THE EFFECT OF BACLOFEN ON THE CARDIOVASCULAR SYSTEM OF THE RAT

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1 The cardiovascular responses to baclofen were investigated in anaesthetized rats.

2 Low doses of baclofen (less than 5×10^{-8} mol), given intravenously, produced a transient fall in blood pressure and heart rate. Higher doses (greater than 5×10^{-7} mol) produced a marked and prolonged increase in blood pressure accompanied by a rise in heart rate and cutaneous arterial dilatation.

3 The pressor and heart rate responses exhibited tachyphylaxis, and were abolished by hexamethonium, cervical cord section, reserpine-treatment and by a combination of α- and β-adrenoceptor antagonists.

4 It is concluded that the increases in blood pressure and heart rate produced by high doses of baclofen are of central sympathetic origin.

Introduction

Baclofen [β-(4-chlorophenyl)-γ-amino butyric acid] is an analogue of γ-aminobutyric acid (GABA) capable of crossing the blood brain barrier (Faigle & Keberle, 1972). It is effective in the treatment of spasticities of spinal origin (Birkmayer, 1972 cited by Benecke & Meyer-Lohmann, 1974), but its mechanism of action is still unclear. It was reported to antagonize the motoneurone-depolarizing action of substance P in the spinal cord (Saito, Konishi & Otsuka, 1975), and in the course of a study of its action on the peripheral effects of substance P it was observed that baclofen produced a marked and prolonged rise in blood pressure of the rat. Since, to our knowledge, this effect of baclofen had not been described previously, the nature of this response was investigated.

Methods

Blood pressure experiments

Male rats, derived from the Wistar strain (200 to 300 g) were anaesthetized with urethane (1000 to 1250 mg/kg) or urethane (625 mg/kg) and sodium pentobarbitone (20 mg/kg). The trachea, femoral vein and left carotid artery were cannulated. Arterial blood pressure was recorded from the carotid artery by means of a Statham P23AC transducer and a Grass Polygraph. In several experiments venous pressure was also recorded via a cannula in the right jugular vein. Heart rate, derived from the arterial pulse pressure wave, was recorded using a Grass EKG Tachograph preamplifier. Heparin (300 units) was administered intravenously. All drugs were administered in warm saline via the femoral vein cannula. Antagonist drugs were given 2 to 3 min before testing agonist responses, except for phenoxybenzamine which was administered 30 min before the agonists. Infusions of noradrenaline were given by means of a Palmer Injection Apparatus. The spinal cord of some rats was cut at the cervical level before heparin administration, and artificial ventilation was maintained using a Palmer small animal respiration pump. One group of rats was pretreated 24 h before the day of experiment with reserpine (10 mg/kg) intraperitoneally.

Photomacroscope experiments

Rats (150 to 250 g) were anaesthetized with urethane and blood pressure and heart rate were recorded as described above. The fur on the right hind leg was shaved and a longitudinal incision was made in the skin of the lateral aspect of the thigh. The skin was carefully separated from underlying tissues, and a flap with the inner surface uppermost, was placed over a translucent perspex table (1.5 cm diameter) on the stage of a Wild Photomakroskop (model M400), according to the method of Chahl & Ladd (1976). The

skin was anchored in position with cotton threads and trans-illuminated with a tungsten-halogen light source. It was kept moist with regular applications of Tyrode solution at 37°C. Magnification was 16×. Photomacrographs were taken at timed intervals before and after intravenous drug administration, and changes in the width of small arteries and veins thus recorded, were correlated with changes occurring simultaneously in the systemic blood pressure. Exposures were controlled automatically with a Wild Photoautomat (model MPS 55).

Drugs

The following drugs were used: acetylcholine chloride (Sigma); atropine sulphate (MacFarlan Smith Ltd); baclofen (Lioresal, Ciba-Geigy); bicuculline (Sigma); γ-aminobutyric acid (Sigma); hexamethonium bromide (Koch-Light); histamine diphosphate (Sigma); 5-hydroxytryptamine creatinine sulphate (Sigma); (−)-isoprenaline bitartrate (Sigma); mepyramine maleate (May and Baker); methysergide hydrogen maleate (Sandoz); nicotine hydrogen tartrate (BDH); (−)-noradrenaline bitartrate (Sigma); phenoxybenzamine hydrochloride (Smith, Kline and French); pindolol (Sandoz); (±)-propranolol hydrochloride (Sigma); reserpine ('Serpasil', Ciba); substance P (Protein Research Foundation, Osaka, Japan). Ascorbic acid 0.1 g/l was added to solutions of noradrenaline and isoprenaline.

Results

Baclofen was found to have two different effects on blood pressure depending on the dose administered. At doses less than 5×10^{-8} mol, a transient fall in blood pressure and heart rate occurred (Figure 1), whereas higher doses (greater than 5×10^{-7} mol) produced a prolonged rise in both blood pressure and heart rate, usually accompanied by a fall in central venous pressure (Figure 2). Intermediate doses produced a fall followed by a rise in blood pressure. The depressor response was not antagonized by atropine, mepyramine or methysergide in experiments where responses to acetylcholine, histamine and 5-hydroxytryptamine respectively, were reduced or abolished (Table 1). However, the decrease in heart rate produced by baclofen was abolished by atropine. In 5 rats the depressor response to baclofen was reduced by propranolol and pindolol, but the response returned earlier than the response to isoprenaline (Figure 1). Propranolol produced greater reduction of the response to baclofen than did pindolol.

The time course of the pressor response to baclofen (2.5×10^{-6} mol) followed over 1 h in 10 rats is shown in Figure 3. It can be seen that the pressor response
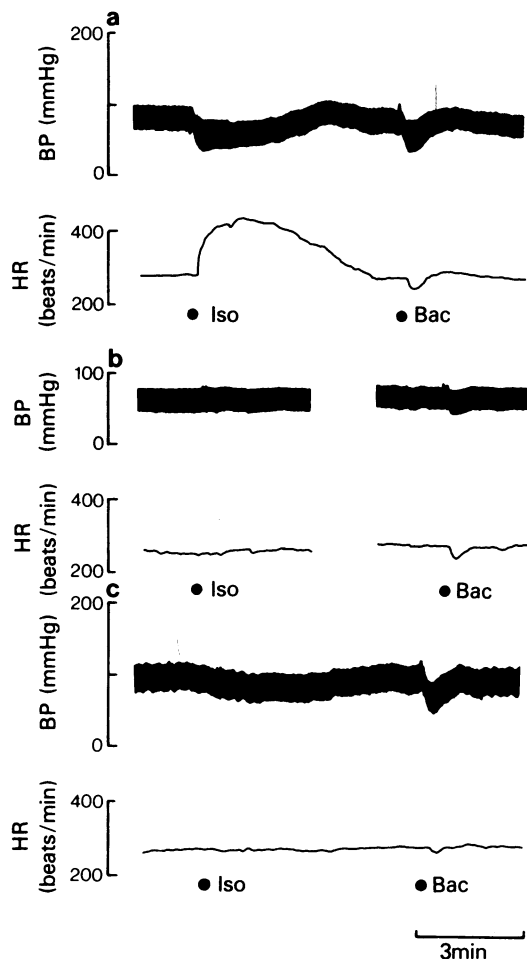

Figure 1 Duration of antagonism by pindolol (6×10^{-7} mol) of arterial blood pressure (BP) and heart rate (HR) responses to isoprenaline (Iso) 2×10^{-9} mol and baclofen (Bac) 2×10^{-8} mol; (a) shows control responses before pindolol administration; (b) responses 5 min after intravenous injection of pindolol; and (c) response 25 min after pindolol. Note that when the depressor response to baclofen had returned to normal, the response to isoprenaline was still greatly reduced.

reached a peak at about 10 min, thereafter it declined slowly, and blood pressure returned to normal after 1 h. The increase in heart rate was slower to reach its peak than was the pressor response but it remained elevated longer. The heart rate response was usually reproducible to a second dose of baclofen, but the pressor response was not, and a second dose administered up to 1 h after the first dose, often produced a fall in blood pressure. The pressor response was reliably observed only when the first dose of baclofen
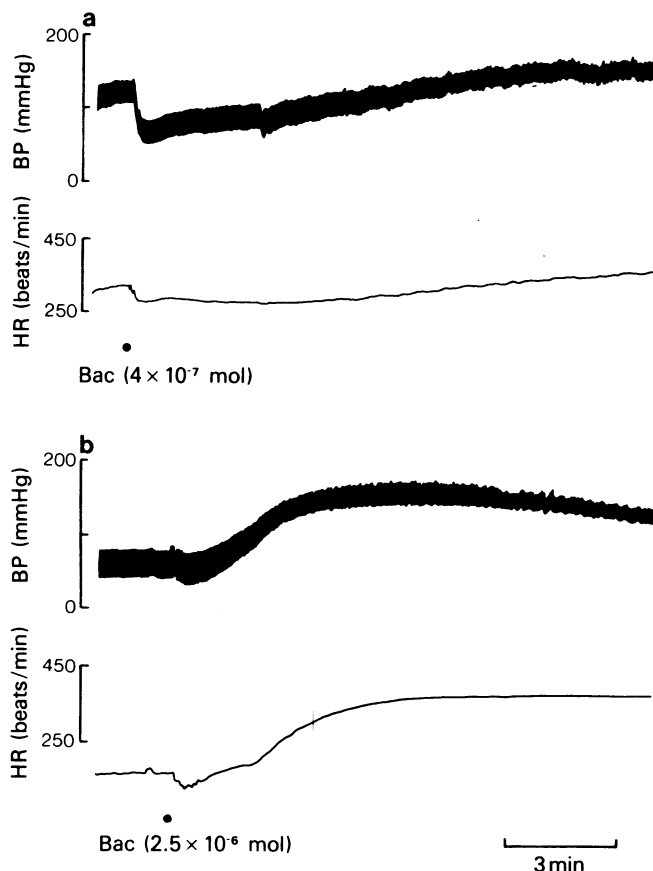
Figure 2 The effect of two doses of baclofen (Bac) on arterial blood pressure (BP) and heart rate (HR): (a) shows a typical response to an intermediate dose of 4×10^{-7} mol, and (b) a response to a high dose of 2.5×10^{-6} mol in another rat. With this dose the pressor response obscured the depressor response. Note the marked and prolonged nature of the pressor response.

was high, and not when gradually increasing doses were given. The pressor response was less marked in younger rats weighing 100 to 150 g. The increases in blood pressure and heart rate produced by baclofen were abolished by cervical cord section, by hexamethonium and also by a combination of phenoxybenzamine and propranolol or by pretreatment of rats with reserpine. When the pressor response to baclofen was abolished a slight prolonged fall in blood pressure occurred with this dose of baclofen.

The photomacroscope experiments showed that the pressor response to baclofen was accompanied by cutaneous arterial dilatation that was maintained for at least 20 min after baclofen administration (Figure 4). Although the pressor response was not reproducible with a second dose of baclofen, the cutaneous arterial dilatation was often greater. In 2 of the 12 rats used for these experiments there was little increase in

blood pressure in response to baclofen and in these rats venous constriction was seen rather than arterial dilatation. In contrast to these findings, infusion of noradrenaline (7×10^{-8} to 7×10^{-7} mol over 5 min) which caused a similar increase in blood pressure and heart rate to baclofen, produced constriction of cutaneous arteries and veins, which persisted only for the duration of the infusion (Figure 4). Baclofen, administered following recovery from a noradrenaline infusion, failed to produce a pressor response, but cutaneous arterial dilatation was still observed. The response to noradrenaline infusion was not altered by prior administration of baclofen.

Substance P, in doses 10^{-11} to 10^{-10} mol, produced a fall in blood pressure usually accompanied by a rise in heart rate. The response to substance P was not antagonized by prior administration of baclofen (10^{-8} to 10^{-7} mol) and the fall in blood pressure
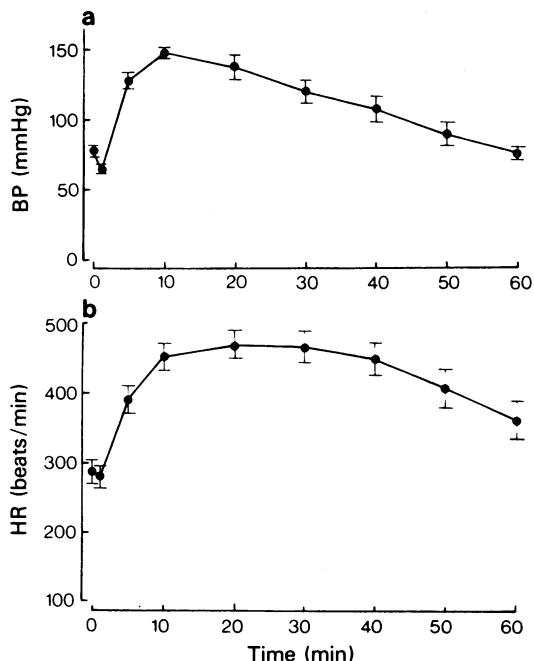
Figure 3 Time course of the increase in arterial blood pressure (a) and heart rate (b) produced by baclofen $(2.5 \times 10^{-6} \text{ mol})$. Points are average values for mean blood pressure (BP) and heart rate (HR) measured at intervals after intravenous baclofen administration in 10 rats. Vertical bars represent standard errors.

produced by substance P was usually greater after a pressor dose of baclofen $(2.5 \times 10^{-6} \text{ mol})$ probably due to the higher blood pressure.

When responses to low doses of GABA and baclofen $(10^{-8} \text{ to } 10^{-7} \text{ mol})$ were compared it was found that GABA was less potent in producing a fall in blood pressure than baclofen, but it had a greater depressant action on heart rate. Tachyphylaxis to the depressor action of GABA but not to baclofen occurred. Higher doses of GABA $(2.5 \times 10^{-6} \text{ mol})$ did not produce a pressor response but caused a prolonged fall in blood pressure. This response to GABA was unaffected by a subconvulsant dose of bicuculline $(7 \times 10^{-8} \text{ mol})$ whereas the pressor and heart rate responses to baclofen were enhanced and more prolonged.

Discussion

The results of these experiments have shown that baclofen in low doses produces a transient fall in arterial blood pressure, but at higher doses it produces a marked and prolonged pressor response and increase in heart rate. The depressor response to baclofen was

not mediated by release of acetylcholine, histamine or 5-hydroxytryptamine. However, it was blocked transiently by β-adrenoceptor blocking drugs, including pindolol, which is reported to have less membrane stabilizing activity relative to β-receptor blocking activity (Fitzgerald, 1972). The significance of this observation is not clear. It was not possible to determine whether or not the depressor response to baclofen was of central nervous system origin since the blood pressure was too low after hexamethonium or cervical cord section for the depressor response to baclofen to be observed. However, a cholinergic component appeared to be involved in the heart rate decrease produced by low doses of baclofen, since it was abolished by atropine. At higher doses of baclofen the depressor response was overridden by a pressor response. This response and the tachycardia which accompanied it, were of central sympathetic origin since they were abolished by cervical cord section, by treatment of rats with hexamethonium, and by a combination of α- and β-adrenoceptor antagonists. Baclofen has been found to have only a hypotensive effect in man and other animals (Brogden, Speight & Avery, 1974; Olpe, Demiéville, Baltzer, Bencze, Koella, Wolf & Haas, 1978). The different results observed in the present experiments might be explained by a species variation or by the tachyphylactic nature of the pressor response to baclofen. It is possible that other workers have failed to observe the pressor response because gradually increasing doses were administered.

The photomacroscope experiments indicated that the pressor response to baclofen was accompanied by cutaneous arterial dilatation. This was unexpected in light of the finding that infused noradrenaline, which caused a similar rise in blood pressure, produced cutaneous arterial and venous constriction. It would seem, therefore, that central sympathetic stimulation in the rat results in selectively greater constriction in regions other than in the skin. Alternatively, it is possible that in the skin the dilator response to baclofen, which at lower doses resulted in a fall in blood pressure, predominated over the central sympathetic effect. This is supported by the observation that high doses of baclofen in reserpine-treated rats or in those treated with α- and β-adrenoceptor antagonists produced a prolonged depressor response.

The pressor response to baclofen was not mimicked by GABA, probably because GABA did not cross the blood brain barrier. However, in these experiments the pressor action of baclofen did not appear to be due to an agonist action on central GABA receptors since it was enhanced rather than reduced by the GABA antagonist, bicuculline (Curtis, Duggan, Felix & Johnston, 1971). Other workers have also concluded that the action of baclofen might not be on central GABA receptors, but rather on central 5-hydroxytryptamine (Waldmeier & Fehr, 1978) or
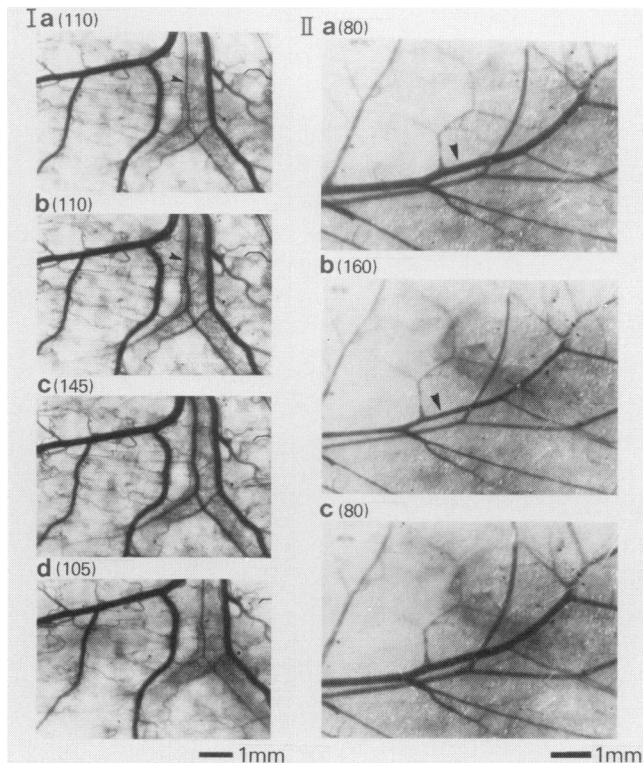
Figure 4 Photomacrographs showing responses of rat cutaneous vasculature to (I) intravenous baclofen (2.5×10^{-6} mol) and (II) intravenous infusion of noradrenaline (3.5×10^{-7} mol over 5 min). In each series, photograph (a) shows the state of the vasculature before drug administration and (b) shows the response 2 min after baclofen administration or start of noradrenaline infusion; (c) and (d) in I were taken 10 min and 30 min after baclofen administration and (c) in II was taken 2 min after cessation of noradrenaline infusion. Note, at arrows, arterial dilatation with baclofen and arterial and venous constriction with noradrenaline infusion. Arterial dilatation with baclofen did not parallel the rise in systemic blood pressure since the dilatation seen in (b) occurred before the rise in blood pressure and was maintained when blood pressure was elevated (c). (d) Shows recovery to normal after the pressor response had subsided in this rat. The weight range of rats used in these experiments was lower than that of rats used in the other experiments (see Methods) and their pressor responses to baclofen tended to be less sustained than indicated by the mean responses shown in Figure 3. Numbers in parentheses are mean systemic arterial blood pressures at the time photomacrographs were taken. Magnification $16 \times$.

Table 1   The effect of various pretreatments on the depressor and pressor responses of rats to baclofen

Pretreatment	No. of experiments	Response to agonist	Depressor response to baclofen (10^{-8} mol)
Atropine (7×10^{-7} mol)	12	Acetylcholine (10^{-9} mol) abolished	Unchanged (but heart rate fall abolished)
Mepyramine (5×10^{-7} mol)	3	Histamine (5×10^{-9} mol) abolished	Unchanged
Methysergide (2×10^{-7} mol)	3	5-Hydroxytryptamine (10^{-8} mol) depressor reversed to pressor	Unchanged
Propranolol (3×10^{-6} mol)	5	Isoprenaline (2×10^{-9} mol) abolished	Reduced transiently (see Fig. 1)
Pindolol (6×10^{-7} mol)	5		

			Pressor response to baclofen (2.5×10^{-6} mol)
Cervical cord section	5	—	Abolished
Hexamethonium (2.75×10^{-6} mol)	10	Nicotine (2×10^{-7} mol) abolished	Abolished
Phenoxybenzamine (6×10^{-6} mol) and propranolol (3×10^{-6} mol)	10	Noradrenaline (3×10^{-9} mol) and Isoprenaline (2×10^{-9} mol) abolished	Abolished
Reserpine (10 mg/kg i.p.) 24 h previously	5	—	Abolished
Bicuculline (7×10^{-8} mol)	5	—	Enhanced and prolonged

dopaminergic mechanisms (Da Prada & Keller, 1976; Waldmeier & Maitre, 1978). The reason for the tachyphylactic nature of the response and its suppression by prior infusion of noradrenaline is unknown, but it is perhaps relevant that tolerance to the effects of baclofen on dopaminergic neurones has been observed (Gianutsos & Moore, 1978).

Baclofen did not antagonize the peripheral action of substance P on the cardiovascular system. Fotherby, Morrish & Ryall (1976) also found that peripheral actions of substance P were not antagonized by baclofen.

The effect of baclofen on central cardiovascular centres described here may be useful in elucidating the mechanism of action of baclofen in the central nervous system.

Note added in Proof

Since acceptance of this paper, the pressor effect of baclofen has been described by: PERSSON, B. & HENNING, M. (1979). Cardiovascular effects of baclofen in the rat. *J. Pharm. Pharmac.*, **31**, 799–800.

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