Effects of bromocriptine on blood pressure and plasma $\beta$-endorphin in spontaneously hypertensive rats


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Summary

1. Immunoreactive $\beta$-endorphin (IR-$\beta$EP) was two- to three-fold higher in pituitary neuro-intermediate lobes (N-IL) of spontaneously hypertensive rats (SHR) than of normotensive Wistar-Kyoto (NT-WKY) controls.

2. Plasma levels of IR-$\beta$EP were lower in SHR than in NT-WKY rats.

3. Intravenous injections of morphine lowered blood pressure of both SHR and NT-WKY rats to the same level; naloxone restored blood pressure of both groups to pre-morphine values.

4. Infusion of bromocriptine in SHR for 1 week lowered blood pressure and N-IL IR-$\beta$EP concentration.

5. These results confirm and extend postulated dopaminergic defect in this model of hypertension.

Key words: bromocriptine, $\beta$-endorphin, morphine, pituitary, neuro-intermediate lobe.

Abbreviations: IR-$\beta$EP, immunoreactive $\beta$-endorphin; N-IL, pituitary neuro-intermediate lobe; NT-WKY, normotensive Wistar-Kyoto; SHR, spontaneously hypertensive rat.

Introduction

The spontaneously hypertensive rat [1] (SHR) has many endocrine abnormalities compared with the normotensive Wistar-Kyoto (NT-WKY) rat including hyperprolactinaemia [2], increased plasma thyrotrophic hormone [3], increased pituitary, plasma and urinary levels of vasopressin [4], increased levels of immunoreactive $\beta$-endorphin (IR-$\beta$EP) in pituitary neuro-intermediate lobe (N-IL) and decreased plasma levels of IR-$\beta$EP [5]. The secretion of these hormones is considered to be under tonic dopaminergic control; studies in vitro have shown that dopamine suppresses the release of vasopressin and neurophysin from the pituitary [6]. The dopaminergic agonist, bromocriptine, produces a rapid, profound fall in blood pressure of SHR [6]; other antihypertensive agents, e.g. captopril, have been shown to reduce the urinary output of vasopressin in SHR [7]. As opioids are hypotensive agents, and $\beta$-endorphin release may be impaired in SHR, we compared the effects of morphine and naloxone on blood pressure of SHR and NT-WKY rats, and studied the effects of bromocriptine on blood pressure and tissue $\beta$-endorphin levels.

Methods

Female SHR ($n = 9$) and NT-WKY rats ($n = 9$) were anaesthetized with Inactin, which has no depressor effects in rats [8]; in each rat the left jugular vein and carotid artery were cannulated. Pulsatile and mean arterial pressure were recorded continuously on a Grass polygraph with Statham p 23 Db pressure transducers. After 30 min, morphine (2 mg/kg) was injected intravenously, followed 1 h later by naloxone (1 mg/kg); blood pressure was monitored for a further hour.

Two groups of eight female SHR had osmotic minipumps (Alzet model 2002) implanted intraperitoneally under ether anaesthesia. Bromocriptine (22 $\mu$g/h) or vehicle was infused for 1 week and blood pressures were measured daily by a tail-cuff method. Animals were killed by
decapitation, trunk blood was collected into heparinized tubes on ice, and plasma frozen until assay. Pituitary glands were dissected into anterior lobe and neuro-intermediate lobe, placed in HCl (0.1 mol/l) on ice, boiled, homogenized, centrifuged and the supernatants appropriately diluted for radioimmunoassay [9]. Statistical analysis was by unpaired t-test and by two-way analysis of variance.

Results

Morphine (2 mg/kg) given intravenously significantly lowered mean blood pressure of SHR (n = 9) from 176 ± 6 to 117 ± 11 mmHg (mean ± SEM) and of NT-WKY rats (n = 9) from 142 ± 3 to 111 ± 5 mmHg (P < 0.005). These falls in blood pressure were 34% of control values for SHR and 22% of control values for NT-WKY rats. Intravenous naloxone (1 mg/kg) restored blood pressure of SHR to 177 ± 4 mmHg and of NT-WKY rats to 149 ± 6 mmHg; these values were not significantly different from those from the two groups during their control, pre-morphine period.

Blood pressures of the bromocriptine-treated group of SHR fell significantly from 153 ± 4 to 118 ± 4 mmHg (F7,49 = 3.8, P < 0.005); blood pressures of the vehicle-treated group of SHR did not change significantly (163 ± 4 to 145 ± 6 mmHg, F7,49 = 1.4, P > 0.05). Bromocriptine-treated SHR had significantly (P < 0.05) lower levels of N-IL IR-PEP than vehicle-treated SHR; no difference in anterior pituitary IR-PEP levels was found between treatments. Though the mean level of plasma IR-PEP in bromocriptine-tested rats was double that of the vehicle-tested group, the difference was not statistically significant (0.1 > P > 0.05) owing to the wide variance in the bromocriptine-treated group.

Discussion

The results presented here show that an exogenous opiate (morphine) lowers blood pressure of SHR more than that of NR-WKY rats both absolutely and relatively, and that this hypotensive action was completely reversed by a modest dose of naloxone. As previously reported [5], differences in immunoreactive β-endorphin levels in the neuro-intermediate lobe and plasma of SHR, compared with NT-WKY rats, are consistent with a role of endogenous opioids in the elevated blood pressure of SHR. The elevated neuro-intermediate lobe content of immunoreactive β-endorphin supports the dopaminergic defect postulated [6] in this model of hypertension. The lack of statistical significance for the increased mean plasma level of β-endorphin in the bromocriptine-treated SHR, compared with the vehicle-treated SHR, warrants further comment. The dose of bromocriptine in this group was low (22 μg/h) because of the low solubility of the drug. Higher doses, accordingly, may provide a more consistent effect on plasma levels of immunoreactive β-endorphin; this possibility is at present being investigated.

The postulated dopaminergic defect in SHR is further supported by observations that hypothalamic dopamine levels are decreased in SHR compared with NT-WKY rats [10]. Abnormalities in prolactin, thyrotrophic hormone, vasopressin, and β-endorphin, together with the hypotensive response to SHR to a dopamine agonist, also seem consistent with a dopaminergic defect. The reports, however, that agents such as vasopressin antiserum [11] will lower blood pressure of SHR to normal raise a conceptual difficulty. If the SHR is defective in tubero-infundibular and tuberohypophyseal dopamine control of the release of several pituitary hormones, it is difficult to understand how correction of only one reduces SHR blood pressure to normal.

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References

Bromocriptine effects in SHR


