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β-ADRENOCEPTOR AGONISTS ENHANCE 5-HYDROXYTRYPTAMINE-MEDIATED BEHAVIOURAL RESPONSES

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1 The β-adrenoceptor agonists, salbutamol, terbutaline and clenbuterol, were investigated for their effect on 5-hydroxytryptamine-mediated (5-HT) hyperactivity.

2 The lipophilic β-adrenoceptor agonist, clenbuterol (5 mg/kg) enhanced the behaviours induced by quipazine (25 mg/kg), including headweaving, forepaw treading and hind-limb abduction and thus increased automated activity recording. Clenbuterol (5 mg/kg) also enhanced the hyperactivity syndrome produced by the 5-HT agonist, 5-methoxy *N,N*-dimethyltryptamine (2 mg/kg) and the combination of tranylcypromine (10 mg/kg) and L-tryptophan (50 mg/kg). Salbutamol and terbutaline potentiated quipazine-induced hyperactivity only when given at the higher dose of 20 mg/kg.

3 The effect of clenbuterol in enhancing quipazine hyperactivity was blocked by the centrally acting β_1-adrenoceptor antagonist, metoprolol (5 mg/kg), but not by the β_2-adrenoceptor antagonist, butoxamine (5 mg/kg) or the peripherally acting β_1-adrenoceptor antagonist, atenolol (5 mg/kg).

4 Clenbuterol (5 mg/kg) did not enhance the circling responses produced by methamphetamine (0.5 mg/kg) in unilateral nigrostriatal-lesioned rats.

5 The results suggest that β-adrenoceptor agonists in common with some established antidepressant treatments produce enhancement of 5-HT-mediated behavioural responses.

Introduction

Repeated electroconvulsive shock (ECS), an effective antidepressant treatment in man (see Royal College Psychiat., 1977; Kendall, 1981), produces enhanced 5-hydroxytryptamine-mediated (5-HT) behavioural responses in experimental animals (Evans, Grahame-Smith, Green & Tordoff, 1976; Costain, Green & Grahame-Smith, 1979). It has been suggested that chronic tricyclic antidepressant administration can produce enhancement of some 5-HT-mediated behaviours (Friedman & Dallob, 1979) and both repeated ECS (De Montigny, 1981) and chronic tricyclic administration (De Montigny & Aghajanian, 1978) increase the response to iontophoretically applied 5-HT. However, many tricyclic antidepressants possess 5-HT antagonist properties (for review see Peroutka & Snyder, 1981). The precise role of 5-HT in the antidepressant effect of tricyclic drugs therefore remains uncertain.

Recently it has been found that salbutamol, a β-adrenoceptor agonist, exerts a rapid antidepressant action in depressed patients (Lecrubier, Peuch, Jouvent, Simon & Widlocher, 1980). We have therefore studied the effect of the acute administration of various β-adrenoceptor agonists on 5-HT-mediated hyperactivity responses produced either by administration of tranylcypromine and L-tryptophan (Grahame-Smith, 1971a), or the 5-HT agonists, quipazine (Green, Youdim & Grahame-Smith, 1976) and 5-methoxy *N,N*-dimethyltryptamine (5-MeODMT) (Grahame-Smith, 1971b). In addition, we have investigated the effect of β-adrenergic stimulation on dopamine-mediated behaviour, since repeated ECS has also been shown to produce enhancement of these responses (Green, 1980).

Methods

Animals

Male, Sprague-Dawley derived rats were used in all experiments. Rats for unilateral 6-hydroxydopamine lesioning of the substantia nigra weighed 250–300 g at the time of operation. Rats used in other experiments weighed 180–200 g. They were housed in groups of six in an 08 h 00 min–20 h 00 min light-dark cycle at constant temperature (20°C ± 1°C) and fed on an *ad libitum* diet of modified 41B pellets and

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tap water. All behavioural studies were performed between 09 h 30 min and 17 h 30 min.

Behavioural measures

5-HT-mediated behaviours were examined in the following ways. Groups of three rats were pretreated with the β-adrenoceptor agonist simultaneously with tranylcypromine (10 mg/kg) and 30 min later given L-tryptophan (50 mg/kg). Alternatively, pairs of rats were pretreated with the β-adrenoceptor agonist and 15 min later given either quipazine (25 mg/kg) or 5-MeODMT (2 mg/kg). Subsequent hyperactivity responses were measured on Automex meters (PMS Instruments, Slough). Results were analysed using Student's unpaired *t* test.

In some experiments the individual behavioural changes which occur following quipazine administration were rated. The following changes were scored at 10 min intervals (the observer being 'blind'): forepaw treading, headweaving, hind-limb abduction and Straub tail. The scoring was that previously employed (Deakin & Green, 1978; Green, Hall & Rees, 1981): 0 = absent; 1 = equivocal; 2 = present; 3 = severe. Results were analysed using Wilcoxon non-parametric statistics.

Dopamine-mediated behavioural responses were tested using the unilateral nigrostriatal-lesioned rat model of Ungerstedt (1971a, b). 6-Hydroxydopamine (8 μg) was unilaterally infused into the substantia nigra as previously described by Heal, Green & Buylaert (1980). Circling activity to both apomorphine and methamphetamine was measured in glass rotameter bowls (28 cm in diameter and 26 cm in height). Circling during 1 min was recorded at 10 min intervals following injection. Only rats that circled more than 5 turns/min to both apomorphine (2 mg/kg) and methamphetamine (2 mg/kg) were used. Results were analysed using Student's paired *t* test and analysis of variance.

Drugs

Drugs were obtained from the following sources: tranylcypromine (Smith, Kline & French), L-tryptophan, 5-MeODMT (Sigma), quipazine (Miles Laboratories), apomorphine (MacFarlan-Smith), clenbuterol (Boehringer-Ingelheim), terbutaline (Bricanyl, Astra), salbutamol (Ventolin, Allen & Hanburys), methamphetamine and butoxamine (Burroughs Wellcome), atenolol (ICI Pharmaceuticals), metoprolol (Astra).

All drugs were dissolved in 0.9% w/v NaCl solution (saline), except for the proprietary preparations mentioned above, which were diluted in pH 3 saline. Drugs were administered intraperitoneally, except where otherwise stated.

Results

Effect of β-adrenoceptor agonists on 5-hydroxytryptamine-mediated behaviours

None of the β-adrenoceptor agonists administered at doses employed in the subsequent experiments stimulated locomotor activity or produced stereotyped behaviour. However, when administered 15 min before quipazine (25 mg/kg), clenbuterol, produced marked enhancement of the behavioural responses at a dose of 5 mg/kg. This enhancement was detected by an increase in automated counts recorded on the Automex meters (Figure 1). In addition, the behavioural responses of headweaving, forepaw treading and hind-limb abduction were enhanced at all time points after the first 10 min. The Straub tail response was not enhanced (Figure 1). In view of this close correlation between the enhanced behaviours and the automated recorded counts, subsequent experiments are described only in terms of the automated counts.

Clenbuterol was still effective in increasing 5-HT-mediated responses at a dose of 0.25 mg/kg (Table 1). In contrast, neither salbutamol nor terbutaline enhanced the 5-HT-mediated hyperactivity syndrome produced by quipazine at a dose of 5 mg/kg. However, a dose of 20 mg/kg did result in an enhanced response (Table 1).

The effect of clenbuterol in enhancing 5-HT-mediated behaviour was confirmed by using other 5-HT-mediated behavioural models. Clenbuterol (5 mg/kg) enhanced the hyperactivity produced by the 5-HT agonist, 5-MeODMT (2.0 mg/kg) (Table 2) and also that seen following administration of the

Table 1 The effect of β-adrenoceptor agonists on the 5-hydroxytryptamine (5-HT)-mediated hyperactivity produced by quipazine

Pretreatment	*Activity counts (mean ± s.d.)*
Saline	2344 ± 265 (7)
Clenbuterol (0.25 mg/kg)	3093 ± 191 (4)**
Clenbuterol (5 mg/kg)	3516 ± 328 (3)**
Saline (pH 3)	2183 ± 372 (7)
Salbutamol (5 mg/kg)	2396 ± 623 (4)
Terbutaline (5 mg/kg)	2203 ± 359 (3)
Salbutamol (20 mg/kg)	3030 ± 178 (3)*
Terbutaline (20 mg/kg)	3541 ± 785 (3)*

The β-adrenoceptor agonist was injected intraperitoneally (i.p.) 15 min before quipazine, 25 mg/kg i.p. Activity counts are the number of counts for the 50 min following quipazine administration recorded by pairs of rats placed on Automex meter. The figure in parentheses is the number of pairs of animals tested.
Different from appropriate saline control: $*P<0.01$; $**P<0.001$.

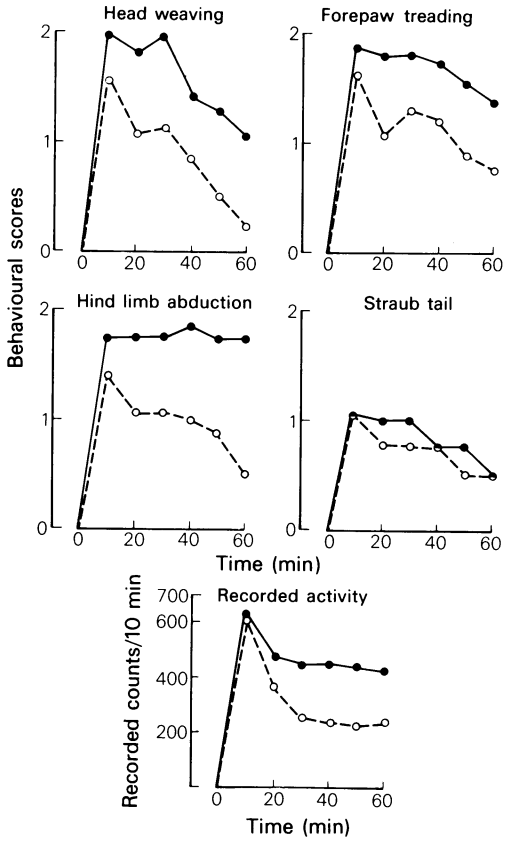

Figure 1 Effect of clenbuterol (5 mg/kg) pretreatment on the behavioural responses and recorded activity of pairs of rats following administration of quipazine (25 mg/kg). Rats were pretreated with saline (○) or clenbuterol (●) (5 mg/kg i.p.). Quipazine (25 mg/kg i.p.) was injected 15 min later (time zero) and the behavioural responses measured at 10 min intervals thereafter. Results shown as mean behavioural scores (8 animals in each group) against time after quipazine injection. Headweaving was enhanced ($P<0.01$) during the period 20–60 min. Forepaw treading ($P<0.02$ at 20 min; $P<0.05$ during period 30–60 min), hind-limb abduction ($P<0.05$ at 20 min; $P<0.01$ during period 30–60 min) and recorded activity ($P<0.05$ at 30, 50 and 60 min; $P<0.02$ at 40 min) were also enhanced by clenbuterol pretreatment. Total recorded activity also increased during the 60 min following quipazine ($P<0.025$).

monoamine oxidase inhibitor, tranylcypromine, (10 mg/kg) and L-tryptophan (50 mg/kg), a combination known to increase brain 5-HT concentrations (Table 2).

Effect of β-adrenoceptor antagonists on the clenbuterol-induced enhancement of quipazine hyperactivity

The β-adrenoceptor antagonists were injected 15 min before a subcutaneous injection of clenbuterol (2 mg/kg). Fifteen min later, quipazine (25 mg/kg) was administered. While metoprolol (5 mg/kg) blocked the clenbuterol-induced enhancement of quipazine hyperactivity, atenolol (5 mg/kg) and butoxamine (5 mg/kg) were without effect (Table 3). None of the β-adrenoceptor antagonists significantly reduced the baseline responses to quipazine (Table 3).

Effects of clenbuterol pretreatment of dopamine-mediated behavioural responses

Rats with unilateral lesions of the substantia nigra were first pretreated with clenbuterol (5 mg/kg). Fifteen min later the circling responses were tested to either methamphetamine (0.5 mg/kg) or apomorphine (0.5 mg/kg). The clenbuterol administration did not alter the ipsilateral circling response to the dopamine displacing agent, methamphetamine (Figure 2). The contralateral circling response to the dopamine agonist, apomorphine, was not different at

Table 2 The effect of clenbuterol on the hyperactivity syndromes produced by 5-methoxy *N,N*-dimethyltryptamine (5-MeODMT), and tranylcypromine (TCP) and L-tryptophan

Treatment		Activity counts (mean ± s.d.)
Saline	+ 5-MeODMT	807 ± 65 (4)
Clenbuterol	+ 5-MeODMT	1152 ± 92 (4)**
Saline	+ TCP/L-tryptophan	2306 ± 420 (4)
Clenbuterol	+ TCP/L-tryptophan	3492 ± 393 (4)*

Clenbuterol (5 mg/kg) was injected 15 min before 5-MeODMT (2 mg/kg) or together with TCP (10 mg/kg) 30 min before L-tryptophan (50 mg/kg). Results show the mean ± s.d. of activity counts in the 20 min following 5-MeODMT, or the 90 min following tryptophan. Animals were tested either in pairs (5-MeODMT) or in groups of three (TCP/L-tryptophan). The figure in parentheses refers to the number of groups of animals tested. Different from appropriate saline control: $*P<0.01$; $**P<0.001$.

Table 3 Effect of β-adrenoceptor antagonists on clenbuterol-induced enhancement of quipazine hyperactivity

Pretreatment		Activity counts (mean ± s.d)
Saline	+ saline	2108 ± 448 (3)
Saline	+ clenbuterol	2908 ± 189 (4)*
Metoprolol	+ saline	2005 ± 333 (5)
Metoprolol	+ clenbuterol	2298 ± 310 (5)
Butoxamine	+ saline	1723 ± 372 (3)
Butoxamine	+ clenbuterol	3355 ± 570 (3)**
Atenolol	+ saline	2090 ± 74 (3)
Atenolol	+ clenbuterol	2671 ± 230 (3)**

The β-adrenoceptor antagonists were injected i.p. in a dose of 5 mg/kg 15 min before either saline or clenbuterol 2 mg/kg subcutaneously. Quipazine 25 mg/kg i.p. was administered 15 min later. Activity counts were recorded as described in Table 1. The figure in parentheses is the number of pairs of animals tested. Different from appropriate saline control: $*P<0.05$; $**P<0.02$.

any time point or in total turns during the 60 min of the experiment. However, the rate of decline of the response was slower in the clenbuterol-treated rats (Figure 2).

Discussion

Clenbuterol, a β-adrenoceptor agonist (Engelhardt, 1976), enhanced the quipazine-induced behavioural syndrome and in particular was shown to enhance those behaviours thought to be mediated specifically by 5-hydroxytryptamine (Jacobs, 1974; Deakin & Green, 1978: Green *et al*, 1981; Deakin & Dashwood, 1981). Salbutamol and terbutaline also enhanced the 5-HT-mediated hyperactivity. The much greater potency of clenbuterol in producing this enhancement may reflect its lipophilicity, which results in good bioavailability in the central nervous system (Kopitar & Zimmer, 1976). In contrast, salbutamol and terbutaline have poor lipid solubility, and do not enter the brain well (Martin, Hobson, Page & Harrison, 1971; Bodin, Hansson, Ramsay & Ryrfeldt, 1972). A further indication that 5-HT-mediated be-

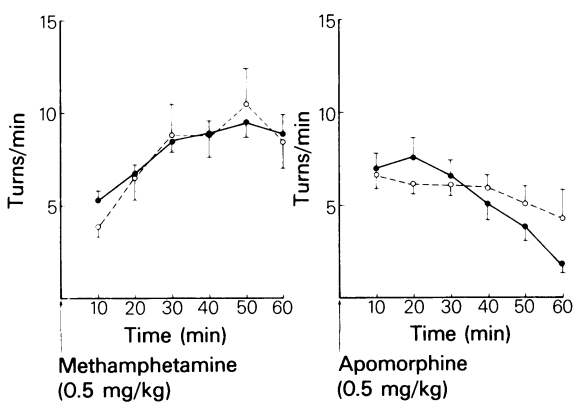

Figure 2 The effect of clenbuterol on circling responses of unilateral nigrostratal-lesioned rats. The circling responses of unilateral nigrostriatal-lesioned rats to methamphetamine (0.5 mg/kg) and apomorphine (0.5 mg/kg) were assessed following pretreatment with clenbuterol (5 mg/kg) 15 min earlier: (●) drug; (○) clenbuterol plus drug. Points represent the mean of number of turns in 1 min measured at 10 min intervals; vertical lines show s.e.mean. There was no difference in total turns or at any time point following either drug. However, the rate of decline was slower following clenbuterol in the apomorphine-treated rats ($P<0.005$).

haviours are enhanced by β-adrenoceptor agonists is the potentiation by salbutamol of the 5-hydroxytryptophan-induced head twitch (Delini-Stula, Vassout, Radeke & Ortmann, 1979). Recently both fenoterol and terbutaline have been shown to enhance this behaviour (Ortmann, Martin, Radeke & Delini-Stula, 1981) and we have observed that clenbuterol is also active in this respect (Cowen, Green & Nimgoankar, unpublished observation).

The interpretation that clenbuterol is acting centrally to produce enhancement of 5-HT-mediated behaviour is strengthened by the finding that the β_1-adrenoceptor antagonist, metoprolol, which enters the brain, blocked the clenbuterol-induced enhancement of quipazine hyperactivity, while atenolol, a β_1-adrenoceptor antagonist with limited brain penetration (Day, Hemsworth & Street, 1977), did not.

It is of interest that while the β-adrenoceptor agonists tested are classified as selective for β_2-adrenoceptors, the effect of clenbuterol was blocked by metoprolol, but not by the β_2-adrenoceptor antagonist, butoxamine. However, the selectivity of β-adrenoceptor agonists is not absolute, and may be dose-related (Lecler, Rouot, Vetty & Schwartz, 1981). It is therefore possible that clenbuterol produces enhancement of 5-HT-mediated responses by activation of central β_1-adrenoceptors, but the present experiments do not allow firm conclusions to be drawn on this point.

Non-selective β-adrenoceptor antagonists reduce 5-HT-mediated responses (Costain & Green, 1978; Weinstock, 1980) perhaps by direct blockade of 5-HT receptors (Middlemiss, Blakeborough & Leather, 1977). This finding raises the possibility that β-adrenoceptor agonists may produce their enhancement of 5-HT-mediated responses by interacting directly with 5-HT systems. However, none of the β-adrenoceptor agonists administered alone induced behaviours like those produced by increased brain 5-HT function (Grahame-Smith, 1971a), and, in addition, the effect of clenbuterol was blocked by the selective β_1-adrenoceptor antagonist, metoprolol. These experiments confirm an earlier report (Costain & Green, 1978) that selective β-adrenoceptor antagonists, either β_1 or β_2, do not inhibit the hyperactivity produced by increased 5-HT function.

The present experiments did not demonstrate an enhancing effect of clenbuterol on dopamine-mediated behaviours other than a slowing of the rate of decline of apomorphine-induced circling. The significance of this observation is unclear since there were no indications of a change in response following methamphetamine. It may be that the slower decline is evidence of clenbuterol producing a change in the pharmacokinetic characteristics of apomorphine. Since the circling responses are a measure of nigrostriatal function, we cannot exclude the possibility that clenbuterol may alter dopamine-mediated responses in other brain regions.

It has been suggested that the antidepressant effect of salbutamol might be associated with an action on β-adrenoceptor function (Lerer, Ebstein & Belmaker, 1981). However, our data and those of Waldmeier (1981) suggest that changes in 5-HT biochemistry and function might also be involved. If the antidepressant effect of salbutamol is associated with the stimulation of central β-adrenoceptors it is possible that the relative antidepressant potency of clenbuterol may be somewhat greater.

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