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Central β-adrenoceptors can modulate 5-hydroxytryptamine-induced tremor in rats

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1 The effects of two β_2-adrenoceptor agonists with different lipophilicities were studied on tremor induced by L-5-hydroxytryptophan (L-5-HTP) in pargyline- and carbidopa-pretreated rats.

2 Tremor was recorded and analysed by an objective method based on accelerometry.

3 Clenbuterol, a lipophilic β_2-selective agonist, dose-dependently enhanced tremor intensity, whereas the hydrophilic β_2-agonist terbutaline had no effect.

4 The clenbuterol-induced enhancement of tremor was completely abolished by the β_2-selective antagonist ICI 118,551 but unchanged by the β_1-selective antagonist metoprolol.

5 The results suggest that centrally located β_2-adrenoceptors can mediate a modulation of 5-hydroxytryptamine-induced tremor in rats.

Introduction

Although the existence of β-adrenoceptors in the brain is now established, their functional significance remains largely unknown. It has been shown that β-adrenoceptor agonists acutely potentiate various forms of 5-hydroxytryptamine (5-HT)-mediated behaviour (Ortmann *et al.*, 1981; Cowen *et al.*, 1982; Nimgaonkar *et al.*, 1983) and increase 5-HT synthesis (Waldmeier, 1981). Thus, it has been proposed that there is an interaction between β-adrenoceptor agonists and central 5-HT systems, but the underlying mechanism of this interaction is unclear. In these previous studies, the effects of β-agonists have mainly been assessed by automated recording of hyperactivity and/or subjective scoring of other components of the 5-HT-induced syndrome (see Jacobs, 1976; Green & Heal, 1985).

Recently, an objective accelerometry-based method for tremor recording in conscious, unrestrained rats has been developed in our laboratory (Hallberg *et al.*, 1985). This provided an alternative way of studying the possible role of central β-adrenoceptor involvement in the modulation of 5-HT-mediated behaviour. In the present study, tremor was induced by a low dose of L-5-hydroxytryptophan (L-HTP) in rats pretreated with the irreversible monoamine oxidase inhibitor (MAOI) pargyline and the peripherally acting decarboxylase inhibitor carbidopa.

The aim of the study was to verify the involvement of a central β-adrenoceptor by comparing the effects of the lipophilic β_2-agonist clenbuterol (Kopitar & Zimmer, 1976) and the hydrophilic β_2-agonist terbutaline (Bodin *et al.*, 1972), and also to define the receptor subtype involved by subsequent blockade with the β_1-selective antagonist metroprolol (Åblad *et al.*, 1973) and the β_2-selective antagonist ICI 118,551 (Bilski *et al.*, 1983).

Methods

Animals

Male Sprague-Dawley rats, weighing 250–300 g, were used. They were housed in groups of three and kept on a 0700 h 00 min–1900 h 00 min light-dark cycle at constant temperature with free access to food and water. Rats were deprived of food the night before experiments, which were always performed between 09 h 00min and 15 h 00min.

Tremor measurements

Following the L-5-HTP injection, tremor intensity was continuously recorded for 120 min by means of a small accelerometer (Entran Devices Inc) mounted on the back of the freely moving rat. The signal was quan-

tified by a Grass Polygraph integrating unit, and the reset marks from the integrator were counted by a desktop computer (Luxor ABC-80). (For a detailed description, see Hallberg *et al.*, 1985.) Tremor intensity is expressed as the total sum of marks registered during the period 11–120 min following L-5-HTP, or as the mean number of marks per min during consecutive 5 min intervals. Student's *t* test was used for statistical analyses.

Drug regime

L-5-HPT (5 and 10 mg kg^{-1}) was administered via a tail vein 18–24 h after the irreversible MAOI pargyline (75 mg kg^{-1} i.p.) and 1 h after the peripherally acting aromatic amino acid decarboxylase inhibitor carbidopa (25 mg kg^{-1} i.p.). The dose of pargyline used in the present study consistently caused almost total MAO inactivation either 18 or 24 h after administration, i.e 92.6 and 92.5% inhibition of enzyme activity, respectively (Ross, personal communication). The β_2-adrenoceptor agonists, clenbuterol (0.1–4 mg kg^{-1} p.o.) and terbutaline (5 mg kg^{-1} p.o.), were given 1 h and 15 min, respectively, before L-5-HTP. The β_2-adrenoceptor antagonist ICI 118,551 (erythro-DL-1(7-methylindan-4-yloxy)-3-isopropylaminobutan -2-ol; 1 mg kg^{-1} i.p.) and the β_1-adrenoceptor antagonist metoprolol (2 mg kg^{-1} i.p.) were administered 30 min after L-5-HTP. Carbidopa, clenbuterol, and terbutaline were suspended in 1% Na-carboxymethyl cellulose. Immediately before administration, L-5-HTP was dissolved in a minute volume of 1 M HCl, diluted with 0.9% w/v NaCl solution (saline) and neutralized by $NaHCO_3$. All other drugs were dissolved in saline.

All doses refer to the salt and were given in a volume of 2 ml kg^{-1}. Oral administration was carried out with a stomach cannula. The following drugs were used: L-5-HTP and pargyline HCl (Sigma), carbidopa (Merck, Sharp & Dohme) generously donated by the supplier, metoprolol bitartrate (Hässle), terbutaline sulphate (Draco), clenbuterol HCl (Boehringer Ingelheim).

Results

Effects of β-adrenoceptor agonists on L-5-HTP-induced tremor

When rats pretreated with pargyline and carbidopa were given L-5-HTP (5 mg kg^{-1} i.v.), a consistent body tremor developed within about 30 min and continued for more than 2 h (Figure 1). Clenbuterol (0.1, 2, and 4 mg kg^{-1} p.o.) given 1 h before L-5-HTP caused a dose-dependent potentiation of tremor intensity, which was statistically significant with the two higher doses (Table 1a). Furthermore, a higher intensity of basal tremor induced by a higher dose of L-5-HTP (10 mg kg^{-1} i.v.) was also significantly potentiated by clenbuterol (2 mg kg^{-1} p.o.) pretreatment (Table 2a). Rats given clenbuterol alone in the same dose range did not develop tremor during an observation period of 4 h.

In contrast, pretreatment with terbutaline (5 mg kg^{-1} p.o.) 15 min before L-5-HTP (5 mg kg^{-1} i.v.) had no effect on tremor intensity (Table 1b).

Effect of β-adrenoceptor antagonists on the clenbuterol-induced potentiation of tremor induced by L-5-HTP

The potentiation of tremor produced by clenbuterol (2 mg kg^{-1}) was completely inhibited when ICI 118,551 (1 mg kg^{-1} i.p.) was given 30 min after L-5-HTP (5 mg kg^{-1} i.v.). Tremor intensity was suppressed to the same level as that in rats receiving saline instead of clenbuterol (Figure 1). On the other hand, metoprolol (2 mg kg^{-1} i.p.), also given 30 min after L-5-HTP, failed to alter the tremor potentiation produced by clenbuterol. Tremor intensity in the metoprolol-treated rats (expressed as the total sum of marks ± s.e.mean recorded during the period 11–120 min following L-5-HTP) was 3637 ± 314.1 ($n = 5$), which is not significantly different from 3678 ± 290.0 ($n = 6$) recorded in the corresponding saline-treated rats (cf. Figure 1).

When ICI 118,551 was administered 30 min after

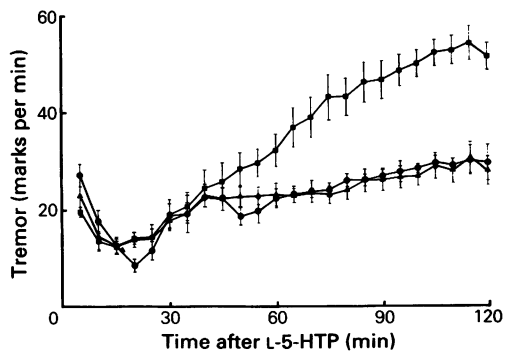

Figure 1 The effect of ICI 118,551 on clenbuterol-induced potentiation of tremor. Tremor was induced by L-5-hydroxytryptophan (L-5-HTP; 5 mg kg^{-1} i.v.) in rats pretreated with pargyline and carbidopa. Clenbuterol (2 mg kg^{-1}) or saline was administered orally 1 h before L-5-HTP, and ICI 118,551 (1 mg kg^{-1} i.p.) or saline was given 30 min after L-5-HTP. Each point represents the mean tremor intensity , with vertical lines showing s.e.mean, in consecutive 5 min intervals for 120 min after L-5-HTP, in groups is rats given clenbuterol + saline (■), $n = 6$; clenbuterol + ICI 118,551 (▲(, $n = 7$; and saline + saline (●), $n = 11$.

Table 1 Effect of β_2-agonists on 5-hydroxytryptamine-mediated tremor

Treatment	*Tremor intensity* *Marks*	Δ %	n
a			
Saline	2370 ± 144.0		(8)
Clenbuterol (0.1 mg kg^{-1})	3053 ± 348.5	+ 28.8	(6)
Clenbuterol (2.0 mg kg^{-1})	3558 ± 271.0**	+ 50.1	(7)
Clenbuterol (4.0 mg kg^{-1})	4164 ± 178.7***	+ 75.7	(5)
b			
Saline	2256 ± 162.7		(10)
Terbutaline (5 mg kg^{-1})	2288 ± 223.9	+ 1.4	(10)

Tremor was induced by L-5-hydroxytryptophan (L-5-HTP; 5 mg kg^{-1} i.v.) in rats pretreated with pargyline and carbidopa. (a) Saline or clenbuterol was given orally 1 h before L-5-HTP. (b) Saline or terbutaline was given orally 15 min before L-5-HTP. Tremor intensity is expressed as the total sum of marks ± s.e.mean recorded between 11 and 120 min following L-5-HTP administration in (*n*) rats. Also shown is the change in tremor intensity caused by clenbuterol or terbutaline, expressed as a % of the intensity in saline-treated rats. Values which are significantly different from those simultaneously recorded in saline-treated rats are indicated by asterisks: $^{**}P < 0.01$, $^{***}P < 0.001$.

L-5-HTP (10 mg kg^{-1} i.v.) to rats that were not pretreated with clenbuterol, no reduction in tremor intensity was observed (Table 2b).

Discussion

Several investigations have shown that administration of the 5-HT precursor L-5-HTP, alone or in combination with a MAOI, results in a behavioural syndrome that can be used for studies of brain 5-HT activity (Jacobs, 1976; Sloviter *et al.*, 1978; Ortmann *et al.*, 1980; for a review see Ortmann, 1984). It has been previously shown that L-5-HTP administered in relatively low doses (5–20 mg kg^{-1} i.v.) to rats pretreated with pargyline and the peripherally acting decarboxylase inhibitor carbidopa produces a distinct tremor with a dose-dependent intensity (Hallberg *et al.*, 1985).

Administration of hydrophilic β_2-agonists to conscious unrestrained rats has been shown not to induce tremor (Hallberg & Almgren, 1985), in contrast to the situation in man, where β_2-agonists readily produce tremor (Marsden *et al.*, 1967; Larsson & Svedmyr, 1977). Neither did clenbuterol, a β_2-adrenoceptor selective agonist (Engelhardt, 1976) that readily enters the brain (Kopitar & Zimmer, 1976), induce tremor when given alone in a dose of 0.1–4.0 mg kg^{-1} to rats

Table 2 The effect of clenbuterol and ICI 118,551 on tremor induced by L-5-hydroxytryptophan (L-5-HTP, 10 mg kg^{-1} i.v.)

Treatment	*Tremor intensity* *Marks*	Δ %	n
a			
Saline	3855 ± 241.8		(8)
Clenbuterol (2 mg kg^{-1} p.o.)	5534 ± 260.6***	+ 43.6	(6)
b			
Saline + saline	3931 ± 162.1		(5)
Saline + ICI 118,551 (1 mg kg^{-1} i.p.)	3970 ± 141.0	+ 1.0	(6)

(a) Saline or clenbuterol was given orally 1 h before L-5-HTP. (b) Saline was given orally 1 h before L-5-HTP and saline or ICI 118,551 was given 30 min after L-5-HTP. Tremor intensity is expressed as the total sum of marks ± s.e.mean registered between 11 and 120 min after L-5-HTP administration in (*n*) rats. Also shown is the change in tremor intensity caused by clenbuterol or ICI 118,551, expressed as a % of the intensity in the corresponding saline-treated rats. Values which are significantly different from those in saline-treated rats are indicated by asterisks: $^{***}P < 0.001$.

in the present study, which were subsequently kept under observation for 4 h.

In the present study, clenbuterol dose-dependently potentiated L-5-HTP-induced tremor intensity. Furthermore, various levels of 'basal' L-5-HTP-induced tremor could be potentiated by clenbuterol. In contrast, the β_2-agonist terbutaline (Bergman *et al.*, 1969), which is highly hydrophilic (Bodin *et al.*, 1972), did not potentiate the L-5-HTP-induced tremor. These data indicate that the β-adrenoceptors involved are located inside the blood-brain barrier. The time intervals between administration of agonist and L-5-HTP were based on pharmacokinetic data given by Kopitar & Zimmer (1976) for clenbuterol, and Nilsson *et al.* (1973) for terbutaline, and were chosen to obtain maximal plasma concentrations of the agonists during tremor recording.

The clenbuterol-induced potentiation is apparently associated with β_2-adrenoceptors, since it was completely inhibited by ICI 118,551, a β_2-selective antagonist (Bilski *et al.*, 1983), but was unaffected by metoprolol, an antagonist with β_1-selective properties (Åblad *et al.*, 1973). The ability of metoprolol to penetrate into the brain has been demonstrated by drug concentration measurements in brain tissue and in the CSF (Day *et al.*, 1977; Cruickshank, 1980). ICI 118,551 is likely to penetrate the blood-brain barrier even better, since the calculated partition coefficient in octanol/water greatly exceeds that of metoprolol and even that of the highly liposoluble β-adrenoceptor antagonist propranolol. Thus, the results with the antagonists give further support to the concept of a central localization of the β_2-adrenoceptors involved.

An interesting finding was that ICI 118,551 had no effect on the 'basal', i.e. unpotentiated, tremor when given after L-5-HTP. In this experiment, a higher L-5-HTP dose was given (10 mg kg^{-1} i.v.), since no effect of ICI 118,551 was found on the tremor induced by 5 mg kg^{-1} of L-5-HTP (data not shown). The tremor resulting from the lower dose of L-5-HTP is rather mild, and a reduction of a higher basal tremor intensity would have been more readily detectable. This finding cannot be explained at present and requires further investigation.

Recently, Nimgaonkar *et al.* (1983) showed that the clenbuterol-induced increase in brain 5-HT turnover was accompanied by a rise in free fatty acid (FFA) plasma concentration. An increase in plasma FFA has been shown to displace tryptophan from plasma albumin binding sites and thereby cause an increase in free tryptophan available for 5-HT synthesis (Curzon & Fernando, 1976). Thus, Nimgaonkar *et al.* (1983) conclude that there is probably no causal relationship between the acute clenbuterol-induced enhancement of brain 5-HT metabolism and the enhancement of 5-HT-mediated behaviour. This view is strongly supported by our observations, since metoprolol, which inhibits the catecholamine-induced rise in FFA (Åblad *et al.*, 1975), had no effect on the clenbuterol-induced potentiation of 5-HT-mediated tremor, whereas ICI 118,551, which has no effect on lipolysis (Smith *et al.*, 1983), inhibited the potentiation.

Although our present results are mainly in accordance with earlier findings by other investigators, some discrepancies remain. Both Ortmann *et al.* (1981) and Cowen *et al.* (1982) observed a potentiation of 5-HT-mediated behaviour with terbutaline. However, they gave intraperitoneal doses that were 5–6 times higher than the present oral doses, in all probability yielding considerably higher plasma terbutaline concentrations than in the present experiments (Nilsson *et al.*, 1973). Although terbutaline is highly hydrophilic, it is possible that some drug enters the brain after such high doses, and this would explain the apparent discrepancy. The dose of terbutaline given in the present experiments, 5 mg kg^{-1} p.o., is sufficient for adequate peripheral β_2-adrenoceptor stimulation (Malatray *et al.*, 1977).

Cowen *et al.* (1982) found that the β_2-antagonist butoxamine had no effect on the clenbuterol-induced hyperactivity produced by the 5-HT agonist quipazine, in contrast to the clear-cut effect of ICI 118,551 in the present study. This difference is probably due to the low potency of butoxamine (O'Donnell & Wanstall, 1979). In the same study, Cowen *et al.* also showed an inhibitory effect of the β_1-antagonist metoprolol, which was found to have no effect in the present study. Since the doses employed in the two studies, 2 and 5 mg kg^{-1}, i.p. respectively, are within the selectivity range, the discrepancies are, in all probability, due to the differences in experimental models. In the study of Cowen *et al.* (1982) hyperactivity was measured for 60 min after quipazine in rats pretreated with metoprolol, whereas the effect on tremor in our study was quantified for 120 min after L-5-HTP with metoprolol present for the last 90 min. Also the possibility that dopamine is more involved in hyperlocomotion than in tremor and related behaviour (see Green & Heal, 1985) might be of importance. The remaining discrepancies may be due to variations in pharmacological models and in methods for data evaluation.

Opinions vary as to whether it is the 5-HT_1-receptor (Lucki *et al.*, 1983) or the 5-HT_2-receptor (Peroutka *et al.*, 1981; Ortmann *et al.*, 1982) that is mainly responsible for the behavioural effects following central 5-HT activation. Clenbuterol, metoprolol, and ICI 118,551 have been shown to inhibit [^{3}H]-spiperone (5-HT_2-receptor) binding, but only at concentrations in the μM or higher range (Green *et al.*, 1983). Also propranolol is active in this concentration range at the 5-HT_1-receptor, as demonstrated with [^{3}H]-5-HT binding (Middlemiss, 1984). Therefore, it is unlikely that the

effect of these β-adrenoceptor active drugs on 5-HT behaviour is due to a direct action on central 5-HT_1- or 5-HT_2-receptors.

In conclusion, the present results suggest that centrally located β_2-adrenoceptors can mediate a modulation of 5-HT-induced tremor in rats. Furthermore, the tremor component of the 5-HT-syndrome can provide a useful supplementary model for evaluating drug effects on central 5-HT-systems.

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