Br. J. Pharmac. (1980), **68**, 75–82

β-ADRENOCEPTOR ANTAGONISTS: STUDIES ON BEHAVIOUR (DELAYED DIFFERENTIATION) IN THE MONKEY (*Macaca mulatta*)

A.N. NICHOLSON & CATHERINE M. WRIGHT

Royal Air Force Institute of Aviation Medicine, Farnborough, Hampshire

1 Activity of six β-adrenoceptor antagonists was studied on behavioural activity (delayed differentiation) in the monkey (*Macaca mulatta*). The drugs, three relatively lipophilic antagonists (propranolol, oxprenolol and metoprolol), and three relatively hydrophilic antagonists (acebutolol, atenolol and sotalol), were given by intraperitoneal injection (5 to 30 mg/kg).

2 With atenolol (25 to 30 mg/kg), total response time was increased, but there was no effect on the number of correct responses. With acebutolol (25 to 30 mg/kg), the number of correct responses was reduced, but there was no effect on total response time. With metoprolol (25 to 30 mg/kg), there was an increase in total response time and a decrease in the number of correct responses, and correct responses were decreased 4 h after injection over the whole dose range (5 to 30 mg/kg).

3 Some animals failed to respond or complete the task with 30 mg/kg oxprenolol, 25 mg/kg sotalol and 20 mg/kg propranolol. With 25 mg/kg oxprenolol, the total response time was increased and the number of correct responses was decreased. With 5–20 mg/kg sotalol, total response time was increased, but there was no effect on the number of correct responses. With 15 mg/kg of (±)-propranolol and its isomers, there were increases in total response time and decreases in correct responses.

4 The studies suggest that lipophilic antagonists, such as propranolol, oxprenolol and metoprolol, are likely to have, at least, effects on the central nervous system, while hydrophilic antagonists may modify the peripheral nervous system. In the dose-ranges studied, propranolol had the greatest, and atenolol and acebutolol had the least effects. Atenolol and acebutolol may prove to be particularly useful in man when disturbances of the nervous system are to be avoided.

Introduction

β-Adrenoceptor antagonists modify the activity of the nervous system, and it has been shown, particularly in the rodent, that they possess anticonvulsant and tranquillizing properties, modify drug-induced sleeping times, decrease motor activity, and reduce drug-induced hyperthermia (Leszkovszky & Tardos, 1965; Murmann, Almirante & Saccani-Guelfi, 1966; Laverty & Taylor, 1968; Mantegazza, Naimzada & Riva, 1968; Hermansen, 1969; Smith, Hayashida & Kim, 1970; Bainbridge & Greenwood, 1971; Singh, Bhandari & Mahawar, 1971; Shah, Jindal, Patel & Kelkar, 1974; Weinstock & Speiser, 1974; Delini-Stula & Meier, 1976). The effects may differ between the antagonists, and behaviour may be less likely to be modified by some than by others. It is in this context that we have studied several antagonists on delayed differentiation behaviour in the monkey (*Macaca mulatta*). However, the question arises whether effects are due to β-adrenoceptor antagonism or to some other non-specific activity, and so we have included the optical isomers of propranolol which have similar non-specific activity, but different potencies as antagonists.

Methods

Behavioural studies

Five male monkeys (*Macaca mulatta*) with a mean body weight of 11.3 (9.4 to 14.7) kg were trained on a delayed differentiation task (Konorski, 1959; Roberts & Bradley, 1967; Nicholson, Wright & Ferres, 1973). The task required each animal to differentiate between two visual stimuli, each of 2 s duration and separated by a 4 s delay, by pressing a lever during the presentation of the second stimulus if the stimuli were like (Go response), and to refrain

0007-1188/80/010075-08 $01.00

from pressing the lever if the stimuli were unlike (No-Go response). Correct Go and No-Go responses were rewarded with a food pellet. In the event of an error the trial was repeated until a correct response was made, but the initial response only was used in the analysis of the data. Each experiment involved five sessions of 50 trials spread over three days. During the first day, there were two sessions separated by 3 h to confirm criterion performance (80% correct). If criterion performance was attained, the effect of an intraperitoneal injection of drug or placebo control (saline or polyethylene glycol as appropriate) was studied during the second day, when testing sessions were held at the same time of the day as the control assessments of the day before, but 1 and 4 h after injection. On the third day the single testing session was held 24 h after the injection of the second day. The order of injection of drugs and of placebos was randomized for each monkey. Seven days separated each injection. The drugs were propranolol hydrochloride, acebutolol hydrochloride, sotalol hydrochloride, metoprolol tartrate, oxprenolol and atenolol. Studies were also carried out with (+)- and (−)-propranolol hydrochloride. The doses studied were 5, 10, 15, 20, 25 and 30 mg/kg body weight, but the full range was not achieved with all drugs. Drugs were dissolved in 5 ml saline (0.9% w/v NaCl solution), except for atenolol which was dissolved in 5 ml polyethylene glycol.

Studies on heart rate

To establish the β-adrenoceptor antagonistic activity of (±)- and (+)-propranolol within the dose-ranges used for the behavioural studies, the effects of each drug at 15 mg/kg were studied on heart rate. Six male monkeys (*Macaca mulatta*), with a mean body weight of 3.9 (3.2 to 4.5) kg, were used. The ECG was recorded with two gold-plated electrodes attached to the skin of the chest wall with colloidin. The leads of the electrodes were connected to a small radio transmitter held in the pocket of a light-weight jacket (Clark Electro-Medical Instruments). The animals were familiar with wearing the jacket which allowed complete freedom of movement. Each experiment consisted of two sessions. On the first day an intraperitoneal injection of saline was given, and on the second day an intraperitoneal injection of 15 mg/kg (+)- or (±)-propranolol in 5 ml saline was given. The animals were left undisturbed for a period of 5 h after injection, and the ECG was recorded. With each monkey two experiments were carried out with (+)-propranolol, and one with (±)-propranolol. The order of the drug treatments was randomized, and 7 days separated each drug injection. The ECG signal was picked up by a radio-receiver, and relayed to a pen recorder for visual display and to magnetic tape for subsequent computer counting of heart rate.

Results

Behavioural studies

It was the intention of the study to assess the effects of each drug over the total dose-range. However, with certain drugs at the higher doses, the animals either failed to respond or failed to complete the task, and so the analysis of effects was limited to doses in which all animals completed the task. Analyses over the complete dose-range (5 to 30 mg/kg) were possible with atenolol, acebutolol and metoprolol, but analyses were limited to the dose-range 5 to 25 mg/kg with oxprenolol and to the dose-range 5 to 20 mg/kg with sotalol. With propranolol and its isomers the animals completed the task over the dose-range 5 to 15 mg/kg only. Analysis of variance was the statistical method, and as the variability of the data for performance at 1 and 4 h after injection differed, separate analyses were carried out for each time. Change in total response time for Go responses, and change in number of correct responses, each related to placebo effects, were studied. It was not possible to establish differential effects on the Go or No-Go response in animals which completed all responses in the session.

With the several analyses of groups of drugs (Tables 1–4), it is useful to summarize the consistent effects. With atenolol, total response time was increased ($P < 0.05$) at 1 h over the dose-range 25 to 30 mg/kg, but there was no effect on the number of correct responses. An effect on total response time within the dose-range 5 to 10 mg/kg was due to a pronounced increase in one monkey only with 10 mg/kg and this effect was not observed with 5, 15 and 20 mg/kg. With acebutolol there was no effect on total response time, but the number of correct responses was reduced ($P < 0.05$) at 1 h over the dose-range 25 to 30 mg/kg. With metoprolol there was an increase in total response time ($P < 0.001$) and a decrease in the number of correct responses ($P < 0.01$) at 1 h over the dose-range 25 to 30 mg/kg, and a decrease in the number of correct responses ($P < 0.05$) at 4 h was observed over the whole dose-range in one of the analyses (Table 3).

Some animals failed to complete the task with 30 mg/kg oxprenolol, 25 mg/kg sotalol and with 20 mg/kg propranolol and its isomers. With oxprenolol there was no consistent effect over the dose-range 5 to 20 mg/kg, but a separate analysis showed that the total response time was increased and number of correct responses reduced ($P < 0.01$) at 1 and 4 h after 25 mg/kg. With sotalol total response time was increased at 1 h over the dose-range 5 to 10 mg/kg and at 1 and

4 h over the dose-range 15 to 20 mg/kg, and a separate analysis showed that the increase in total response time persisted to 24 h after injection ($P < 0.01$). With propranolol and its isomers (15 mg/kg) total response time was increased and number of correct responses was decreased, and decreased correct responses were seen with (±)- and (+)-propranolol at 10 mg/kg.

Studies on heart rate

The effects of injection of saline, (±)-propranolol and (+)-propranolol on heart rate are given in Table 5 and illustrated in Figure 1. In the undisturbed monkey, heart rate fell rapidly, and a steady rate was reached about 2 h after injection of saline. The same pattern was observed with (±)-propranolol and (+)-propranolol. With each drug the mean heart rate over each hourly interval after injection was lower than that after saline ($P < 0.01$), and the change in mean heart rate after (±)-propranolol was greater than that after (+)-propranolol ($P < 0.001$).

Discussion

Ability to respond, total response time and number of correct responses were changed with the β-adreno-

Table 1 Change of total response time (ms) for Go responses and in number of correct responses compared with placebo 1 h and 4 h after injection of drug (mean values for 5 monkeys)

	Time after injection	*5 mg/kg*		*10 mg/kg*		*15 mg/kg*	
		TRT	*CR*	*TRT*	*CR*	*TRT*	*CR*
Atenolol							
	1 h	29.2	−1.4	49.8	−0.2	−5.6	0.2
		NS	NS	*	NS	NS	NS
	4 h	2.4	−0.2	19.8	−0.4	−6.2	1.4
		NS	NS	NS	NS	NS	NS
Acebutolol							
	1 h	8.2	−0.5	−7.6	−1.5	14.2	−1.1
		NS	NS	NS	NS	NS	NS
	4 h	−0.2	0.1	−19.4	−0.7	11.0	−1.1
		NS	NS	NS	NS	NS	NS
Metoprolol							
	1 h	−7.0	0.4	26.0	−0.5	8.0	−0.2
		NS	NS	NS	NS	NS	NS
	4 h	−0.2	−0.8	31.6	−2.5	2.4	−1.2
		NS	NS	NS	**	NS	NS
Oxprenolol							
	1 h	15.2	−1.2	1.6	−2.1	32.2	−1.4
		NS	NS	NS	*	NS	NS
	4 h	25.6	−1.8	33.6	−0.5	−2.0	0.4
		NS	*	NS	NS	NS	NS
Sotalol							
	1 h	19.4	−0.8	62.8	−0.6	37.8	−2.0
		NS	NS	**	NS	NS	NS
	4 h	17.8	−0.2	32.8	−1.0	14.4	−1.0
		NS	NS	NS	NS	NS	NS
(±)-Propranolol							
	1 h	2.4	28.2	−3.3	103.8	−4.3	
		NS	NS	NS	**	***	***
	4 h	3.0	−0.1	−17.0	−0.1	7.4	−0.1
		NS	NS	NS	NS	NS	NS

TRT = change in total response time; CR = change in number of correct responses; NS = not significant.

Least significant differences
* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

TRT	1 h	46.8	62.2	81.1
CR	1 h	2.1	2.7	3.6
	4 h	1.7	2.3	3.0

Table 2 Change of total response time (ms) for Go responses and in number of correct responses compared with placebo 1 h and 4 h after injection of drug (mean for 5 monkeys)

	Time after injection	*5 mg/kg*		*10 mg/kg*		*15 mg/kg*	
		TRT	*CR*	*TRT*	*CR*	*TRT*	*CR*
(±)-Propranolol							
	1 h	2.4	0.2	28.2	−3.3	103.8	−4.3
		NS	NS	NS	**	***	***
	4 h	3.0	−0.1	−17.0	−0.1	7.4	−0.1
		NS	NS	NS	NS	NS	NS
(+)-Propanolol							
	1 h	20.8	−1.1	40.2	−1.9	76.6	−2.5
		NS	NS	NS	NS	**	*
	4 h	2.6	0.2	−6.0	−2.9	14.4	−3.3
		NS	NS	NS	**	NS	***
(−)-Propanolol							
	1 h	16.8	1.2	19.0	−0.1	113.8	−2.5
		NS	NS	NS	NS	***	*
	4 h	9.8	−0.3	11.2	0.75	42.0	−1.7
		NS	NS	NS	NS	NS	*

TRT = change in total response time; CR = change in number of correct responses; NS = not significant.

Least significant differences

		* $P < 0.05$	** $P < 0.01$	*** $P < 0.001$
TRT	1 h	46.8	62.6	81.1
CR	1 h	2.1	2.7	3.6
	4 h	1.7	2.3	3.0

Table 3 Change of total response time (ms) for Go responses and in number of correct responses compared with placebo 1 h and 4 h after injection of drug (mean for 5 monkeys)

	Time after injection	*5 & 10 mg/kg*		*15 & 20 mg/kg*		*25 & 30 mg/kg*	
		TRT	*CR*	*TRT*	*CR*	*TRT*	*CR*
Atenolol							
	1 h	39.5	−0.8	10.8	−0.7	51.9	0.0
		NS	NS	NS	NS	*	NS
	4 h	11.1	−0.3	−7.5	1.0	37.6	−0.9
		NS	NS	NS	NS	NS	NS
Acebutolol							
	1 h	0.3	−1.0	7.2	−0.8	0.1	−2.0
		NS	NS	NS	NS	NS	*
	4 h	−9.8	−0.3	0.8	−0.8	−7.7	−0.6
		NS	NS	NS	NS	NS	NS
Metoprolol							
	1 h	9.5	−0.1	23.9	−1.2	102.7	−3.0
		NS	NS	NS	NS	***	**
	4 h	15.7	−1.7	17.8	−1.8	41.7	−1.7
		NS	*	NS	*	NS	*

TRT = change in total response time; CR = change in number of correct responses; NS = not significant.

Least significant differences

		* $P < 0.05$	** $P < 0.01$	*** $P < 0.001$
TRT	1 h	40.8	55.3	74.0
	4 h	45.7	61.1	83.0
CR	1 h	1.8	2.5	3.3
	4 h	1.7	2.3	3.0

ceptor antagonists, but the effects of these closely related drugs differed within the same dose-range. Total response time was increased by all drugs except acebutolol, and the number of correct responses was decreased by all drugs except atenolol and sotalol. Effects of (±)-propranolol were evident at 10 mg/kg, but effects of atenolol and acebutolol were observed only from 25 to 30 mg/kg. These findings suggest that activity other than β-adrenoceptor antagonism *per se* may be relevant to the appearance of impaired performance with these drugs, and, in particular, that effects on the number of correct responses may be

Table 4 Change of total response time (ms) for Go responses and in number of correct responses compared with placebo 1 h and 4 h after injection of drug (mean for 5 monkeys)

	Time after injection	*5 & 10 mg*		*15 & 20 mg/kg*	
		TRT	*CR*	*TRT*	*CR*
Atenolol					
	1 h	39.5	−0.8	10.8	−0.7
		*	NS	NS	NS
	4 h	11.1	−0.3	−7.5	1.0
		NS	NS	NS	NS
Acebutolol					
	1 h	0.3	−1.0	7.2	−0.8
		NS	NS	NS	NS
	4 h	−9.8	−0.3	0.8	−0.8
		NS	NS	NS	NS
Metoprolol					
	1 h	9.5	−0.1	23.9	−1.2
		NS	NS	NS	NS
	4 h	15.7	−1.7	17.8	−1.8
		NS	NS	NS	*
Oxprenolol					
	1 h	8.4	−1.7	35.1	−2.0
		NS	NS	NS	NS
	4 h	29.6	−1.2	0.3	−0.4
		NS	NS	NS	NS
Sotalol					
	1 h	41.1	−0.7	79.0	−2.1
		*	NS	***	NS
	4 h	25.3	−0.6	67.6	−1.4
		NS	NS	**	NS

TRT = change in total response time; CP = change in number of correct responses; NS = not significant.

Least significant differences				
		* $P < 0.05$	** $P < 0.01$	*** $P < 0.001$
TRT	1 h	39.1	53.3	72.2
	4 h	45.0	61.3	83.0
CR	4 h	1.8	2.5	3.4

Table 5. Change in mean heart rate (beats/min) averaged over 1 h intervals with 15 mg/kg (±)-propranolol and (+)-propranolol intraperitoneally compared with placebo (means for 6 monkeys)

	Interval (h after injection)				
	0–1	1–2	2–3	3–4	4–5
(+)-Propranolol	−14.8	−16.4	−9.5	−11.5	−6.8
	***	***	***	***	**
(±)-Propranolol	−25.1	−26.1	−25.1	−25.8	−22.2
	***	***	***	***	***

Least significant differences (means for 36) * $P < 0.05 = 4.9$; ** $P < 0.01 = 6.6$; *** $P < 0.001 = 8.7$

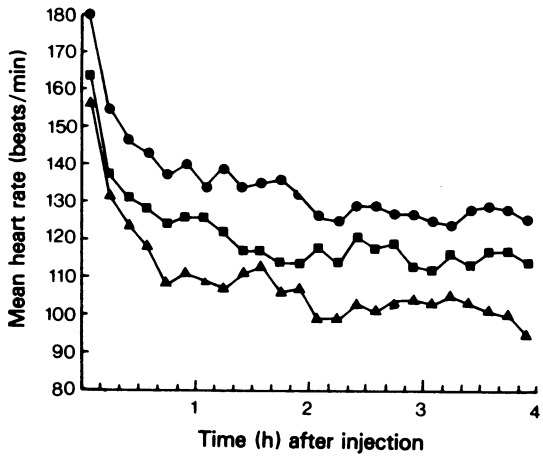

Figure 1 Mean heart rate (beats/min) averaged over 10 min intervals for 4 h after injection of saline (●), (+)-propranolol (■) and (±)-propranolol (▲). Mean values for 6 monkeys.

related to the lipophilic nature of each compound. Propranolol has high lipid solubility and enters the brain with ease, whereas atenolol and sotalol enter the brain with difficulty. Oxprenolol, metoprolol and acebutolol are less lipophilic than propranolol, but more so than atenolol and sotalol (Laverty & Taylor, 1968; Hayes & Cooper, 1971; Maxwell & Collins, 1974; Garvey & Ram, 1975a, b; Masuoka & Hansson, 1967; Day, Hemsworth & Street, 1977), and had effects on the number of correct responses between that of atenolol and sotalol on one hand, and (±)-propranolol on the other.

Though impaired ability to match stimuli would appear to be related to the ease with which an antagonist crosses the blood-brain barrier, it is uncertain whether β-adrenoceptor blockade is the causative mechanism. It has been suggested that non-specific activity may be involved (Hermansen, 1969; Bainbridge & Greenwood, 1971; Shah *et al.*, 1974; Weinstock & Speiser, 1974). (+)-Propranolol had a similar behavioural effect to (−)-propranolol, but, though it has little β-adrenoceptor antagonistic activity (Howe & Shanks, 1966), it has equipotent membrane stabilizing activity (Barrett & Cullum, 1968). Atenolol and sotalol did not affect responses and have little or no membrane stabilizing activity, but these drugs are relatively hydrophilic, and so central effects would not be expected.

The similar behavioural effects of (−)- and (+)-propranolol suggest that membrane stabilization may be a basis for the central effects of β-adrenoceptor antagonists which are relatively lipophilic. The present studies have shown that, in the high doses used in the behavioural experiments, (+)-propranolol has a negative chronotropic effect on the heart and though there is evidence that central β-adrenoceptors are stereospecific, (Alexander, Davis & Lefkowitz, 1975; Romero, Zatz, Kebabian & Axelrod, 1975; U'Prichard & Snyder, 1977; Nahorski & Willcocks, 1978), it would appear that it is not possible to exclude completely central β-adrenoceptor blocking activity as a mechanism for behavioural effects. However, the differential effects of (±)- and (+)-propranolol observed on heart rate, but not on behaviour, would favour a non-specific mechanism.

Other central mechanisms may be involved. Some β-adrenoceptor antagonists block central 5-hydroxytryptamine (5-HT) receptors, as well as those in smooth muscle and sympathetic ganglia (Schechter & Weinstock, 1974; Weinstock & Schechter, 1975; Green & Grahame-Smith, 1976; Weinstock, Weiss & Gitter, 1977), and inhibit specific [^{3}H]-5-HT binding to crude synaptosomal membranes (Middlemiss, Blakeborough & Leather, 1977). Interaction with 5-HT systems appears to be stereospecific, and so, as (+)-propranolol impaired behaviour, such a mechanism is unlikely. Whether β-adrenoceptor antagonists also alter central noradrenergic transmission has not been established, although propranolol and other β-adrenoceptor antagonists modify peripheral noradrenergic transmission. The mechanism is uncertain, but unlikely to depend on β-adrenoceptor antagonism or membrane stabilizing activity (Barrett & Nunn, 1970; Myelcharane & Raper, 1970; 1973; Eliash & Weinstock, 1971; Saelens, Daniell & Webb, 1977).

Increased total response time was also observed with the lipophilic antagonists and with the hydrophilic antagonists, atenolol and sotalol, but not with acebutolol. Sotalol has the least potency as a β-adrenoceptor antagonist but had a pronounced effect on total response time, whereas acetubolol, with similar potency to sotalol, did not increase total response time. Neuromuscular blocking effects appear to be unrelated to β-adrenoceptor antagonism, though direct effects on pre- and post-synaptic structures of the skeletal neuromuscular junction have been shown (Usubiaga, 1968; Wislicki, 1969; Davis, 1970; Lilleheil & Røed, 1971; Paradelis, Theocharidis & Logaras, 1973), and these effects may be the mechanism for increases in total response time. However, central mechanisms cannot be excluded, though if a central mechanism was likely, decreased responses and increased total response time may have been expected to follow a similar pattern in each drug related to dose.

With most drugs, impaired performance persisted to 4 h only at the higher doses of the responding range, but with metoprolol (5 to 20 mg/kg), although there was no effect 1 h after injection, there were decreased correct responses at 4 h, and it was only with

the higher doses (25 to 30 mg/kg) that performance was impaired at 1 h. The delayed effect at low doses may have been due to the relatively low lipophilicity of metoprolol compared with propranolol and oxprenolol. It is also of interest that the effects of sotalol on total response time persisted to 24 h. This effect may be due to a relatively long elimination half life which has been described in both animals and man (Schnelle & Garrett, 1973; Brown, Carruthers, Kelly, McDevitt & Shanks, 1976).

The present studies may be relevant to the use of β-adrenoceptor antagonists in man. It would appear that propranolol, metoprolol and oxprenolol, are likely to have central effects, while the hydrophilic antagonists would be more likely to affect the peripheral nervous system alone. It is considered that atenolol and acebutolol are the most promising antagonists for use in man when both impaired central and peripheral nervous function are to be avoided, and it must be emphasised that with atenolol and acebutolol consistent effects were observed only at doses far beyond those used in clinical practice.

The authors are indebted to Miss H. Ferres for statistical advice, and to Miss A. Clancy, Mr T. Bradley and Mr R. Tudor, students of the Department of Pharmacy and Pharmacology, University of Bath, who assisted in these experiments. The drugs were kindly supplied by ICI Ltd (propranolol and its isomers, and atenolol), Ciba-Geigy Ltd (metoprolol and oxprenolol), May & Baker Ltd (acebutolol) and Duncan Flockhart & Co Ltd (sotalol).

References

ALEXANDER, R.W., DAVIS, J.N. & LEFKOWITZ, R.J. (1975). Direct identification and characterisation of β-adrenergic receptors in rat brain. *Nature, Lond.*, **258**, 437–439.

BRAINBRIDGE, J.G. & GREENWOOD, D.T. (1971). Tranquillising effects of propranolol demonstrated in rats. *Neuropharmac.*, **10**, 453–458.

BARRETT, A.M. & CULLUM, V.A. (1968). The biological properties of the optical isomers of propranolol and their effects on cardiac arrhythmias. *Br. J. Pharmac.*, **34**, 43–55.

BARRETT, A.M. & NUNN, B. (1970). Adrenergic neuron blocking properties of (±)-propranolol and (+)-propranolol. *J. Pharm. Pharmac.*, **22**, 806–810.

BROWN, H.C., CARRUTHERS, S.G., KELLY, J.G., MCDEVITT, D.G. & SHANKS, R.G. (1976). Observations on the efficacy and pharmacokinetics of sotalol after oral administration. *Eur. J. clin. Pharmac.*, **9**, 367–372.

DAVIS, W.G. (1970). A comparison of the local anaesthetic-, 'quinidine-like'- and adrenergic β-blocking activities of five β-receptor antagonists. *J. Pharm. Pharmac.*, **22**, 284–290.

DAY, M.D., HEMSWORTH, B.A. & STREET, J.A. (1977). The central uptake of β-adrenoceptor antagonists. *J. Pharm. Pharmac.*, **29**, suppl., 52P.

DELINI-STULA, A. & MEIER, M. (1976). Inhibitory effects of propranolol and oxprenolol on excitation induced by a MAO inhibitor and reserpine in the mouse. *Neuropharmac.*, **15**, 383–388.

ELIASH, S. & WEINSTOCK, M. (1971). Role of adrenergic neurone blockade in the hypotensive action of propranolol. *Br. J. Pharmac.*, **43**, 287–294.

GARVEY, H.L. & RAM, N. (1975a). Comparative antihypertensive effects and tissue distribution of β-adrenergic blocking drugs. *J. Pharmac. exp. Ther.*, **194**, 220–233.

GARVEY, H.L. & RAM, N. (1975b). Centrally induced hypotensive effects of β-adrenergic blocking drugs. *Eur. J. Pharmac.*, **33**, 283–294.

GREEN, A.R. & GRAHAME-SMITH, D.G. (1976). (−)-Propranolol inhibits the behavioural responses of rats to increased 5-hydroxytryptamine in the central nervous system. *Nature, Lond.*, **262**, 594–596.

HAYES, A. & COOPER, R.G. (1971). Studies on the absorption, distribution and excretion of propranolol in rat, dog and monkey. *J. Pharmac. exp. Ther.*, **176**, 302–311.

HERMANSEN, K. (1969). Effect of different β-adrenergic receptor blocking agents on hexobarbital induced narcosis in mice. *Acta pharmac. tox.*, **27**, 453–460.

HOWE, R. & SHANKS, R.G. (1966). Optical isomers of propranolol. *Nature, Lond.*, **210**, 1336–1338.

KONORSKI, J. (1959). A new method of physiological investigation of recent memory in animals. *Bull. Acad. pol. Sci. Sér. Sci. biol.*, **7**, 115–117.

LAVERTY, R. & TAYLOR, K.M. (1968). Propranolol uptake into the central nervous system and the effect on rat behaviour and amine metabolism. *J. Pharm. Pharmac.*, **20**, 605–609.

LESZKOVSZKY, G. & TARDOS, L. (1965). Some effects of propranolol on the central nervous system. *J. Pharm. Pharmac.*, **17**, 518–519.

LILLEHEIL, G. & RØED, A. (1971). Antitetanic effect of propranolol on mammalian motor-nerve and skeletal muscle, and combined action of propranolol and neostigmine on the neuro-muscular transmission. *Archs int. Pharmacodyn.*, **194**, 129–140.

MANTEGAZZA, P., NAIMZADA, K.M. & RIVA, M. (1968). Effects of propranolol on some activities of amphetamine. *Eur. J. Pharmac.*, **4**, 25–30.

MASUOKA, D. & HANSSON, E. (1967). Autoradiographic distribution studies of adrenergic blocking agents. II. ^{14}C-propranolol, a β-receptor-type blocker. *Acta pharmac. tox.*, **25**, 447–455.

MAXWELL, D.R. & COLLINS, R.F. (1974). Acebutolol (sectral): I—Review of the pharmacology and pharmacokinetics. *Clin. Trials J.* No **3**, 9–17.

MIDDLEMISS, D.N., BLAKEBOROUGH, L. & LEATHER, S.R. (1977). Direct evidence for an interaction of β-adrenergic blockers with the 5-HT receptor. *Nature, Lond.*, **267**, 289–290.

MURMANN, W., ALMIRANTE, L. & SACCANI-GUELFI, M. (1966). Central nervous system effects of four β-adrenergic receptor blocking agents. *J. Pharm. Pharmac.*, **18**, 317–318.

MYELCHARANE, E.J. & RAPER, C. (1970). Prejunctional actions of some β-adrenoceptor antagonists in the vas

deferens preparation of the guinea-pig. *Br. J. Pharmac.*, **39**, 128–138.

MYELCHARANE, E.J. & RAPER, C. (1973). Further studies on the adrenergic neuron blocking activity of some β-adrenoceptor antagonists and guanethidine. *J. Pharm. Pharmac.*, **25**, 213–220.

NAHORSKI, S.R. & WILLCOCKS, A.L. (1978). Characteristics and regional variation of β-adrenoceptor sub-types in rat brain. *7th International Congress of Pharmacology, Abstracts, 2940.*

NICHOLSON, A.N., WRIGHT, C.M. & FERRES, H.M. (1973). Impaired performance on delayed matching in monkeys by heptabarbitone, pentobarbitone sodium and quinalbarbitone sodium. *Neuropharmac.*, **12**, 311–317.

PARADELIS, A.G., THEOCHARIDIS, N.C. & LOGARAS, G. (1973). Effect of propranolol on the isolated phrenic nerve-diaphragm preparation of the rat. *Arzneimittel-Forsch.*, **23**, 38–40.

ROBERTS, M.H.T. & BRADLEY, P.B. (1967). Studies on the effects of drugs on performance of a delayed discrimination. *Physiol. Behav.*, **2**, 389–397.

ROMERO, J.A., ZATZ, M., KEBABIAN, J.W. & AXELROD, J. (1975). Circadian cycles in binding of ^{3}H-alprenolol to β-adrenergic receptor sites in rat pineal. *Nature, Lond.*, **258**, 435–436.

SAELENS, D.A., DANIELL, H.B. & WEBB, J.G. (1977). Studies on the interactions of propranolol with adrenergic neurons. *J. Pharmac. exp. Ther.*, **202**, 635–645.

SCHECHTER, Y. & WEINSTOCK, M. (1974). β-Adrenoceptor blocking agents and responses to adrenaline and 5-hydroxytryptamine in rat isolated stomach and uterus. *Br. J. Pharmac.*, **52**, 283–287.

SCHNELLE, K. & GARRETT, E.R. (1973). Pharmacokinetics of the β-adrenergic blocker sotalol in dogs. *J. Pharm. Sci.*, **62**, 362–375.

SHAH, U.H., JINDAL, M.N., PATEL, V.K. & KELKAR, V.V. (1974). Central actions of some β-adrenoceptor blocking agents. *Arzneimittel-Forsch.*, **24**, 1581–1584.

SINGH, K.P., BHANDARI, D.S. & MAHAWAR, M.M. (1971). Effects of propranolol (a β-adrenergic blocking agent) on some central nervous system parameters. *Indian J. med. Res.*, **59**, 786–794.

SMITH, A., HAYASHIDA, K. & KIM, Y. (1970). Inhibition by propranolol of ethanol-induced narcosis. *J. Pharm. Pharmac.*, **22**, 644–645.

U'PRICHARD, D.C. & SNYDER, S.H. (1977). Differential labelling of α and β-noradrenergic receptors in calf cerebellum membranes with ^{3}H-adrenaline. *Nature, Lond.*, **270**, 261–262.

USUBIAGA, J.E. (1968). Neuromuscular effects of β-adrenergic blockers and their interaction with skeletal muscle relaxants. *Anaesthesiology*, **29**, 484–492.

WEINSTOCK, M. & SPEISER, Z. (1974). Modification by propranolol and related compounds of motor activity and stereotype behaviour induced in the rat by amphetamine. *Eur. J. Pharmac.*, **25**, 29–35.

WEINSTOCK, M. & SCHECHTER Y. (1975). Antagonism by propranolol of the ganglion stimulant action of 5-hydroxytryptamine. *Eur. J. Pharmac.*, **32**, 293–301.

WEINSTOCK, M., WEISS, C. & GITTER, S. (1977). Blockade of 5-hydroxytryptamine receptors in the central nervous system by β-adrenoceptor antagonists. *Neuropharmac.*, **16**, 273–276.

WISLICKI, L. (1969). Excitatory and depressant effects of β-adrenoceptor blocking agents on skeletal muscle. *Archs int. Pharmacodyn.*, **182**, 310–317.

(Received January 29, 1979.
Revised April 15, 1979.)