Central dopaminergic mechanisms in young patients with essential hypertension

R. E. KOLLOCH, K. O. STUMPE, U. ISMER, O. KLETZKY
AND V. DEQUATTRO
Medizinische Universitäts-Poliklinik Bonn, Federal Republic of Germany, and Medical Center, University of Southern California, Los Angeles, CA, U.S.A.

Summary

1. Central dopaminergic pathways are possibly related to noradrenergic tone and may be important in the pathogenesis of essential hypertension. Basal plasma prolactin levels have been used as a marker of dopaminergic activity in the hypothalamus. The prolactin response to thyrotropin-releasing hormone (TRH) gives evidence of the dynamics of prolactin secretion.

2. To evaluate further the role of dopaminergic mechanisms in hypertension three groups of young male hypertensive patients were studied and compared with healthy male volunteers. In group 1 prolactin secretion was evaluated overnight at 60 min intervals from 22.00 to 06.00 hours. In group 2 we measured plasma prolactin concentrations before and sequentially after intravenous injection of 200 μg of TRH. In group 3 we measured prolactin, plasma and urinary noradrenaline and normetadrenaline during various degrees of physical and mental activity.

3. Basal prolactin, noradrenaline and normetadrenaline levels were higher in the hypertensive patients as compared with normotensive controls. In the hypertensive patients the prolactin response to TRH was significantly attenuated. Treatment with bromocriptine, a centrally acting dopaminergic agonist, lowered the blood pressure and suppressed the elevated prolactin and noradrenaline levels in the hypertensive patients. During bromocriptine therapy the prolactin response to TRH was not different in normotensive and hypertensive subjects.

4. These results suggest an abnormal regulation of the prolactin secretion in young hypertensive patients with evidence of increased sympathetic tone, supporting the concept that central dopaminergic mechanisms may be involved in the development or maintenance of essential hypertension.

Key words: bromocriptine, dopaminergic mechanisms, hypertension, noradrenaline, prolactin, thyrotropin.

Introduction

The role of the dopaminergic system in the development and maintenance of essential hypertension has not been established. Previously plasma prolactin levels were found to be raised in a subgroup of young patients with essential hypertension [1]. Because prolactin secretion is mainly under dopaminergic control, it was hypothesized that the increased prolactin levels may reflect reduced central dopaminergic activity. The dopaminergic agonist bromocriptine reduced the elevated prolactin levels and lowered blood pressure in the hypertensive patients. These findings prompted the hypothesis that central dopaminergic factors may participate in blood pressure regulation and the pathogenesis of essential hypertension [1].

The present study was designed to characterize further the possible role of dopaminergic mechanisms in hypertension. Three groups of patients were studied, firstly to confirm and to extend our previous observation of hyperprolactinaemia in a larger population of young hypertensive patients, secondly, to analyse the dynamics of prolactin secretion in hypertension and thirdly, to evaluate the mechanism of action of bromocriptine in lowering blood pressure.

Patients and protocol

Three groups of hypertensive patients were
studied and compared with 33 normal volunteers. The total patient population consisted of 34 male hypertensive patients with mild uncomplicated essential hypertension, whose average blood pressure was greater than 140/90 mmHg when taken on at least three separate occasions. They ranged in age from 18 to 35 years (average 26 ± 3 years) and had never taken antihypertensive drugs. All patients and normotensive controls were on an unrestricted diet. Their daily sodium excretion ranged from 120 to 190 mmol.

All subjects were studied by the same investigator in a single blind fashion during a placebo period and after 1 week of treatment with bromocriptine (5–15 mg/day). Group 1 and 2 patients were admitted to the Medizinische Universitäts-Poliklinik in Bonn, group 3 patients to the Clinical Research Centre of the Los Angeles County—University of Southern California Medical Center.

Group 1. In 13 hypertensive and 12 normotensive subjects day/night profile of prolactin secretion and blood pressure was evaluated in 60 min intervals from 22.00 to 06.00 hours. All subjects remained supine from 19.00 to 08.00 hours.

Group 2. To evaluate the hypothalamus—pituitary—prolactin axis we measured prolactin levels in 14 hypertensive and 12 normotensive subjects before and 5, 10, 20, 30, 60 and 120 min after intravenous bolus injection of 200 μg of thyrotropin-releasing hormone.

Group 3. In seven hypertensive and six normotensive subjects we measured blood pressure, heart rate, plasma prolactin, noradrenaline and plasma renin activity during 1 h periods in supine, sitting and standing positions, during mental stress and 3 min isometric handgrip exercise. One hour urine collections were performed in all conditions to determine the excretion of sodium and noradrenaline. Urine collections over 24 h were made for measurements of noradrenaline and normetadrenaline.

**Analytical methods**

Plasma prolactin was measured by radio-immunoassay by means of the second-antibody technique [2]. Plasma renin activity was determined by radioimmunoassay [3]. Plasma and urinary noradrenaline and normetadrenaline were measured by a radioenzymatic assay [4, 5].

Values were expressed as means ± SEM. Statistical analysis was performed to calculate group differences, paired data analysis and statistical significance.

**Results**

**Group 1**

Hypertensive patients and normotensive controls exhibited typical day/night plasma prolactin rhythm with peak values between 02.00 and 06.00 hours. The hypertensive patients had significantly higher mean plasma concentrations of prolactin (325–515 μ-units/ml) than the normotensive controls (225–374 μ-units/ml) at all times during the period of observation (P < 0.001).

One week of treatment with bromocriptine resulted in a marked suppression of plasma prolactin levels in all subjects (P < 0.001). Hypertensive patients still had higher plasma concentrations of prolactin (110 ± 25 vs 74 ± 25 μ-units/ml) but the difference did not reach statistical significance.

In the hypertensive patients bromocriptine lowered the nocturnal supine blood pressure from 150 ± 9/102 ± 4 mmHg to 126 ± 7/86 ± 3 mmHg (P < 0.005). In the normotensive controls the mean reduction of blood pressure of 7/5 mmHg was not significant.

**Group 2**

During TRH-stimulation tests hypertensive patients had significantly higher mean prolactin baseline levels than normotensive controls (329 ± 59 vs 192 ± 24 μ-units/ml; P < 0.01). The plasma prolactin response to TRH was significantly attenuated (Fig. 1) in hypertensive patients.

**Group 3**

Compared with normotensive subjects this group of young hypertensive patients had increased supine plasma concentrations of noradrenaline (404 ± 42 vs 234 ± 32 ng/l; P < 0.005), normetadrenaline (85 ± 10 vs 62 ± 8 ng/l; P < 0.05) as well as increased excretion of normetadrenaline in 24 h urine (140 ± 19 ng/mg of creatinine; P < 0.05), and noradrenaline in 1 h supine urine samples (42 ± 6 vs 21 ± 5 ng/mg of creatinine; P < 0.005).

The hypertensive patients had significantly higher plasma concentrations of prolactin than the normotensive controls during the various conditions (P < 0.005).

After 1 week of treatment with bromocriptine plasma noradrenaline was significantly reduced in the hypertensive patients in supine (404 ± 42 vs 278 ± 32 ng/l; P < 0.05), sitting (500 ± 36 vs 370 ± 49 ng/l; P < 0.05) and standing (701 ± 45
Dopaminergic mechanisms in hypertension

TRH stimulation in hypertensive patients provides further evidence that the hypothalamus–pituitary–prolactin axis is disturbed in these patients. It may be possible that the elevated prolactin levels exert an inhibitory effect upon the TRH response at the hypothalamic and/or pituitary level or that the pituitary had a limited capacity of response to TRH [6].

In group 3 patients hyperprolactinaemia appears to be associated with increased sympathetic tone, as evidenced by increased plasma concentration of noradrenaline and normetadrenaline as well as increased excretion of these two compounds in urine. It has been proposed that an interaction takes place between central dopaminergic and noradrenergic neurons [7, 8]. It was therefore of great interest to determine whether defective dopaminergic control is the common cause of hyperprolactinaemia and increased sympathetic activity. Bromocriptine, a centrally acting dopaminergic agonist, effectively lowered blood pressure in young hypertensive patients during various conditions.

The blood pressure-lowering effect was associated with a suppression of the elevated prolactin levels and a marked reduction of sympathetic tone, as evidenced by the decrease of plasma noradrenaline concentration and urinary noradrenaline and normetadrenaline excretion.

The blood pressure reduction is thought to be related at least in part to suppression of central sympathetic tone. Previous findings of reduced noradrenaline in the cerebrospinal fluid in normotensive subjects [9] and lack of an antagonism by domperidone (a peripheral dopamine receptor antagonist) of the cardiovascular effects of bromocriptine [10], combined with the minimal effects of bromocriptine on both sodium excretion and renin in our patients, suggest to us that the hypotensive actions of bromocriptine were not related to effects on peripheral dopamine receptors in the kidneys.

Our data give further support to the working hypothesis that reduced central dopaminergic activity may be a factor in the maintenance of essential hypertension and that this defect is corrected by bromocriptine, leading to the restoration of sympathetic nerve tone, prolactin levels and blood pressure to normal.

Discussion

In the present study we have demonstrated that in young hypertensive patients hyperprolactinaemia is present in the supine position from 22.00 to 06.00 hours and during various degrees of physical and mental activity in daytime.

The attenuated plasma prolactin response to

Acknowledgments

Supported in part by an Advanced Research Fellowship to R.E.K. from the American Heart Association. Great Los Angeles Affiliate, Clinical Research Center Grant FH 21 and a
Grant from the Land Nordrhein-Westfalen. R.E.K. was also supported in part by the Deutsche Forschungsgemeinschaft. We gratefully acknowledge the expert technical assistance of Miyoko Higuchi and Daantje Meijer.

References


