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CENTRAL α- AND β-ADRENOCEPTORS MODIFYING ARTERIAL BLOOD PRESSURE AND HEART RATE IN CONSCIOUS CATS

M.D. DAY & A.G. ROACH

Pharmacological Laboratories, Department of Pharmacy, University of Aston in Birmingham, Birmingham B4 7ET

1 In conscious unrestrained cats noradrenaline, α-methylnoradrenaline and clonidine, infused into the lateral cerebral ventricles (i.c.v.) caused dose-related falls in blood pressure and heart rate; both effects were abolished after i.c.v. phentolamine.

2 In 12 out of 20 cats, i.c.v. isoprenaline and salbutamol when given caused dose-related pressor responses and tachycardias. These effects were abolished after i.c.v. β-adrenoceptor blocking drugs but were unaffected by α-adrenoceptor blocking agents.

3 In 5 out of 20 cats, i.c.v. isoprenaline regularly produced dose-related falls in blood pressure with associated tachycardias; both effects were abolished after i.c.v. β-adrenoceptor blocking agents.

4 Intracerebroventricular dopamine produced cardiovascular responses which were qualitatively similar to those produced by i.c.v. isoprenaline.

5 Intracerebroventricular adrenaline produced complex responses in untreated animals but typical α-effects were obtained after prior i.c.v. treatment with a β-adrenoceptor blocking agent and typical β-effects after i.c.v. pretreatment with an α-adrenoceptor blocking agent.

6 The cardiovascular changes produced by i.c.v. β-adrenoceptor agonists were abolished after systemic administration of hexamethonium or bethanidine.

7 The results are discussed in the light of the mode of action of β-adrenoceptor stimulants and β-adrenoceptor blocking agents in the treatment of hypertension.

Introduction

Much evidence has accumulated in recent years for the presence in the CNS of α-adrenoceptors, stimulation of which leads to bradycardia and a fall in systemic arterial blood pressure. The administration of L-DOPA or noradrenaline into the brain of the dog (McCubbin, Kaneko & Page, 1960) and of α-methyldopa in the cat and rat (Henning & Van Zwieten, 1968; Day, Roach & Whiting, 1972; 1973) all caused hypotensive effects. Heise & Kroneberg (1972) showed that the fall in blood pressure produced by peripherally administered α-methyldopa in anaesthetized cats could be prevented by prior treatment with α-adrenoceptor blocking agents. Similarly, the anti-hypertensive effects of clonidine may also be mediated via central α-adrenoceptor stimulation since its action in anaesthetized dogs and cats is also abolished by antagonists at α-adrenoceptors (Schmitt, Schmitt & Fénard, 1971). The evidence for central α-adrenoceptor participation in blood pressure control has recently been reviewed by Van Zwieten (1973).

In addition to α-adrenoceptor participation in blood pressure control, there is a growing body of evidence implicating β-adrenoceptors. Administration of isoprenaline into the brains of anaesthetized dogs (Bhargava, Mishra & Tangri, 1972), cats (Gagnon & Melville, 1967) and rabbits (Toda, Matsuda & Shimamoto, 1969) is reported to cause tachycardia with an associated fall in systemic arterial blood pressure, both effects being reduced or abolished by β-adrenoceptor blocking agents given into the brain. However, the results of Schmitt & Fénard (1971) were at variance with the above since they found that in anaesthetized dogs and cats intracerebroventricular (i.c.v.) injections of isoprenaline caused a fall in both blood pressure and heart-rate. Stern, Hoffman & Braun (1971) reported that (±)-propranolol produced a fall in blood pressure after carotid artery or vertebral artery infusion in the anaesthetized dog. Srivastava, Kulshrestha, Singh & Bhargava (1973) made a similar observation after injection of racemic propranolol into the

lateral cerebral ventricles in the same preparation. However, this effect of propranolol cannot be definitely attributed to β-adrenoceptor blockade since Kelliher & Buckley (1970) reported that (+)-propranolol, which has very low β-adrenoceptor blocking activity, caused a similar hypotension in anaesthetized cats after i.c.v. injection to that resulting from the active (−)-isomer.

This paper describes work in which agonists and antagonists at α- and β-adrenoceptors have been injected into the cerebral ventricles of conscious cats, rabbits and rats. A preliminary account of some of the work in conscious cats has already been published (Day & Roach, 1972, 1973).

Methods

Experiments using conscious cats.

Twenty cats of either sex weighing between 2.5 and 5 kg were used in this study. Anaesthesia was produced with a mixture of nitrous oxide (80%) and halothane (1-3%) in oxygen and catheters were implanted in the thoracic aorta via the left common carotid artery (for systemic blood pressure and heart-rate recording), and in the left jugular vein (for i.v. drug administration) by the method of Day & Whiting (1972). A modified Collison cannula (Cooling, Day & Roach, 1974) was implanted into the left lateral cerebral ventricle of each cat (Feldberg & Sherwood, 1953). The cannulations and implant were performed in one operation which normally took about 90 min to complete. Prior to and following the operation, the cats were placed in the experimental cages daily for periods of 2-4 h to become accustomed to the surroundings.

Blood pressure was recorded via an electronic transducer (Devices/C.E.C. type 4-327-4221) and heart-rate computed from the blood pressure pulse (Devices Instantaneous Ratemeter 2751), both being recorded with an electronic recorder.

All drugs for intracerebroventricular (i.c.v.) administration were made up in 0.9% w/v sodium chloride solution (saline) and were infused in a total volume of 100 μl over a 4 min period using a constant infusion pump (Scientific and Research Instruments Ltd).

Experiments using anaesthetized cats

Six cats were used, all of which had been previously cannulated for chronic studies as described above. Three were anaesthetized with a gaseous mixture of nitrous oxide (80%) and halothane (1-3%) in oxygen for the duration of the experiment and were subsequently allowed to recover. The remaining animals were anaesthetized with chloralose (80 mg/kg i.v.) and were not allowed to recover.

Experiments using conscious rabbits

Ten New Zealand white rabbits of either sex weighing 2-4 kg were used. They were prepared for blood pressure and heart-rate recording and for i.v. and i.c.v. administration of drugs in the same way as the cats.

Experiments using conscious rats

Cannulae were implanted into the left lateral cerebral ventricles of ten male rats (200-500 g) under gaseous anaesthesia, as described by Hayden, Johnson & Maickel (1966). One week later, flexible plastic cannulae were inserted into the right common carotid artery and the right jugular vein, as described by Popovic & Popovic (1960).

Drugs for i.c.v. administration were made up in saline and injected in 10 μl volumes using a micro-syringe.

Drugs used

(−)-Noradrenaline hydrochloride (Sigma); (−)-α-methyl-noradrenaline (Corbasil, Hoechst); clonidine hydrochloride (C.H. Boehringer Sohn); phentolamine methane sulphonate (Rogitine, Ciba); (−)-adrenaline acid tartrate (BDH), (−)-isoprenaline sulphate (BDH); salbutamol (Allen and Hanburys, Ltd); dopamine hydrochloride (Sigma); (±)-propranolol hydrochloride, (+)-propranolol, (−)-propranolol (ICI); (±)-alprenolol, (+)-alprenolol (Astra); sotalol (MJ1999, Mead Johnson); practolol (ICI); pempidine tartrate (May & Baker Ltd); hexamethonium bromide (Koch-Light Labs Ltd); bethanidine sulphate (Burroughs Wellcome & Co.); atropine methonitrate (BDH); lignocaine hydrochloride (BDH).

All doses of drugs quoted are expressed in terms of the salts except those of salbutamol, (+)- and (−)-propranolol, (+)-alprenolol and practolol which are expressed in terms of the base.

Results

Experiments using conscious unrestrained cats

Agonists and antagonists at α-adrenoceptors. The effects on heart rate and systemic arterial blood pressure of three α-adrenoceptor agonists given into the lateral ventricles were recorded. All three agonists, noradrenaline (15, 20 and 30 μg),

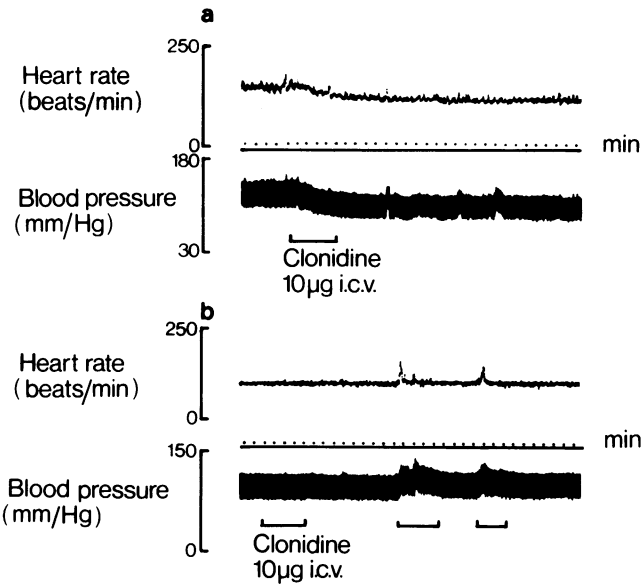

Fig. 1 Blood pressure and heart-rate records from a conscious cat. In (a) clonidine (10 μg i.c.v.) was infused during the 4 min period indicated and caused a fall in blood pressure with bradycardia; both these responses to clonidine were abolished in (b) 60 min after the administration of phentolamine (600 μg i.c.v.). The horizontal bars in (b) indicate cardiovascular changes caused by the cat moving.

α-methylnoradrenaline (15, 30 and 40 μg) and clonidine (2.5, 5 and 10 μg), produced dose-related falls in heart-rate and in both systolic and diastolic systemic blood pressures. The maximal effects of a given dose of noradrenaline and α-methylnoradrenaline were usually reached 4-6 min after administration. Blood pressure and heart-rate returned to control levels about 30 min after noradrenaline and 45 to 60 min after α-methylnoradrenaline. The maximal response to clonidine usually occurred 35-45 min after infusion and did not completely subside until after 90-120 minutes. The maximal effects on blood pressure and heart-rate of the three α-adrenoceptor agonists are summarized in Table 1.

The α-adrenoceptor blocking agent phentolamine (0.5-1 mg) infused into the ventricles regularly caused a small rise in resting heart-rate and arterial blood pressure. The responses to each of the α-adrenoceptor agonists were abolished when administered 60 min after phentolamine (Figure 1). Responses to peripherally administered

Table 1 Maximal blood pressure and heart-rate responses (mean ± s.e.) induced by three α-adrenoceptor agonists administered into the lateral cerebral ventricles of conscious cats.

α-agonist	*Total dose (μg i.c.v.)*	*No. of responses*	*Arterial blood pressure decrease (mm Hg) Systolic*	*Diastolic*	*Heart-rate decrease (beats/min)*	*No. of cats*
Noradrenaline	15	4	12.3 ± 3.6	16.2 ± 2.9	20.3 ± 3.1	
	20	4	19.4 ± 2.9	16.7 ± 2.3	25.7 ± 2.7	12
	30	6	23.6 ± 2.5	19.1 ± 2.0	29.4 ± 2.5	
α-Methyl	15	5	10.7 ± 2.1	12.1 ± 3.2	15.1 ± 3.6	
noradrenaline	30	6	24.1 ± 1.8	25.6 ± 2.8	28.6 ± 2.3	7
	40	3	27.4 ± 3.9	30.0 ± 4.3	35.5 ± 5.1	
Clonidine	2.5	5	18.8 ± 2.1	16.0 ± 2.0	15.6 ± 4.3	
	5.0	5	21.5 ± 2.6	18.3 ± 2.3	27.4 ± 3.2	10
	10	5	28.3 ± 1.9	23.7 ± 2.1	35.8 ± 4.7	

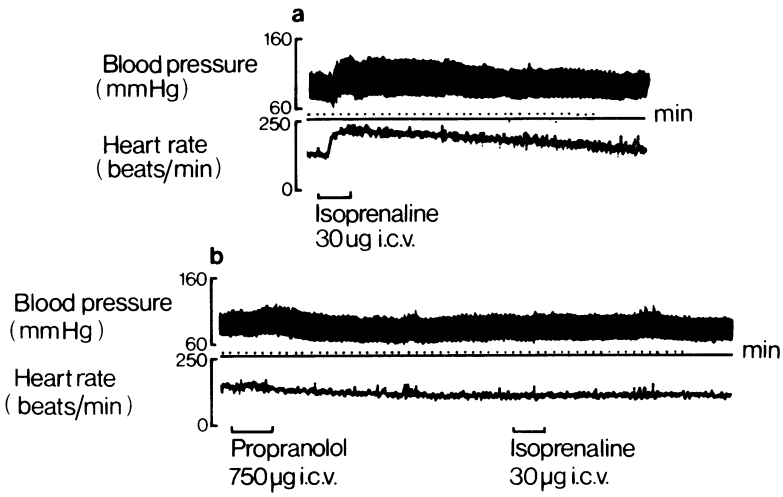

Fig. 2 Blood pressure and heart-rate records from a conscious cat. In (a) isoprenaline (30 µg i.c.v.) was infused over the 4 min period indicated. In (b) propranolol (750 µg i.c.v.) was infused and subsequently the responses to isoprenaline (i.c.v.) were abolished.

α-adrenoceptor agonists remained unaltered after abolition of i.c.v. responses.

Responses to i.c.v administration of the α-adrenoceptor agonists were unaffected by prior i.c.v. administration of the β-adrenoceptor blocking drugs, (±)-propranolol and (±)-alprenolol, each given in doses of 0.5-1 mg.

Agonists and antagonists at β-adrenoceptors. The β-adrenoceptor agonists tested were isoprenaline (5-60 µg) and salbutamol (45 and 60 µg). Isoprenaline was given i.c.v. to 20 cats and in 12 it regularly produced dose-related increases in blood pressure while in five others it produced consistent dose-related falls in blood pressure. In two cats, the blood pressure responses were biphasic and the blood pressure of one cat failed to respond to isoprenaline (60 µg). In all 20 cats, i.c.v. isoprenaline produced a consistent and dose-related tachycardia. The blood pressure and heart-rate changes after i.c.v. isoprenaline reached a peak within 10 min of the end of infusion and had returned to control levels by 45-60 minutes. Salbutamol produced smaller increases in blood pressure and heart-rate than similar doses of isoprenaline. However, the salbutamol responses took 15-25 min to reach a peak and did not subside completely until 2-3 h from the end of the infusion. The mean peak blood pressure and heart-rate responses to i.c.v. isoprenaline are summarized in Table 2.

In each of six cats which regularly responded with pressor responses to isoprenaline (30 µg i.c.v.), i.c.v. administration of either (±)-propranolol or (±)-alprenolol (0.5-1 mg) completely abolished both blood pressure and heart-rate responses to i.c.v. isoprenaline. Figure 2 illustrates an experiment in which isoprenaline (30 µg i.c.v.) caused a marked rise in blood pressure and heart-rate. Administration of (±)-propranolol (750 µg i.c.v.) caused a typical response, consisting of a slight initial pressor response and tachycardia followed by a prolonged fall in blood pressure with associated bradycardia. Isoprenaline (30 µg i.c.v.) after (±)-propranolol did not affect blood pressure or heart-rate.

In each of the group of five cats in which i.c.v. isoprenaline regularly produced falls in blood pressure with associated tachycardia, these responses were unaffected by phentolamine (0.5 mg i.c.v.) but were abolished after either i.c.v. (±)-propranolol or (±)-alprenolol at doses of 0.5-1 mg.

The effects of i.c.v. isoprenaline, salbutamol and the β-adrenoceptor antagonists were apparently confined to the brain since abolition of central responses to β-agonists with the β-blockers did not affect responses to i.v. isoprenaline or salbutamol.

In five cats which regularly responded with pressor responses to isoprenaline (30 µg i.c.v.), salbutamol (60 µg i.c.v.) or dopamine (45 µg i.c.v.) pretreatment with (+)-propranolol (500 µg i.c.v.) did not significantly affect the responses whilst they were abolished after the same treatment with (−)-propranolol. Similarly, (±)-alprenolol

(0.5-1 mg i.c.v.) blocked the effects of i.c.v. β-agonists whilst the (+)-isomer at the same dose levels was ineffective (see Figure 3).

Sotalol (2 mg i.c.v.) and practolol (2 mg i.c.v.), β-adrenoceptor blocking drugs with low local anaesthetic activity, reduced markedly the blood pressure and heart-rate increases induced by isoprenaline (30 μg i.c.v.) while the local anaesthetic lignocaine (500 μg i.c.v.) lacked effect.

Adrenaline. Adrenaline is known to possess both α- and β-adrenoceptor stimulant properties when given peripherally and was therefore given i.c.v. to each of 12 cats. When given alone, adrenaline (60 and 120 μg i.c.v.) produced complex blood pressure responses consisting of pressor and depressor components and similarly variable effects on heart-rate. However, in five cats pretreated with (±)-propranolol (500 μg i.c.v.) 1 h previously the response to i.c.v. adrenaline was a dose-related fall in heart-rate and in both systolic and diastolic blood pressures. These effects were abolished by the subsequent i.c.v. administration of phentolamine (0.5 mg). Similarly, in seven cats initially treated with phentolamine (0.5 mg i.c.v.), i.c.v. adrenaline caused a dose-related increase in heart-rate and blood pressure and these effects were abolished by i.c.v. administration of either (±)-propranolol or (±)-alprenolol, in doses of 0.5-1 mg (Table 3).

Dopamine. Dopamine is known to be present in the brain and is generally believed to possess a neurotransmitter function in addition to acting as a precursor of noradrenaline. Dopamine (30 and 45 μg) was administered i.c.v. to six cats. Both doses regularly produced increases in heart-rate and blood pressure. The time courses of the responses were similar to those for isoprenaline, the peak being reached in about 10 min and the response being complete in 30-45 minutes. The mean peak blood pressure and heart-rate responses are summarized in Table 4 and it can be seen that whereas dopamine was more potent than isoprenaline in raising the blood pressure it was much less effective in causing tachycardia (compare Tables 2 and 4). In particular, dopamine is more potent than isoprenaline in elevating the diastolic blood pressure.

Prior treatment with phentolamine (0.5 mg i.c.v.) did not affect the cardiovascular changes brought about by i.c.v. dopamine but both blood pressure and heart-rate responses were completely abolished by pretreatment with (±)-propranolol or (±)-alprenolol (0.5-1 mg i.c.v.). Figure 3 illustrates an experiment in which the pressor response and slight tachycardia after dopamine (30 μg i.c.v.) were abolished after (±)-alprenolol (750 μg i.c.v.) but were unaffected by the same dose of (+)-alprenolol.

Dopamine (30-45 μg i.c.v.) produced typical pressor responses and slight tachycardia when administered to three cats from the group of five that responded with hypotensive responses after i.c.v. isoprenaline. The pressor effects of i.c.v. dopamine in these cats were abolished after central pretreatment with either (±)-propranolol or (±)-alprenolol (0.5-1.0 mg).

Effect of drugs modifying peripheral autonomic function. In each of six cats the pressor responses and tachycardias induced by i.c.v. administration of either isoprenaline, dopamine or adrenaline (after phentolamine) were abolished after autonomic ganglion blockade with pempidine (5 mg/kg i.v.) or hexamethonium (5 mg/kg i.v.).

Table 2 Maximal blood pressure and heart rate responses (mean ± s.e.) produced by i.c.v. salbutamol and isoprenaline in conscious cats. The data for isoprenaline are divided into groups; those obtained from cats which consistently responded to repeated applications of isoprenaline with pressor responses and those obtained from cats which consistently gave depressor responses to isoprenaline.

β-agonist	*Total dose (μg i.c.v.)*	*No. of responses*	*Arterial blood pressure change (mm Hg)*		*Heart rate increase (beats/min)*	*No. of cats*
			Systolic	*Diastolic*		
Salbutamol	45	10	+9.4 ± 2.6	+8.3 ± 1.5	45.3 ± 3.2	5
	60	12	+15.6 ± 1.8	+12.3 ± 2.1	58.1 ± 2.8	
Isoprenaline	5	16	+5.3 ± 1.9	+4.8 ± 2.3	15.9 ± 2.4	
(pressor responses)	15	20	+10.9 ± 2.6	+6.5 ± 2.7	25.3 ± 3.3	12
	30	46	+23.9 ± 1.5	+14.5 ± 1.6	76.8 ± 2.8	
	60	26	+26.8 ± 2.9	+15.7 ± 3.1	83.3 ± 3.4	
Isoprenaline	15	10	−9.4 ± 2.2	−8.9 ± 2.7	24.9 ± 3.9	
(depressor responses)	30	23	−16.0 ± 3.1	−18.7 ± 2.4	78.1 ± 4.8	5
	60	9	−22.0 ± 3.4	−24.6 ± 3.7	83.1 ± 5.2	

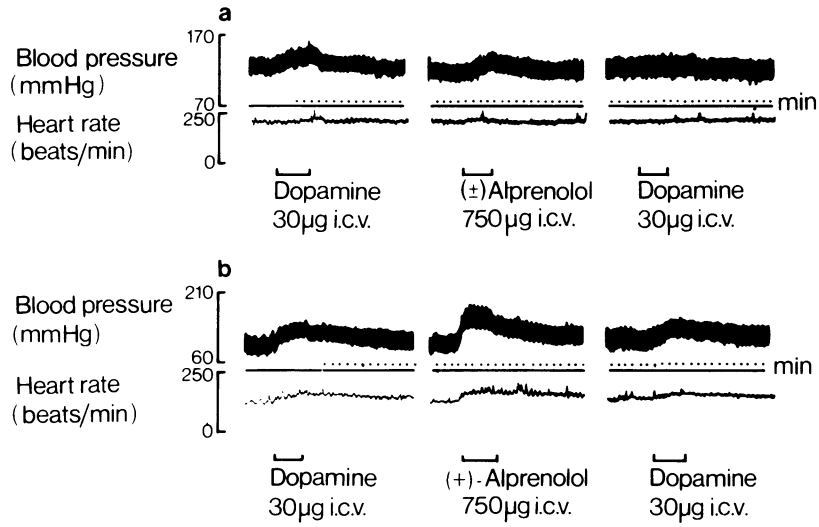

Fig. 3 Blood pressure and heart-rate records from a conscious cat. Record (a) shows (±)-alprenolol (750 μg i.c.v.) abolishing the cardiovascular changes induced by dopamine (30 μg i.c.v.). Record (b), which was obtained from the same cat on a different day, shows the lack of effect of (+)-alprenolol (750 μg i.c.v.) on the responses to dopamine (30 μg i.c.v.). In both experiments, the second dopamine (i.c.v.) infusion was made 60 min after the alprenolol infusion.

Similarly, in six other experiments the responses to i.c.v. isoprenaline or dopamine were abolished after peripheral adrenergic neurone blockade with bethanidine (5 mg/kg i.v.). The effect of atropine methonitrate (0.5 mg/kg i.v.) was tested on nine occasions in four cats each of which regularly responded with pressor responses to isoprenaline (30 μg i.c.v.). Thirty minutes after atropine methonitrate the mean tachycardia in response to i.c.v. isoprenaline was increased from 80 ± 2.9 to 139 ± 4.3 beats/min, the mean systolic blood pressure increased from 25 ± 1.2 to

Table 3 Maximal changes in blood pressure and heart-rate (mean ± s.e.) induced by i.c.v. adrenaline in conscious cats pretreated with either (±)-propranolol (0.5 mg i.c.v.) or phentolamine (0.5 mg i.c.v.).

Drugs (i.c.v.)	*Total dose (μg i.c.v.)*	*No. of responses*	*Arterial blood pressure change (mm Hg)* *Systolic*	*Diastolic*	*Heart rate change (beats/min)*	*No. of cats*
Adrenaline	60	3	−10.7 ± 3.5	−15.1 ± 4.1	−20.9 ± 5.1	5
(after (±)-propranolol	120	4	−18.9 ± 4.3	−19.3 ± 3.9	−32.6 ± 4.8	
Adrenaline	60	10	+18.9 ± 2.4	+14.3 ± 2.5	+39.7 ± 3.0	7
(after phentolamine)	120	12	+25.0 ± 3.8	+20.7 ± 3.1	+49.3 ± 4.2	

Table 4 Maximal increases in blood pressure and heart rate (mean ± s.e.) produced by i.c.v. dopamine in conscious cats.

Drug (i.c.v.)	*Total dose (μg i.c.v.)*	*No. of responses*	*Arterial blood pressure increase (mm Hg)* *Systolic*	*Diastolic*	*Heart rate increase (beats/min)*	*No. of cats*
Dopamine	30	15	28.5 ± 3.2	25.5 ± 3.6	15.5 ± 4.1	6
	45	10	36.8 ± 5.0	31.4 ± 4.8	22.1 ± 4.9	

Table 5 Comparison of maximal pressor responses and tachycardias produced by i.c.v. isoprenaline in conscious rabbits and rats. Values are mean ± s.e. of groups of 10.

	Rabbit		*Rat*	
Isoprenaline dose (i.c.v.)	*150 μg*	*300 μg*	*0.3 μg*	*0.5 μg*
Blood pressure increase (mm Hg)				
Systolic	10.2 ± 3.7	19.6 ± 4.6	20.6 ± 5.0	25.3 ± 4.9
Diastolic	11.1 ± 4.1	18.9 ± 4.3	19.3 ± 3.9	22.9 ± 4.4
Heart rate increase (beats/min)	35.6 ± 6.3	50.4 ± 5.9	49.7 ± 6.8	58.6 ± 7.1

32 ± 1.0 mmHg and the mean diastolic rose from 14 ± 0.8 to 16 ± 1.1 mmHg.

Experiments using anaesthetized cats

Three cats were anaesthetized with a gaseous mixture of halothane (1-3%), nitrous oxide and oxygen. All these cats had responded in the conscious state with blood pressure rises and tachycardia to isoprenaline (30 μg i.c.v.). Under gaseous anaesthesia the responses to i.c.v. isoprenaline were unaltered in extent and time course.

Three further cats were anaesthetized with chloralose (80 mg/kg i.v.). This group included one cat which regularly responded to i.c.v. isoprenaline in the conscious state with a fall in blood pressure. As with the previous group the responses to i.c.v. isoprenaline were unchanged in the anaesthetized state when compared with the corresponding responses obtained in the conscious animal.

Experiments using conscious rabbits and rats

Isoprenaline was infused i.c.v. into a group of ten conscious rabbits and into ten conscious rats. Both species produced qualitatively similar results, each animal responding with a dose-related rise in blood pressure and heart-rate. The results for each group are summarized in Table 5.

Discussion

In conscious cats, α-adrenoceptor stimulant substances such as noradrenaline, α-methylnoradrenaline and clonidine caused falls in both heart-rate and in systemic arterial blood pressure when administered into the cerebral ventricles, confirming effects reported by others in anaesthetized animals. These effects are apparently mediated via stimulation of α-adrenoceptors in the brain since they were abolished after the i.c.v. administration of phentolamine but were unaffected by i.c.v. propranolol or alprenolol. Schmitt, Schmitt, Boissier, Guidicelli & Fichelle (1968) proposed that the α-adrenoceptors involved in the cardiovascular responses to substances such as clonidine are situated in the medulla oblongata and that activation of them induces a reduction in sympathetic efferent tone to the resistance vessels of the vasculature and to the heart resulting in hypotension and bradycardia. Such a mechanism would explain the antihypertensive effects of α-methyldopa, L-DOPA and clonidine in clinical use. In our experiments, we have regularly noticed a slight tachycardia and increase in blood pressure after i.c.v. phentolamine which would be consistent with its reducing the normal level of α-adrenoceptor activation and might also explain the relative ineffectiveness of α-adrenoceptor blockers in the treatment of hypertension (Beilin & Juel-Jensen, 1972).

In addition to central α-adrenoceptors, activation of which produces bradycardia and hypotension, our results suggest the presence of central β-adrenoceptors with opposing effects. In the majority of cats used in this study, i.c.v. isoprenaline caused dose-related increases in both blood pressure and heart-rate and these effects were abolished after i.c.v. β-adrenoceptor blocking agents. After i.c.v. isoprenaline, the systolic pressure was more markedly increased than was the diastolic pressure and, in addition, abolition of peripheral vagal tone with atropine methonitrate caused a further increase in the systolic pressure and heart-rate responses to i.c.v. isoprenaline. These observations suggest that the increase in blood pressure to i.c.v. isoprenaline has a marked cardiac component and that the blood pressure changes may be a result of the tachycardia. In 25% of the cats used, i.c.v. isoprenaline regularly produced falls in blood pressure but the heart rate increases were similar to those observed in the cats which responded with increases in blood pressure. The depressor effects of i.c.v. isoprenaline were apparently central in origin since they were abolished by i.c.v. administration of β-adrenoceptor blockers in doses which did not alter the responses to systemically administered isoprena-

line. The blood pressure and heart-rate responses to i.c.v. β-adrenoceptor agonists were apparently mediated via the peripheral sympathetic system since both responses were abolished after peripheral autonomic ganglion blockade. Moreover, the effects were also abolished after peripheral adrenergic neurone blockade with bethanidine, suggesting that release of catecholamines from the adrenal medulla did not contribute significantly to the responses.

Other workers have reported hypotensive responses to i.c.v. isoprenaline in anaesthetized cats (Gagnon & Melville, 1967), dogs (Bhargava *et al.*, 1972), and rabbits (Toda *et al.*, 1969). Although we observed hypotensive responses in some cats, in groups of ten conscious rabbits and rats we observed small increases in blood pressure and in all animals there were marked increases in heart rate in response to i.c.v. isoprenaline. The difference between previous reports and the present experiments is apparently, for the cat at least, not explicable solely by a difference between anaesthetized and conscious animals. We found that the response to i.c.v. isoprenaline was unchanged, whether pressor or depressor, in cats tested in both conscious and anaesthetized states.

The results obtained with i.c.v. adrenaline in the cat afforded convincing evidence of the presence of both α- and β-adrenoceptors producing opposing effects in the brain. Thus, effects due to stimulation of either α- or β-adrenoceptors could be elicited with i.c.v. adrenaline when administered after an appropriate blocking agent. Surprisingly, i.c.v. dopamine produced effects resembling those of β-adrenoceptor stimulation in contrast to its peripheral effects. However, there were differences between the central effects of dopamine and isoprenaline. Firstly, i.c.v. dopamine always caused a rise in blood pressure, even in those cats which responded with a fall to i.c.v. isoprenaline. Secondly, dopamine produced a more marked effect on the diastolic pressure than did isoprenaline and it was much less active in causing tachycardia than isoprenaline. A quantitative difference between i.c.v. dopamine and isoprenaline was the dose required to produce centrally-mediated cardiovascular changes. The i.c.v. dose of isoprenaline was many times higher than that required by the systemic route to produce marked effects whereas the effective i.c.v. and peripheral doses of dopamine were similar. However, the effects of i.c.v. dopamine and isoprenaline were both abolished by similar i.c.v. doses of β-adrenoceptor blockers and were similarly unaffected by i.c.v. phentolamine. It would appear, therefore, that more than one type of central β-adrenoceptor may exist, although little is known about the precise position of adrenoceptors within the brain or about the structures reached by drugs given by the i.c.v. route.

The β-adrenoceptor blocking drugs, (±)-propranolol and (±)-alprenolol, are known to be potent local anaesthetics and experiments were performed to confirm that it was not this property which caused the abolition of responses to i.c.v. β-adrenoceptor stimulants. It was clear from these studies that the (+)-isomers, which are equi-potent with the (−)-isomers as local anaesthetics but are relatively inactive as β-adrenoceptor blockers (see Fitzgerald, 1969), did not significantly affect the responses to i.c.v. β-adrenoceptor agonists. Moreover, the local anaesthetic lignocaine did not affect responses to i.c.v. β-adrenoceptor agonists whereas β-adrenoceptor blockers sotalol and practolol, which have low local anaesthetic potency, markedly reduced these responses. It was of interest to note that i.c.v. (+)- propranolol and (+)-alprenolol caused marked initial pressor effects resembling the responses to i.c.v. isoprenaline. This property was also shown by i.c.v. lignocaine; thus it may be that some of the so-called partial agonist activity of the β-adrenoceptor blockers may be related to their local anaesthetic activity. Dollery, Lewis, Myers & Reid (1973) have made a similar suggestion from their experiments in conscious rabbits.

Despite the initial stimulant effects, all the β-adrenoceptor blocking drugs used produced falls in both blood pressure and heart-rate of long duration. It is tempting to speculate that some at least of the useful clinical properties of these drugs are due to effects on central β-adrenoceptors.

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