Adrenaline-induced hypertension in rats

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Summary

1. Rats implanted with osmotic minipumps delivering adrenaline intraperitoneally at the rate of 2.9 nmol/h had significantly higher systolic and diastolic pressures from days 2 to 6 after implantation than sham-operated control rats.

2. Concomitant treatment with metoprolol tartrate (2.5 mg/kg, intraperitoneally, twice daily) prevented the elevation in blood pressure induced by adrenaline from osmotic minipumps. Such metoprolol treatment did not affect the blood pressure of control rats.

3. Noradrenaline administered intraperitoneally from osmotic minipumps at the rate of 2.9 nmol/h had no significant effect on blood pressure over a 6-day period of observation.

4. Tachyphylaxis developed to the acute pressor responses to intermittent intravenous infusions of adrenaline in doses of 0.78 μg (4.24 nmol) every 10 min, but after 14 days of such treatment systolic and diastolic blood pressures were significantly greater than in control rats.

5. It is suggested that the increase in blood pressure produced by chronic treatment with adrenaline is due to the uptake and accumulation of adrenaline in noradrenergic nerve terminals, from which it is subsequently released as a cotransmitter that mediates a positive feedback loop on transmission by acting on prejunctional β-adrenoceptors.

Key words: adrenaline, metoprolol, noradrenaline, prejunctional adrenoceptors.

Introduction

Adrenaline has been shown to enhance noradrenergic transmission by acting on prejunctional β-adrenoceptors in vascular [1-4] and cardiac [5, 6] tissue. The concentration of adrenaline producing this effect is within the range occurring in plasma during conditions of stress. Furthermore, adrenaline can be taken up into neuronal transmitter stores and subsequently released as a cotransmitter; it can then mediate a positive feedback loop [3, 5, 6]; thus the enhancement of noradrenergic transmission resulting from increased plasma concentrations of adrenaline can persist for well beyond the period for which the plasma concentration is elevated [6]. The enhancement of noradrenergic transmission produced by exogenous or by cotransmitter adrenaline is abolished by β-adrenoceptor-blocking drugs [1-6].

An increase in adrenaline secretion has been reported in some studies on human hypertension [7-9] and in some forms of animal hypertension [10-13]. Furthermore, treatment of rats with a slow-release depot preparation of adrenaline produced a significant elevation of blood pressure that was prevented by concomitant treatment with the β-adrenoceptor-blocking drug metoprolol [14].

These observations led us to compare the effect of chronic treatment with adrenaline with that of noradrenaline on the blood pressure of rats, and also to test the effects of intermittent treatment with adrenaline.

Methods

Comparison of chronic treatment with adrenaline and noradrenaline on blood pressure

Female Wistar rats weighing 240–300 g were anaesthetized with an intraperitoneal injection of a mixture of sodium amylobarbitone (62.4 mg/kg) and sodium methohexitone (24-9 mg/kg). A polyethylene cannula was inserted into the left common carotid artery and was exteriorized at the back of the neck. This was used for daily measurements of blood pressure and heart rate.
with a Statham transducer. An osmotic minipump (Alzet, Alza Corporation, California, U.S.A; model 2001, infusion rate 1 μl/h) was implanted intraperitoneally. The osmotic minipump was loaded with approximately 0.2 ml of either (–)-adrenaline bitartrate (2.9 mmol/l) or (–)-noradrenaline bitartrate (2.9 mmol/l) in NaCl solution (9.0 g/l) containing ascorbic acid (6 mmol/l). Control rats were sham operated. Some rats were treated with metoprolol tartrate (2.5 mg/kg, intraperitoneally, twice daily) immediately after implantation of the minipump.

Intermittent treatment with adrenaline

Male Wistar rats weighing 220–280 g were anaesthetized as described above. A polyethylene cannula was inserted into the right jugular vein, exteriorized at the back of the neck, and connected to an infusion apparatus. The cannula was protected by a flexible sheath of spiral wire tubing that was attached to a harness fitted to the neck and forequarters of the rat. The infusion pump was refilled daily with (–)-adrenaline bitartrate (0.55 mmol/l) in NaCl solution (9.0 g/l) containing ascorbic acid (0.57 mmol/l). Control rats were infused with adrenaline-free solution. Infusions were given at the rate of 15.4 μl/min for 30 s every 10 min for 14 days. On day 14 of the infusion, a carotid artery cannula was inserted under anaesthesia. Four hours later, when the rats had fully recovered from anaesthesia, blood pressure and heart rate were recorded. In some rats an arterial cannula was inserted at the same time as the venous cannula so that the immediate effects of the intermittent infusion could be determined.

Results

The osmotic minipumps delivered adrenaline or noradrenaline at the rate of 10–12 nmol h⁻¹ kg⁻¹ body weight (equivalent to 1.83–2.20 μg of adrenaline and 1.69–2.03 μg of noradrenaline, as the bases, h⁻¹ kg⁻¹ body weight). At those rates of delivery into the intraperitoneal cavity, there were no detectable effects on blood pressure or heart rate on the day after implantation. However, from day 2 to day 6 after implantation, the systolic and diastolic blood pressures of the adrenaline-treated rats were significantly greater (P < 0.001, analysis of variance) than those of the sham-operated control rats, whereas there were no significant differences (P > 0.02) in blood pressures between noradrenaline-treated and control rats (Fig. 1).

In another series of experiments, metoprolol tartrate (2.5 mg/kg, intraperitoneally, twice daily) was given to rats in which adrenaline-containing minipumps were implanted and to control sham-operated rats. In this case there were no significant differences (P > 0.3) in systolic and diastolic blood pressures between the two groups. Metoprolol-treated control rats did not differ significantly from the untreated controls. However, adrenaline-treated rats had significantly greater (P < 0.001) systolic and diastolic blood pressures than adrenaline-treated rats that were concomitantly treated with metoprolol. There were no significant differences in heart rate between any of the groups.

The intermittent intravenous infusions of adrenaline were in doses of 15–19 nmol/kg over a 30 s period at 10 min intervals. Each dose initially produced a transient increase of about 60 mmHg in blood pressure together with a reflex bradycardia; these acute effects gradually became attenuated and had virtually disappeared after 24 h. After 14 days of intermittent infusions, and 4 h after the last infusion, the mean (n = 6) systolic (152 mmHg, SEM = 5) and diastolic (116 mmHg, SEM = 2.3) blood pressures of the adrenaline-treated rats were significantly higher (P < 0.05, t-test) than the mean (n = 5) systolic (129 mmHg, SEM = 5.2) and diastolic (92.6 mmHg, SEM = 2.6) blood pressures of the control rats. However, the mean heart rates of the adrenaline-treated (315 beats/min, SEM = 45) and control rats...
Discussion

Continuous intraperitoneal administration of noradrenaline from osmotic minipumps at a rate of 2-9 nmol/h had no effect on blood pressure in rats over a 6-day period of treatment and observation. However, it has been reported that intravenous administration of noradrenaline from osmotic minipumps at the much higher rate of 40 nmol/h for 1 week did increase the blood pressure in rats [15]: this increase was not affected by \( \beta \)-adrenoceptor blockade, indicating that it was due to the pressor effect of noradrenaline acting on vascular \( \alpha \)-adrenoceptors.

Continuous intraperitoneal administration of adrenaline from an osmotic minipump at a rate of 2-9 nmol/h that had no immediate effects on blood pressure or heart rate produced significant increases in systolic and diastolic blood pressures in rats after a delay of more than 24 h. The adrenaline-induced increase in blood pressure apparently involved \( \beta \)-adrenoceptors since it was blocked by metoprolol. It is possible that the administered adrenaline is gradually accumulated in noradrenergic nerve terminals and subsequently released as a cotransmitter; then, when sufficient adrenaline has accumulated, the concentration released into neuroeffector junctions may reach a sufficiently high level to activate prejunctional \( \beta \)-adrenoceptors and thereby enhance transmitter release [6].

The effects of chronic treatment with adrenaline in increasing blood pressure and the mechanism proposed for the effect may be relevant to observations on the increased secretion of adrenaline in human essential hypertension and in some animal models of hypertension [7-12].

The experiments with intermittent administration of adrenaline in doses producing initially a pronounced rise in blood pressure in rats were designed as a model of adrenaline release produced by periodic stress. It was also thought that they might provide a model for early labile hypertension. However, tachyphylaxis developed to the acute responses, as is well known to occur with continuous infusions of catecholamines. Nevertheless, after 14 days of intermittent administration, the systemic and diastolic blood pressures were significantly increased over those of control rats, as occurred with smaller amounts of adrenaline administered chronically in a depot preparation [14] or, as reported in this paper, from an osmotic minipump.

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References