Adrenalectomy abolishes antagonism of α -adrenoceptor-mediated hypotension by a β -blocker in conscious rats

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1 The effects of a single bolus injection of propranolol, atenolol or ICI 118,551, non-selective β -, selective β_1 - and selective β_2 -adrenoceptor antagonists, respectively, on mean arterial pressure (MAP) and plasma catecholamine concentrations were examined in seven groups of conscious and unrestrained adrenalectomized rats receiving a continuous infusion of the α -adrenoceptor antagonist phentolamine. In all rats adrenaline was undetectable in the plasma four days after adrenalectomy.

2 In the first three groups, phentolamine significantly decreased MAP and increased the plasma concentrations of noradrenaline. The injection of propranolol, atenolol or ICI 118,551 in Groups I, II and III, respectively, caused a small increase in MAP and a small, but not significant, decrease in plasma noradrenaline concentrations.

3 Groups IV, V and VI were given a continuous infusion of adrenaline for 1 h prior to the infusion of phentolamine, followed by a bolus injection of propranolol, atenolol or ICI 118,551, respectively. Group VII was treated similarly to IV, but was also given daily cortisone replacement after adrenalectomy. Adrenaline slightly, but not significantly, decreased MAP while phentolamine significantly decreased MAP and increased plasma noradrenaline concentrations in all groups. A subsequent injection of a β -blocker caused a significant increase in MAP in each group and a slight decrease in the plasma level of noradrenaline which reached statistical significance in group VII. The pressor effect of propranolol was significantly greater in the cortisone-treated rats (Group VII) than in Group IV.

5 The results suggest that adrenaline and adrenocortical steroids are both involved in the antagonism of α -adrenoceptor-induced hypotension by a β -blocker.

Introduction

A paradoxical pressor response to the administration of a β -adrenoceptor antagonist has been shown to occur in rats anaesthetized with urethane (Kayaalp & Turker, 1967; Dasgupta, 1968; Yamamoto & Sekiya, 1969; 1972; Regoli, 1970; Sugawara *et al.*, 1980; Himori *et al.*, 1984). The pressor response in the anaesthetized rat was enhanced in the presence of an α -adrenoceptor antagonist (Yamamoto & Sekiya, 1969; Regoli, 1970; Sugawara *et al.*, 1980). In contrast to these observations, we have recently found that the injection of propranolol into conscious rats (that were not previously treated with an α -adrenoceptor antagonist) did not produce a pressor response (Tabrizchi & Pang, 1989). However, we have observed that in conscious rats given a continuous infusion of the α -adrenoceptor antagonist phentolamine, a bolus injection of a β_1 -, β_2 - or non-selective β -adrenoceptor antagonist did cause a dose-dependent increase in mean arterial pressure (MAP) (Tabrizchi *et al.*, 1988). This discrepancy between the response to a β -adrenoceptor antagonist in the intact conscious and anaesthetized rat is not readily explained. However, urethane has been reported to antagonize the pressor response induced by an α -adrenoceptor agonist and increase the release of adrenaline from the adrenal medulla (Armstrong *et al.*, 1982). It is interesting that, in most reports where the administration of a β -adrenoceptor antagonist produced a pressor response, high plasma concentrations of catecholamines were found (Pritchard & Ross, 1966; Berlyne *et al.*, 1974; McMurtry, 1974; Tabrizchi *et al.*, 1988). The role of adrenaline in the pressor response to propranolol was suggested in a study by Himori *et al.* (1984) which showed that acute adrenalectomy prevented the pressor effect of propranolol in urethane-anaesthetized rats. Moreover, Grewal &

Kaul (1970) reported that adrenal gland enucleation abolished the pressor response to propranolol in guanethidine-treated renal hypertensive rats.

In the present study we investigated whether adrenaline was involved in the pressor response to a β_1 -, β_2 - or non-selective β -blocker in conscious α -adrenoceptor-blocked rats. Preliminary experiments had shown that adrenal enucleation did not completely eliminate adrenaline from the circulation and thus all rats were totally adrenalectomized four days before the study. Then the response to β -blockade was assessed in the absence or presence of an i.v. adrenaline infusion.

Methods

Surgical preparation

Four days prior to the study, male Sprague-Dawley rats (360–390 g, 12–13 weeks old) were prepared under halothane anaesthesia (1.5% halothane in air). A one-inch midline incision was made on the skin along the back. After moving the incision towards either side of the kidney, a small cut was made on the muscle posterior to the last rib. Both kidneys were located and the adrenals excised. Following surgery, the rats were kept warm (25°C) in the laboratory for observation for 6 h after which they were transferred to the animal housing unit, individually housed at a controlled temperature of 22°C with 12 h light/dark cycle and given free access to food (Purina rat chow) and water. None of the rats died from the surgical procedure. After recovery from surgery for four days, the rats were again anaesthetized with halothane. Cannulae were inserted into the iliac arteries for the measurement of MAP by a pressure transducer (P 23 ID, Statham, CA, U.S.A.) and heart rate (HR) by a tachograph (Model 7P4G, Grass Instrument, Mass, U.S.A.) and into both iliac veins for the administrations of drugs. In some rats, additional cannulae were

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placed in the right external jugular vein for the infusion of drugs. All cannulae were filled with heparinized saline (25 iu ml^{-1}) and tunnelled subcutaneously to the back of the neck, exteriorized and secured. The rats were allowed a recovery period of 6 h in the laboratory before experiments were started.

Experimental protocol

MAP and HR were continuously monitored in these conscious, unrestrained adrenalectomized rats prior to and during the administration of drugs. The rats were given >30 min to familiarize with the environment. There was no sign of any distress during the experiments. The rats were randomly divided into seven groups ($n = 8$ in each group). The first three groups received a continuous i.v. infusion of phentolamine ($0.3 \text{ mg kg}^{-1} \text{ min}^{-1}$) prior to the bolus injection of a β -blocker. At 10 min after the start of the infusion of phentolamine, propranolol ($100 \mu\text{g kg}^{-1}$), atenolol ($100 \mu\text{g kg}^{-1}$) or ICI 118,551 ($30 \mu\text{g kg}^{-1}$) was injected intravenously into rats in groups I, II and III, respectively. The doses of β -blocker chosen were those that completely restored MAP to control levels in intact animals treated with phentolamine (Tabrizchi *et al.*, 1988). These doses of atenolol and ICI 118,551 were selective for the antagonism of β_1 - and β_2 -adrenoceptors, respectively. Another three groups were given a continuous i.v. infusion of adrenaline ($0.3 \text{ mg kg}^{-1} \text{ min}^{-1}$). After a 1 h period of adrenaline infusion, a continuous i.v. infusion of phentolamine was also started followed 10 min later by an i.v. bolus injection of propranolol, atenolol or ICI 118,551 in groups IV, V and VI, respectively (doses as before). Rats in Group VII were given cortisone (50 mg kg^{-1} i.p., twice daily) after adrenalectomy. They were later given adrenaline and phentolamine infusions followed by propranolol as described in group IV. In all rats, three 1 ml arterial blood samples (equivalent to 4% of blood volume each) were taken for the measurement of plasma adrenaline and noradrenaline concentrations. In Groups I to III, a blood sample was taken 5 min before and 6 min following the administration of phentolamine and 1 min after the injection of a β -blocker. In Groups IV to VII, blood samples were taken prior to the infusion of adrenaline, 6 min after the infusion of phentolamine and 1 min after the injection of a β -blocker.

Catecholamine assays

Blood samples were slowly withdrawn into a 1 ml syringe over 20–30 s from the arterial cannula in order to avoid disturbance to the rat. All blood samples removed were replaced by an equal volume of normal saline. As observed previously (King *et al.*, 1985), there was no change in MAP following each blood sampling. The samples were immediately placed on ice, centrifuged and the plasma was removed and stored at -80°C . Plasma samples were assayed within 2 weeks for noradrenaline and adrenaline content by a modified method of reverse-phase ion pair high performance liquid chromatography (h.p.l.c.) with electrochemical detection (Davis *et al.*, 1981). The sensitivity of the catecholamine assay is 0.02 ng ml^{-1} . The coefficient of variation within the same assay (s.d./mean value $\times 100\%$) for 9 repeated measurements is 16 for noradrenaline and 6 for adrenaline. The h.p.l.c. method has been described previously (Tabrizchi *et al.*, 1988).

Drugs

All drugs were made up fresh daily and dissolved in normal saline, except for cortisone (11-dehydrocortisol) which was made into a suspension in 1% Ficoll 70 in normal saline. The following drugs were used: phentolamine HCl (CIBA Pharmaceutical Co., N.J., U.S.A.), propranolol, adrenaline, corti-

sone and atenolol (Sigma Chemical Co., MO, U.S.A.), ICI 118,551 (ICI, Macclesfield, England).

Statistical analysis

The data were assessed for statistical significance by analysis of variance. Repeated measures design was used for comparison of results obtained within the same group of rats and random design, for comparison between different groups of rats. Duncan's multiple range test was used to compare group means. In all cases a probability of error <0.05 was preselected as the criterion for statistical significance. All results are presented as mean $\pm$ s.e.

Results

Effects of β -antagonists in adrenalectomized rats

The infusion of phentolamine in adrenalectomized rats in Groups I, II and III significantly decreased MAP (Figure 1a). HR was increased in each of the groups, but the changes were

Figure 1 Mean arterial pressure (MAP, a), heart rate (HR, b) and plasma noradrenaline concentrations (c) of conscious adrenalectomized rats ($n = 8$ in each group) during control conditions (solid columns), after a continuous infusion of phentolamine (hatched columns) and after a bolus injection of propranolol, atenolol or ICI 118,551 (open columns) in Groups I, II and III, respectively. Values represent mean with s.e. shown by vertical bars. *Significantly different from control; ^bsignificantly different from phentolamine-treatment.

Figure 2 Mean arterial pressure (MAP, a) and heart rate (HR, b) of conscious adrenalectomized rats ($n = 8$ in each group) during control conditions (solid columns), during a continuous infusion of adrenaline (hatched columns), during a continuous infusion of phentolamine (open columns), and after a bolus injection of propranolol, atenolol or ICI 118,551 (cross-hatched columns) in non-cortisone-treated rats (Groups IV, V and VI, respectively), or after the injection of propranolol in cortisone-treated rats (Group VII). Values represent mean with s.e. mean shown by vertical bars. *Significantly different from control; ^bsignificantly different from adrenaline infusion; ^csignificantly different from phentolamine infusion.

only significant in Group II (Figure 1b). The adrenaline level was below the detection limit ($<0.1 \text{ pmol ml}^{-1}$) in all rats. The infusion of phentolamine significantly increased the plasma levels of noradrenaline in all groups (Figure 1c). A single bolus injection of propranolol, atenolol or ICI 118,551 in the adrenalectomized rats in Groups I, II and III, respectively, caused a small, but significant, increase in MAP (Figure 1a) and a small, and not significant, decrease in plasma noradrenaline level (Figure 1c). However, MAP after β -blocker injection was significantly less than that prior to phentolamine infusion. HR was not affected by any one of the β -blockers (Figure 1b).

Effects of β -antagonists in adrenalectomized rats given adrenaline infusion

The infusion of adrenaline over a 1 h-period in adrenalectomized rats in Groups IV, V, VI and VII caused a slight, but not significant, decrease in MAP (Figure 2a). The subsequent infusion of phentolamine significantly further decreased MAP in all groups. Against this background of hypotension, the bolus injection of propranolol, atenolol or ICI 118,551 in the non-cortisone-treated rats (Groups IV, V and VI, respectively) and propranolol in the cortisone-treated rats (Group VII) caused an increase in MAP. This pressor response to propranolol in Group VII was significantly greater than that in Group IV. In all cases, MAP after the injection of a β -blocker was significantly less than that measured prior to phentolamine infusion.

HR was slightly, but not significantly, increased by the infusion of adrenaline in Groups V, VI and VII, but significantly increased in Group IV (Figure 2b). The subsequent infusion of

Figure 3 Plasma adrenaline (a) and noradrenaline (b) concentrations of conscious adrenalectomized rats ($n = 8$ in each group) in control conditions (solid columns), during continuous infusions of adrenaline and phentolamine (hatched columns), and after a bolus injection of propranolol, atenolol or ICI 118,551, respectively (open columns), in non-cortisone-treated rats (Groups IV, V and VI, respectively), and after the injection of propranolol in cortisone-treated rats (Group VII). Values represent mean with s.e. shown by vertical bars. *Significantly different from control; ^bSignificantly different from phentolamine.

phentolamine caused a small increase in HR which reached statistical significance in all groups, except IV. HR after the infusion of both adrenaline and phentolamine in each of the groups was, therefore, significantly greater than the corresponding values in the control condition. The injection of a β -blocker decreased HR which reached statistical significance in all groups, except Group VI.

Plasma adrenaline concentrations were not detectable in the control condition in all groups of adrenalectomized rats (Figure 3a). The infusion of adrenaline in all groups raised plasma concentrations of adrenaline (concentrations were determined during the infusion of phentolamine). Plasma adrenaline concentration was not altered by the injection of any one of the β -antagonists.

The infusion of phentolamine significantly increased plasma concentrations of noradrenaline in all groups (Figure 3b). The injection of a β -antagonist slightly decreased the plasma concentration of noradrenaline, but the decrease was only significant in group VII.

Discussion

We have previously reported that in the conscious rat treated with phentolamine, the injection of atenolol, ICI 118,551 or propranolol caused a pressor response which restored MAP to the level prior to the infusion of phentolamine (Tabrizchi *et al.*, 1988). Furthermore, we have observed that propranolol completely antagonized hypotension induced by an α -blocker, but not that by methacholine or sodium nitroprusside (Tabrizchi & Pang, 1989). Our results suggested the possible existence of an interaction between α - and β -adrenoceptor antagonists. Plasma catecholamine concentrations were markedly elevated following the infusion of phentolamine (Tabrizchi *et al.*, 1988). In order to examine the possibility that adrenaline is essential for the reversal of phentolamine-induced hypotension by a selective or non-selective β -blocker, a series of experiments was conducted in adrenalectomized

rats, both in the absence and presence of infused adrenaline. Arterial plasma concentrations of adrenaline were below the detection limit of 0.1 pmol ml^{-1} in all rats, suggesting the completeness of adrenalectomy.

A study of Gardiner & Bennett (1988) showed that adrenalectomy of Long Evans rats significantly impaired the hypotensive effects of prazosin and idazoxan. This suggests that in the intact rat, β_2 -adrenoceptor-mediated vasodilatation by adrenaline, which was released as a result of the infusion of α -blockers, contributed to the hypotensive response of α -adrenoceptor antagonists. In the present study we have shown that complete adrenalectomy did not significantly affect the hypotensive action of phentolamine. It should be noted that the conditions in the two studies were quite different. Adrenalectomy leaves the adrenal cortex intact. However, we have observed that adrenalectomy did not completely eliminate plasma adrenaline in rats (Tabrizchi & Pang, unpublished observation). It is not clear if circulating adrenaline was completely eliminated in the study carried out by Gardiner & Bennett (1988). The administration of propranolol, atenolol or ICI 118,551 in Group I, II and III, respectively, in the phentolamine-treated adrenalectomized animals caused a small increase in MAP. The ability of atenolol, at a dose which is selective for β_1 -adrenoceptors in the intact rat (Tabrizchi *et al.*, 1988), to cause a pressor response in α -blocked rats confirms previous findings that pressor response to a β -blocker was not due to the blockade of vasodilator β_2 -adrenoceptors (Tabrizchi *et al.*, 1988). The pressor response obtained with each one of the β -antagonists in the adrenalectomized rat was significantly less than that obtained in the intact rats from a previous study (Tabrizchi *et al.*, 1988). Plasma noradrenaline concentrations in these rats prior to and during the infusion of phentolamine, and after the injection of a β -blocker, were similar to the corresponding concentrations reported in a previous study (Tabrizchi *et al.*, 1988). The attenuated pressor response with a β -blocker might suggest that the presence of adrenaline is essential for the interaction between an α - and a β -blocker. Further experiments were carried out to examine the role of adrenaline in the pressor response to a β -blocker.

Adrenalectomized animals were given a continuous infusion of adrenaline. Adrenaline concentrations at 1 h following the start of adrenaline infusion were slightly higher than the concentrations attained in intact rats infused with phentolamine in a previous study (Tabrizchi *et al.*, 1988). These rats were also given phentolamine, which markedly raised noradrenaline concentrations, followed by a bolus injection of propranolol, atenolol or ICI 118,551 in Groups IV, V and VI, respectively. All three β -blockers significantly raised MAP. However, unlike results from a previous study in which the injection of propranolol, atenolol or ICI 118,551 in the intact rat completely antagonized the hypotensive response to phentolamine (Tabrizchi *et al.*, 1988), the β -blockers only partially antagonized the hypotension induced by phentolamine, i.e., each one of the β -blockers raised MAP to levels significantly less than MAP measured 1 h after adrenaline infusion prior to the infusion of phentolamine. Thus, an acute replacement of adrenaline did not completely restore pressor response to a

β -blocker. It is possible that the lack of a full restoration of MAP to the control level by a β -antagonist may have been due to morphological changes which may have occurred in the vasculature as a result of the absence of adrenaline. Structural changes occurred in the vascular smooth muscle of animals treated with reserpine, an adrenergic neurone blocking agent, (Hudgins & Harris, 1970; Aprigliano & Hermsmeyer, 1977; Bevan & Tsuru, 1979) resulting in an increase in the sensitivity to noradrenaline as well as other neurotransmitters such as acetylcholine (Hudgins & Fleming, 1966).

Adrenalectomized rats in Group VII were given daily injections of cortisone which has glucocorticoid and mineralocorticoid activities. The injection of propranolol in this latter group raised MAP to $87 \pm 3\%$ of MAP that was measured immediately prior to the infusion of phentolamine in the adrenaline-treated rats. Although MAP after the injection of propranolol in the cortisone-treated rats (Group VII) was still significantly less than MAP measured immediately prior to the infusion of phentolamine, it was significantly higher than the corresponding MAP ($74 \pm 5\%$ of control MAP) in rats (Group IV) not treated with cortisone. This suggests that the presence of both adrenal corticosteroids and adrenaline contribute to the pressor response of a β -blocker.

Glucocorticoids are known to be important in the maintenance of cardiac contractility and vascular tone (Baxter & Rousseau, 1979). Reduced pressor response and cardiac contractile force to low doses of catecholamines have been reported in anaesthetized adrenalectomized dogs (Lefer & Sutfin, 1964). The 'permissive' action of glucocorticoids in the responses to catecholamines and other hormones (glucagon, insulin, sex hormones, etc.) is well described (Granner, 1979). Decreased hyperglycaemic (Schaeffer *et al.*, 1969) or hepatic gluconeogenic (Exton *et al.*, 1972) responses to adrenaline in adrenalectomized rats have been reported; these deficits were restored by the administration of a glucocorticoid. However, it should be noted that in the present study, chronic replacement of cortisone in adrenalectomized rats enhanced but did not completely restore the pressor response to propranolol.

In conclusion, the injection of propranolol, atenolol or ICI 118,551 in the α -blocked, adrenalectomized rats caused a small increase in MAP. Following the infusion of adrenaline, the injection of propranolol, atenolol or ICI 118,551 in the phentolamine-treated adrenalectomized rat also caused a small increase in MAP. This is in contrast to responses in the intact rat in which the injection of each one of the three β -blockers completely antagonized the hypotension induced by phentolamine. The pressor response to propranolol was significantly enhanced after replacements of both adrenal corticosteroid and adrenaline. These findings suggest that adrenaline and adrenocortical steroids are involved in the antagonism of α -adrenoceptor-induced hypotension by a β -blocker.

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