility for achieving this effect. Thus, the observations of enhanced catalepsy as a result of treatment with selective serotonin reuptake inhibitors, also in combination with 5-HTP as shown here, suggest mediation via postsynaptic 5-HT receptors other than 5-HT_1 or 5-HT_2.

In conclusion, the stimulation of 5-HT_2 receptors, presumably postsynaptically located, results in antagonism of the catalepsy induced by treatment with a dopamine D_2, but not D_1, receptor antagonist. The fact that 5-HTP, in the presence of benserazide and zimeldine, enhanced the raclopride-induced catalepsy, suggests the possibility of postsynaptic 5-HT receptors acting in opposition to the 5-HT_1 and 5-HT_2 receptors, as regards extrapyramidal motor functions in the rat.

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