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β-ADRENOCEPTOR ANTAGONISTS INHIBIT THE BEHAVIOURAL RESPONSES OF RATS TO INCREASED BRAIN 5-HYDROXYTRYPTAMINE

D.W. COSTAIN & A.R. GREEN

MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE

1 The effect of various β-adrenoceptor blocking agents on the 5-hydroxytryptamine (5-HT)-induced hyperactivity response produced in rats by administration of tranylcypromine (10 mg/kg i.p.) followed by L-tryptophan (50 mg/kg i.p.) has been investigated.

2 (±)-Alprenolol, (±)-timolol, (±)-sotalol, (±)-pindolol (all at 40 mg/kg) all inhibited the hyperactivity response to some degree when given 45 min before the tranylcypromine, as did (±)-oxprenolol when given after the L-tryptophan.

3 β-Adrenoceptor antagonists that are not found in the brain in appreciable amount after peripheral injection, (±)-atenolol, (±)-practolol, (±)-labetalol and (±)-acebutalol, did not inhibit the 5-HT-mediated behaviour.

4 Neither the β_1-selective drug (±)-metoprolol, nor the β_2-selective drug (±)-butoxamine inhibited the behavioural response.

5 The drugs that blocked the 5-HT-mediated behaviour did not alter brain 5-HT concentrations, synthesis rate or the accumulation of 5-HT following tranylcypromine/L-tryptophan. However, they did inhibit the hyperactivity produced by the suggested 5-HT agonist, 5-methoxy *N,N*-dimethyltryptamine, indicating that the β-adrenoceptor blocking drugs were inhibiting the post-synaptic 5-HT-mediated response.

6 Circling produced by methamphetamine (3 mg/kg) in unilateral nigro-striatal lesioned rats was not altered by alprenolol, sotalol, pindolol or metaprolol, indicating that these drugs do not alter dopamine-mediated behaviour.

7 It is concluded that non-selective (β_1 and β_2) adrenoceptor antagonists which have a high brain/blood ratio following their peripheral injection, block 5-HT-mediated behavioural responses in the rat.

Introduction

When rats are pretreated with (−)-propranolol the 5-hydroxytryptamine (5-HT)-induced hyperactivity response, which follows administration of tranylcypromine and L-tryptophan, is inhibited (Green & Grahame-Smith, 1976). The results were interpreted as indicating that propranolol was inhibiting the central 5-HT-mediated behaviour by blocking the post-synaptic response to 5-HT.

We have now examined the effect of other β-adrenoceptor antagonists on both brain 5-HT and dopamine-induced behavioural responses. Results suggest that several β-adrenoceptor antagonists besides propranolol inhibit central 5-HT-induced behavioural responses while not affecting dopaminergic responses.

Methods

Animals

Adult male Sprague–Dawley derived rats (Anglia Laboratory Animals, Alconbury, Huntingdon) were used, weighing 150 to 200 g for the hyperactivity experiments and biochemical investigations and weighing 300 g (at operation) in the experiments with unilateral nigro-striatal lesioned rats.

Drugs

Drugs were obtained from the following sources: 6-hydroxydopamine, L-tryptophan, methamphetamine, alprenolol (Sigma, London); tranylcypromine (Smith, Kline & French); oxprenolol (Ciba); acebuta-

lol (May & Baker); sotalol (Duncan Flockhart); metoprolol (Astra); timolol (Merck, Sharp & Dohme); pindolol (Sandoz); labetalol (Allen & Hanburys); propranolol, atenolol, practolol (ICI Pharmaceuticals); butoxamine (Burroughs Wellcome). 6-Hydroxydopamine was prepared and injected as described in the lesion methods (see below). Other drugs were dissolved in 0.9% w/v NaCl solution (saline) except for pindolol and practolol which were suspended in saline containing 1% carboxymethylcellulose and injected intraperitoneally. Doses of drugs refer to the weight of the salt where used.

Biochemical methods

Brain 5-HT was measured by the method of Curzon & Green (1970). 5-HT synthesis was determined by the method of 5-HT accumulation following brain monoamine oxidase inhibition with tranylcypromine as described by Neff & Tozer (1968).

Preparation of 6-hydroxydopamine nigro-striatal lesioned rats

Rats weighing 300 g were anaesthetized with Equithesin (Jensen-Salsbery Labs) and positioned in a stereotaxic apparatus. 6-Hydroxydopamine hydrobromide (2 mg base/ml; freshly dissolved in cold saline containing 1 mg/ml ascorbic acid) was injected unilaterally through a 30 gauge stainless steel needle aimed at the substantia nigra. The co-ordinates of the cannula tip were 2.8, 2.0, 8.0, according to the atlas of Pellegrino & Cushman (1967).

Behavioural measurements

For investigation of the effects of the β-adrenoceptor antagonists on the 5-HT-induced hyperactivity syndrome the following protocol was used initially. Groups of 3 rats were injected with either saline (control) or β-adrenoceptor antagonist (40 mg/kg); 45 min later both groups were injected with tranylcypromine (10 mg/kg), L-tryptophan (50 mg/kg) being given 30 min later. Activity was measured for the 90 min following the tryptophan injection and results are expressed as a mean ± s.d. of the total movements of each experiment during this time and results were analysed by an unpaired t test. Animals were killed at the end of this period and brains removed for analysis of 5-HT. Activity was measured on LKB Animex meters (sensitivity and tuning: 30 μA) as described elsewhere (Grahame-Smith, 1971a; Green & Grahame-Smith, 1974).

Circling in unilateral nigro-striatal lesioned rats was measured in glass rotometer bowls measuring 28 cm in diameter and 26 cm in height. Circling was measured over 1 min at 10 min intervals for the 90 min following administration of methamphetamine (3 mg/kg). Rats which responded to methamphetamine (5 mg/kg) with at least 10 turns/min (ipsilaterally) were used, testing being performed at least 10 days after lesioning. Control experiments carried out before and at the end of the experiments with the β-adrenoceptor antagonists showed that the degree of turning did not alter significantly during this time. The effect of the β-adrenoceptor antagonists on circling was examined by injection of the appropriate drug (40 mg/kg) 45 min before methamphetamine (3 mg/kg). Total turns during the 90 min following methamphetamine were recorded and changes assessed by a paired t test. Results are expressed as percentage change in the total number of turns following administration of the β-adrenoceptor antagonist compared to control values.

Results

Effects of alprenolol and atenolol on tranylcypromine/L-tryptophan-induced hyperactivity

There is a large variation in the degree to which various β-adrenoceptor blocking drugs enter the brain. Both labetalol and atenolol are said to enter the brain in negligible quantity, while practolol and acebutalol can be found in the brain after peripheral injection, although the concentration is very low compared with drugs like propranolol and alprenolol (see references in the footnotes to Table 1). While presumably the brain concentration of practolol and the other drugs could be increased by increasing the dose given, this would necessitate giving toxic doses of these drugs. For the purposes of this study, therefore, these drugs have been designated as having poor entry into the brain.

In the previous study (Green & Grahame-Smith, 1976), (±)-propranolol (40 mg/kg) inhibited the hyperactivity syndrome, while (±)-practolol (40 mg/kg) was without effect. This could be explained on the basis of their entry into the brain. Initially, therefore, we compared the effect of another β-blocker known to enter the brain (alprenolol) with one taken up poorly into the brain (atenolol).

(±)-Alprenolol (40 mg/kg) almost totally blocked the hyperactivity response to tranylcypromine/L-tryptophan while (±)-atenolol (40 mg/kg) was without effect (Figure 1). Alprenolol inhibited all aspects of the behavioural changes seen after tranylcypromine and L-tryptophan.

Effects of other β-adrenoceptor antagonists on the tranylcypromine/L-tryptophan hyperactivity

We next examined the effect of a number of β-adrenoceptor antagonists, both those with good entry into

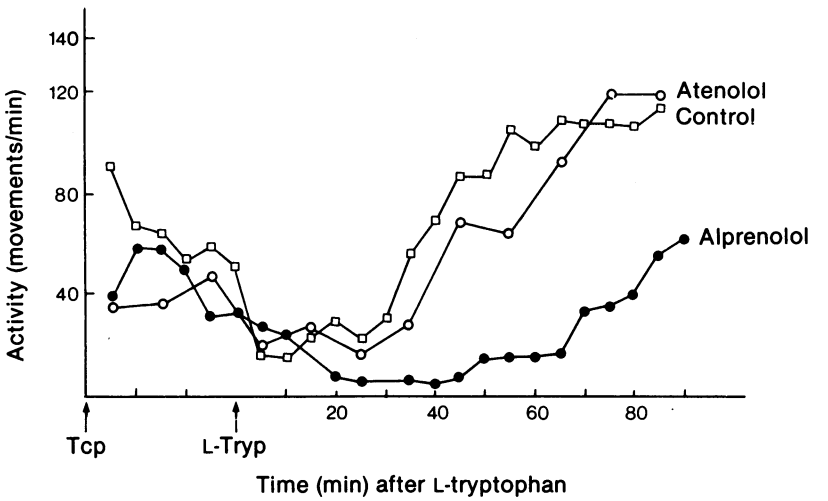

Figure 1 Effects of (±)-alprenolol (●) and (±)-atenolol (○) on tranylcypromine/L-tryptophan-induced hyperactivity (□ = control). Rats were injected with atenolol (40 mg/kg), alprenolol (40 mg/kg) or saline. Forty-five min later all groups were injected with tranylcypromine (Tcp, 10 mg/kg); L-tryptophan (L-Tryp; 50 mg/kg) was given 30 mins later. Figure shows typical response; statistical evaluation given in Table 1.

the brain and those with poor entry. Among these were some showing cardioselectivity (β_1-adrenoceptors only) butoxamine (β_2-adrenoceptors only), and labetalol, which is an α, β_1 and β_2-adrenoceptor antagonist.

The effect of pretreatment with these compounds on the hyperactivity is shown in Table 1. Compounds that have been shown to enter the brain poorly did not block the 5-HT-induced behavioural responses. All β-blockers entering the brain with the exception of metoprolol, butoxamine and oxprenolol inhibited to some extent the behavioural responses.

The *in vitro* data of Middlemiss, Blakeborough & Leather (1977) showed that β_1-selective blockers do not block 5-HT binding to its receptor protein, thereby explaining the failure of metoprolol to block the response. Our results with butoxamine suggest β_2-selectivity also results in the drug being an ineffective inhibitor of the hyperactivity. Oxprenolol, however, is not selective (β_1 and β_2) and was shown to be a potent inhibitor in this *in vitro* test. We therefore examined the reason for its failure to inhibit the syndrome.

Effect of administration of oxprenolol on the tranylcypromine/L-tryptophan hyperactivity when given 30 min after L-tryptophan

The concentration of oxprenolol in the brain falls rapidly soon after its peripheral injection and is almost undetectable in this tissue after 60 min (Riess, Rajagopolar, Imhof, Schmid & Keberle, 1970). This seemed to be the probable reason for this drug failing to inhibit the hyperactivity syndrome since it was being given over 100 min before marked behavioural changes occurred. When (±)-oxprenolol (40 mg/kg) was given 30 min after L-tryptophan it blocked the appearance of the behavioural changes for at least a further 30 min. After this time the hyperactivity rapidly increased to expected levels (Figure 2).

Effects of β-adrenoceptor antagonists on brain 5-hydroxytryptamine metabolism

The concentration of 5-HT in the brain was measured 45 min after administration of the β-adrenoceptor antagonists. Synthesis rates were assessed by examination of the accumulation of 5-HT 60 min after injection of tranylcypromine (10 mg/kg), which had been given 45 min after the β-adrenoceptor antagonist. The accumulation of 5-HT in the brain at the end of the activity experiments (i.e. 90 min after L-tryptophan) was also examined.

While there were minor differences in the steady state concentration of 5-HT in the brain following β-adrenoceptor antagonist administration (Table 2) none of these changes was statistically significant.

Both oxprenolol and labetalol treated rats accumulated less 5-HT than control animals during the 60 min following tranylcypromine. However, neither of these drugs inhibited the behavioural responses and drugs which did inhibit the response showed no alteration of 5-HT synthesis. Nor did any of these drugs inhibit accumulation of 5-HT following tranylcypro-

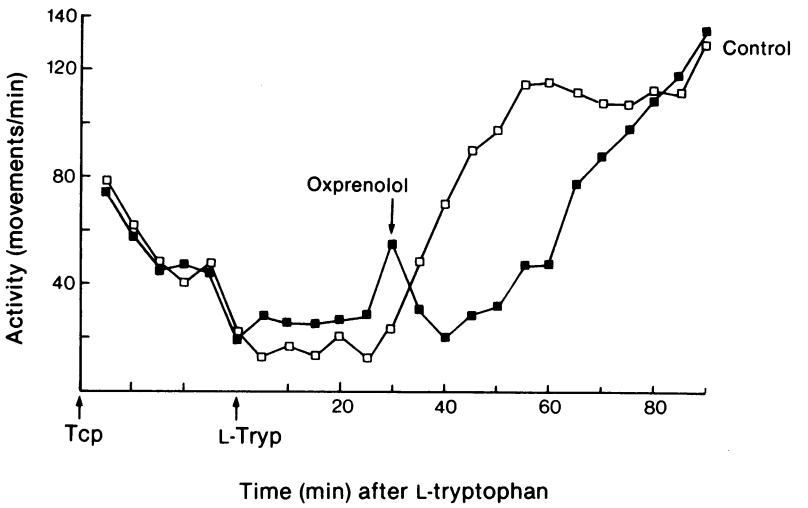

Figure 2 Effect of (±)-oxprenolol on tranylcypromine/L-tryptophan-induced hyperactivity. Rats were injected with tranylcypromine (Tcp, 10 mg/kg) with L-tryptophan (L-Tryp 50 mg/kg) being given 30 min later (□). One group were injected with (±)-oxprenolol 30 min after L-tryptophan as shown (■). Activity was markedly inhibited for at least a further 30 min (total movements during 60 min following administration of oxprenolol 1818 ± 1781 (3), control group 5778 ± 581 (3)). Oxprenolol group different from control group, $P < 0.01$.

Table 1 Effect of β-blockers on tranylcypromine/L-tryptophan-induced hyperactivity

Drug	*Dose (mg/kg)*	*Selectivity*	*Entry* to brain?*	*Locomotor count 90 min after L-Tryp*	P
Saline	—	—	—	6752 ± 1831 (5)	—
(−)-Propranolol	20	β_1 β_2	Good[1]	886 ± 492 (3)	<0.01
(±)-Propranolol	40	β_1 β_2	Good[1]	1041 ± 618 (3)	<0.01
(±)-Alprenolol	40	β_1 β_2	Good[2]	1622 ± 613 (3)	<0.01
(±)-Timolol	40	β_1 β_2	Good[3]	2566 ± 1910 (4)	<0.01
(±)-Sotalol	40	β_1 β_2	Some[4]	3056 ± 1527 (3)	<0.025
(±)-Pindolol	40	β_1 β_2	Good[5]	3539 ± 1152 (4)	<0.01
(±)-Oxprenolol	40	β_1 β_2	Good[6]	4638 ± 1160 (3)	NS
(±)-Metoprolol	40	β_1	Good[7]	5157 ± 1868 (4)	NS
(±)-Butoxamine	40	β_2	Good[8]	5355 ± 1786 (3)	NS
(±)-Acebutolol	40	β_1	Poor[9]	4562 ± 1228 (4)	NS
(±)-Atenolol	40	β_1	Poor[10]	5173 ± 946 (3)	NS
(±)-Practolol	40	β_1	Poor[11]	4728 ± 1840 (4)	NS
(±)-Labetalol	40	α_1 β_1 β_2	Poor[12]	4977 ± 82 (3)	NS

All β-blockers were given 45 min before tranylcypromine (20 mg/kg) with L-tryptophan (50 mg/kg) being given after a further 30 min. Mean total movements ± s.d. in the 90 min following L-tryptophan are shown with number of observations in parentheses. References for the data on entry of drugs to the brain are given by superscript numbers and are as follows: [1]Hayes & Cooper (1971); [2]Bodin, Borg, Johansson, Obianwu & Svensson, (1974); [3]Tocco, Duncan & Delauna (1975); [4]Rinne & Kaitaniemi (1974); [5]Garvey & Ram (1975); [6]Riess *et al.* (1970); [7]Bodin *et al.* (1975); [8]Goth (1974); [9]Collins (1975); [10]Data Sheet Compendium (1977); [11]Scales & Cosgrove (1970); [12]Martin, Hopkins & Bland (1976).

* See comments in first Results section.

mine and L-tryptophan, indicating that their effect on the hyperactivity was not due to an inhibition of 5-HT synthesis (Table 2).

Effects of alprenolol, pindolol and metoprolol on 5-methoxy, N,N-dimethyltryptamine (5-MeODMT)-induced hyperactivity

The hyperactivity produced by the suggested 5-HT agonist 5-MeODMT (Grahame-Smith, 1971b) was inhibited by propranolol (Green & Grahame-Smith, 1976) suggesting it was blocking post-synaptic responses. We have now examined the effects of other β-adrenoceptor antagonists on this response. Three drugs were selected that had quantitatively different actions on the tranylcypromine/L-tryptophan hyperactivity. (±)-Alprenolol, (±)-timolol or (±)-metoprolol (all at a dose of 40 mg/kg) was injected 45 min before tranylcypromine (10 mg/kg). Thirty min after the tranylcypromine the rats were injected with 5-MeODMT (1 mg/kg) and activity measured. The order of effectiveness of the drugs was the same as that seen in the tranylcypromine/L-tryptophan experiments, with metoprolol being ineffective (Figure 3).

Effects of β-adrenoceptor antagonists on methamphetamine-induced circling in unilateral nigro-striatal lesioned rats

In order to see whether any of the β-blocking drugs was affecting dopamine-induced responses we investigated whether they would alter methamphetamine induced circling in unilateral nigro-striatal lesioned rats (see Methods).

The β-adrenoceptor antagonist was given 45 min before methamphetamine (3 mg/kg) and circling measured during the next 90 min. None of the drugs tested had a statistically significant effect on circling, although alprenolol did decrease the total number of turns in all animals tested (Table 3).

Discussion

During the last two years evidence has been accumulating that β-adrenoceptor antagonists have an effect on 5-HT-mediated responses in neural tissues. Weinstock & Schechter (1975) demonstrated that (−)-propranolol but not the (+)-isomer blocked neural transmission produced by 5-HT in the rat cervical ganglion. Subsequently Green & Grahame-Smith (1976) showed that (−)-propranolol, but not the (+)-isomer, inhibited tranylcypromine/L-tryptophan-induced hyperactivity. Recently Weinstock, Weiss & Gitter (1977) found that propranolol, oxprenolol and pindolol antagonized the 5-hydroxytryptophan-induced head twitch in mice, and prevented the induction of sleep by 5-HT in young chicks. These β-adrenoceptor antagonists were also able to block 5-HT-induced contraction of the rat isolated stomach fundus and uterus (Schechter & Weinstock, 1974; Weinstock *et al.*, 1977).

In a study on the effect of β-adrenoceptor antagonists on the binding of [^{3}H]-5-HT to crude synaptic

Table 2 Effect of β-adrenoceptor blocking drugs on brain 5-hydroxytryptamine (5-HT) metabolism

	Brain 5-hydroxytryptamine concn (μg/g brain (wet wt.))		
Injected	*Saline*	*Tranylcypromine*	*Tranylcypromine/L-Tryptophan*
Saline	0.42 ± 0.06 (18)	0.63 ± 0.04 (4)	1.18 ± 0.14 (14)
(−)-Propranolol	0.45 ± 0.06 (8)	0.59 ± 0.08 (8)	1.15 ± 0.20 (8)
(±)-Alprenolol	0.37 ± 0.02 (4)	0.62 ± 0.07 (6)	1.11 ± 0.20 (5)
(±)-Timolol	0.43 ± 0.05 (6)	0.58 ± 0.07 (6)	1.05 ± 0.20 (8)
(±)-Sotalol	0.44 ± 0.12 (6)	0.62 ± 0.10 (6)	1.22 ± 0.25 (6)
(±)-Pindolol	0.47 ± 0.05 (6)	0.59 ± 0.10 (6)	1.00 ± 0.23 (6)
(±)-Oxprenolol	0.37 ± 0.06 (4)	0.54 ± 0.05 (6)*	0.91 ± 0.13 (6)*
(±)-Metoprolol	0.40 ± 0.05 (6)	0.61 ± 0.07 (6)	1.05 ± 0.04 (3)
(±)-Acebutolol	0.40 ± 0.06 (8)	0.64 ± 0.06 (8)	1.05 ± 0.12 (4)
(±)-Atenolol	0.35; 0.36 (2)	0.63 ± 0.05 (6)	ND
(±)-Practolol	0.37 ± 0.02 (4)	0.61 ± 0.06 (4)	0.94 ± 0.07 (3)†
(±)-Labetalol	0.36 ± 0.02 (4)	0.53 ± 0.04 (4)*	1.02; 1.24 (2)

Rats were injected with β-blocking drug and killed 45 min later when brain 5-HT concentrations were measured. The accumulation of 5-HT 60 min after tranylcypromine (10 mg/kg), β-blocker having been given 45 min prior to the tranylcypromine is also shown, as is the accumulation in the brain of 5-HT at the end of the activity experiments (i.e. 90 min after L-tryptophan injection). Results expressed as mean ± s.d. with number of observations in parentheses. Difference from saline injected control: *$P < 0.01$; †$P < 0.05$.

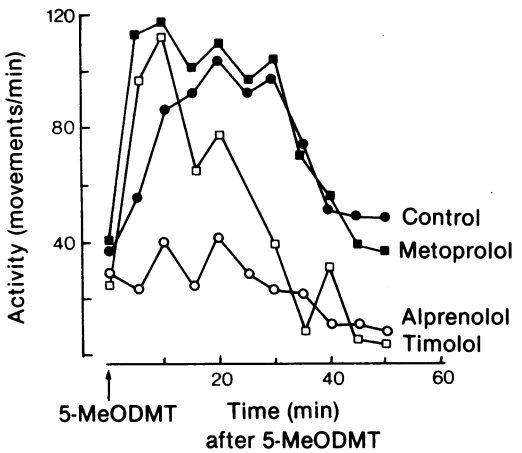

Figure 3 Effect of β-adrenoceptor blockers on 5-methoxy,*N,N*-dimethyl tryptamine-induced activity. Rats were injected with (±)-alprenolol (○), (±)-timolol (□), (±)-metoprolol (■) (all at 40 mg/kg) or saline (●). Forty-five minutes later all groups were given tranylcypromine (10 mg/kg) with 5-methoxy,*N,N*-dimethyl tryptamine (5-MeODMT, 2 mg/kg) after a further 30 min. Typical responses are shown. Total movements during 50 min following 5-MeODMT: control 3730 ± 282 (3), timolol 1794 ± 783 (3) alprenolol 1263 ± 427 (3) metoprolol 3752 ± 674 (3). Alprenolol different from control group: $P < 0.001$; timolol different from control: $P < 0.01$.

membranes, Middlemiss *et al.* (1977) showed that (−)-propranolol was as effective as methysergide in inhibiting the specific binding of 5-HT. They also found (+)-propranolol almost totally ineffective, and were able to show that alprenolol, oxprenolol and pindolol were effective inhibitors of 5-HT binding.

The current study complements these observations showing that all non-specific (i.e. β_1, β_2) antagonists which enter the brain well, block the 5-HT-induced hyperactivity when given at high dosage of the racemate. Middlemiss *et al.* (1977) found that the cardioselective drugs, practolol and atenolol, did not inhibit specific 5-HT binding to synaptic membranes and while neither of these drugs inhibited the hyperactivity syndrome, this could presumably be explained by their poor entry into the brain. However, metoprolol, which is cardioselective (Åblad, Borg, Carlsson, Johnsson, Malmfors & Regådh, 1975) and does enter the brain (Bodin, Borg, Johansson, Ramsay & Skönberg, 1975) had no effect on the hyperactivity. Also, as previously reported (Green & Grahame-Smith, 1976), the β_2 selective antagonist, butoxamine, has no effect on the hyperactivity and it was noted by Schechter & Weinstock (1974) that practolol was relatively ineffective in blocking the effects of 5-HT on the rat fundus. It appears, therefore, from the data now available that only drugs showing both β_1 and β_2-adrenoceptor antagonist activity block central 5-HT-mediated responses.

The fact that the β-adrenoceptor antagonists had no effect on 5-HT synthesis but did block the effects of the 5-HT agonist 5-MeODMT suggests strongly that these drugs are blocking 5-HT-induced responses by acting either at or beyond the 5-HT receptor. It has been demonstrated that a dopaminergic system is involved in the postsynaptic expression of the tranylcypromine/L-tryptophan hyperactivity response and that inhibition of brain dopamine synthesis (Green & Grahame-Smith, 1974) or blockade of dopamine receptors with neuroleptic drugs (Heal, Green, Boullin & Grahame-Smith, 1976), inhibits the postsynaptic 5-HT behavioural responses. However the β-adrenoceptor antagonists do not seem to be acting on the 5-HT-induced behaviour by altering dopaminergic function since they had no effect on circling.

Table 3 Effects of β-adrenoceptor autaponists on methamphetamine-induced circling in unilateral nigrostriatal lesioned rats

Injected	*Total turns during the 90 min after β-blockers as % of control experiment*
Saline	100
Alprenolol	72 ± 18
Sotalol	139 ± 20
Pindolol	104 ± 50
Metoprolol	112 ± 18

Total turns of the 4 control animals during 90 min were 1570, 2410, 910, 920 and this did not alter by more than 10% during the course of the experiment. β-Blocking drugs were given 45 min before methamphetamine (3 mg/kg) and total turns during the 90 min following methamphetamine measured. Results expressed as mean ± s.d. A paired *t* test was used to examine the effect of the β-blockers. None of the drugs examined had a statistically significant effect.

Much interest has focussed on the dopamine blocking actions of antipsychotic drugs (Iversen, 1975). However, if propranolol and other β-adrenoceptor antagonists are found to be effective in schizophrenia as has been suggested (Yorkston, Zaki, Malik, Morrison & Havard, 1974; Carlsson, Engel & Hansson, 1976; Yorkston, Gruzelier, Zaki, Hollander, Pitcher & Sergeant., 1977) this effect might be mediated by a 5-HT mechanism.

Our experiments do not indicate whether β-adrenoceptor antagonists block the 5-HT receptor directly, or alter a central adrenergic system which modulates 5-HT behavioural responses. However the ability of the β-adrenoceptor antagonists to inhibit the 5-HT-mediated responses in several diverse tissues perhaps argues for a direct action of the drugs on the 5-HT receptor. Our data does not allow a comparison of the relative 5-HT receptor blocking activities of these β-adrenoceptor antagonists since factors such as rates of metabolism, tissue distribution and binding of the drugs to the brain all affect the availability of the drug at the receptors.

Haigler & Aghajanian (1974; 1977) have demonstrated electrophysiologically the failure of the peripheral 5-HT receptor antagonists, methysergide, metergoline and cyproheptadine, to block central 5-HT neuronal activity and Deakin & Green (1978) have shown that methysergide and methergoline inhibit only those 6-HT-induced behavioural responses that are hind-brain or spinally mediated. This suggests (see Deakin & Green, 1978, for fuller discussion) that these drugs do not act as functional antagonists at central 5-HT receptors, despite the fact that they appear to inhibit 5-HT binding to synaptic membranes (Middlemiss *et al.*, 1977). Some of the β-adrenoceptor antagonists, in contrast, inhibit all the 5-HT-mediated behavioural responses (Deakin & Green, 1978; this paper) and may thus play a useful role in the investigations of 5-HT neuronal systems.

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