Dopaminergic Control of Sympathetic Tone and Blood Pressure: Evidence in Primary Hypertension

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SUMMARY Bromocriptine (Br) was used to test the hypothesis that central dopaminergic mechanisms modulate sympathetic nerve tone, and that when dopaminergic control is deficient there may result enhanced noradrenergic activity and elevated blood pressure (BP) in some patients with primary hypertension. Seven hypertensive patients (age 29 ± 3 years) were studied after a single oral dose of Br (2.5-5.0 mg) and after 1 week of treatment with Br (5-15 mg/day). The data were compared to those obtained during respective placebo periods. The Br reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) during supine, sitting, and standing positions and mild mental stress but not during isometric handgrip exercise. Orthostatic hypotension occurred in all patients after the first dose of Br but was present only in one patient after 1 week of treatment. Pretreatment levels of plasma norepinephrine (NE) in supine and standing positions were elevated as compared to previously obtained data of normal controls. After 1 week of Br therapy, plasma NE was reduced 40% to 50% in supine, sitting, and standing positions, and during isometric handgrip exercise (p < 0.05). Plasma NE after a single dose of Br was not different from that found after 1 week of the drug. Excretion rates of urinary NE and normetanephrine (NM) were lower (p < 0.002 and p < 0.005 respectively) during Br as compared to pretreatment values. Sodium excretion tended to be higher and plasma renin activity (PRA) lower after 1 week of Br, but the differences were not significant. Dopaminergic stimulation by Br, probably central in location, reduces sympathetic outflow and thereby might contribute to lowering of BP in primary hypertension. These findings support the hypothesis that reduced central dopaminergic activity may be a factor in the cause and maintenance of primary hypertension. (Hypertension 2: 390-394, 1980)

KEY WORDS • primary hypertension • dopaminergic mechanisms • bromocriptine • blood pressure • sympathetic activity • norepinephrine

REDUCED central dopaminergic activity may be a factor in the maintenance of primary hypertension.1 Bromocriptine (Br), a centrally acting dopaminergic agonist, lowers blood pressure (BP) in hypertensive patients as well as causes orthostatic hypotension in normotensives.4,5 In our present study, Br was used to test the hypothesis that dopaminergic mechanisms modulate sympathetic nerve tone and thereby BP control in hypertensives.

The evidence suggests that Br acted centrally to lower sympathetic nerve tone and arterial BP in the young hypertensives who were the subjects of this study.

Patients

We studied seven men with mild uncomplicated primary hypertension whose average BP was greater than 140/90 mm Hg when taken on three separate occasions. None of the patients had ever taken antihypertensive medications and none had sequelae of their elevated BP. Their ages ranged from 18-35 years, average, 29 ± 3 years. We also studied nine age-matched normotensive volunteers (age 18-35 years, mean: 31 ± 2) by collecting blood for catecholamines after 1 hour supine and their 24-hour urines during regular physical activity.

Protocol

All patients signed an informed consent approved by the institutional review committee after being appraised of the nature of the study and the attendant potential risks. Patients were studied in a single blind fashion during a placebo period and then with in-
creasing doses of Br. Patients were admitted to the Clinical Research Center of the Los Angeles County University of Southern California Medical Center. The study was performed on Day 2. Patients were fasting overnight, did not smoke, nor take tea or coffee during the period of study. Blood pressures and heart rates were taken during 1-hour periods in supine, sitting, sitting during mental stress, and then standing positions. The mental stress consisted of solving difficult visual puzzles with the instruction to finish them on time so the results could be compared with those of the other subjects. Blood samples were taken at the end of each period. Blood pressures, pulse rates and blood samples also were taken in the sitting position before and after 3 minutes of isometric handgrip exercise consisting of a work load of 30% maximum voluntary contraction. Patients were familiarized with the handgrip apparatus during several visits prior to the study. Urine was collected fractionally each 1 hour during all conditions and included the 3 minute period of handgrip exercise. Urine was preserved with 3 cc 6N HCl. The urine was also collected for 24 hours in a bottle containing 15 cc of 6N HCl.

Two hours after the first dose of 2.5 or 5.0 mg Br had been given, the patients rested supine for 1 hour. At the end of this period, BP, pulse rates, and blood samples were taken. The patient then stood for 1 hour, and these measurements were repeated. These were the acute effects of Br. The daily dose of Br then was gradually increased until the diastolic pressure (DBP) was less than 90 mm Hg or the final dose of 15 mg per day was reached. After 1 week of treatment, the patient was readmitted to the Research Center, and the chronic effects of Br were studied by repeating the measurements taken prior to the drug.

Assays

Plasma was preserved in EGTA and glutathione; NE and epinephrine (E) were measured by the radioenzymatic assay of Peuler and Johnson. Urine NE was measured by the fluorimetric method of Crout. Plasma renin activity (PRA) was measured by the radioimmunoassay method of Haber et al. All quotients of plasma were preserved in EDTA for the normetanephrine (NMN) assay. Plasma and urinary NMN were measured by a radioenzymatic method. Urinary sodium (Na) was measured using flame photometry.

Statistics

Values were expressed as mean ± SEM, and values of patients on Br were compared with those while on placebo by Student's t test for paired data.

Results

Basal Plasma and Urinary Catecholamines in Normotensive and Hypertensive Subjects

These young hypertensives had increased plasma NE and NMN and increased urinary NE and NMN excretion after 1 hour of supine rest (fig. 1).

Effects of Bromocriptine on Supine and Standing Blood Pressure after 1 Single Dose and 1 Week of Therapy

The mean SBP of the hypertensives was reduced approximately 17% and 24% in the supine and standing position after a single dose of Br (p < 0.005 and < 0.001). The reduction in SBP was maintained after 1 week of Br therapy. Reduction in DBP, although significant, was of a somewhat lesser magnitude (fig. 2).

Effects of 1 Week of Bromocriptine Therapy on the Concentrations of Plasma NE, Urinary NE and NMN, MAP, and Pulse Rates During the Basal State and after Postural, Mental and Physical Stress

There were stepwise increments of mean arterial blood pressure (MAP), pulse rates, and plasma NE during the periods progressing from mental to postural to isometric exercise stress during placebo (figs. 3 and 4). The changes in pulse rate during isometric exercise (p < 0.05) and the changes in plasma NE after standing and exercise were significant (p < 0.01 and < 0.01). After 1 week of Br therapy, however, there were 10%-15% reductions in
MAP in all conditions except isometric exercise, no changes in pulse rates (fig. 3), and 20%-50% reduction in plasma NE in all situations except mental stress (fig. 4). Further, there were 30% to 50% reductions in urinary NE excretion during the various conditions (supine \( p < 0.01 \); sitting \( p < 0.01 \); mental stress \( p < 0.01 \); standing and exercise \( p < 0.001 \)). There were reductions of urinary NE and NMN of 30% and 22% respectively during Br therapy (as shown by the 24-hour collections taken before and after).

Sodium Excretion and PRA in Patients During Postural, Mental, and Physical Stress Before and After Bromocriptine

The 24-hour urine Na excretion was in the range of 110 to 190 mEq per day. Fractionated Na excretion was highest at a mean of 11 ± 6.0 mEq/hr during the supine position and decreased gradually but not significantly to 4.5 ± 4.0 mEq/hr during standing. Sodium excretion during the exercise period was 4.5 ± 4.0 mEq/hr. On the other hand, mean PRA
rose from 0.40 ± 0.45 to 0.90 ± 0.35 ng/ml/hr from supine to standing; it then decreased slightly during the exercise period to 0.8 ± 0.35 ng/ml/hr. However, none of the changes in PRA was significant.

The Br produced 10%-30% increases in Na excretion and 20%-40% reduction in PRA during the various conditions, but none of the changes was significant.

Discussion

The role of the dopaminergic system in the development and maintenance of primary hypertension has not been established. In an earlier study, prolactin levels were found to be raised in a subgroup of young patients with mild high renin 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 centrally acting dopaminergic agonist, Br, reduced the elevated prolactin levels and lowered the BP in the hypertensive patients. Therefore, it was tempting to speculate that dopaminergic mechanisms might be involved in the development and maintenance of primary hypertension.1 In another study,4 we observed raised plasma NE in some patients with high renin hypertension. It thus was of great interest to determine if increased noradrenergic activity was the common abnormality in both groups of high renin patients and whether this sympathetic nerve activity was related to the cause of the hypertension and to defective dopaminergic control as well. We have found in this study that Br effectively lowered SBP and DBP in young patients with primary hypertension during various conditions, while orthostatic hypotension occurred mainly as a first dose effect. The BP-lowering effect was associated with a marked reduction of sympathetic nerve tone, evidenced by the decrease of plasma NE concentration and urinary NE and NMN excretion.

The mechanism by which Br affects sympathetic activity is not completely understood. It is proposed that an interaction takes place between central dopaminergic and noradrenergic neurons. There is evidence that dopaminergic stimulation with either apomorphine or piribedil affects NE turnover and reduces brain NE content.3,11 Furthermore, Br has been shown to reduce the concentration of NE in the spinal fluid, suggesting that the drug reduces central sympathetic outflow.3 On the other hand, it has been suggested that peripheral NE release may be inhibited by stimulation of presynaptic dopamine receptors in noradrenergic neurons.12-14 However, the preliminary finding that blockade of peripheral dopamine receptors with domperidone does not prevent the cardiovascular effects of Br favors the view that the drug acts mainly through a central mechanism.15 Multiple types of dopaminergic receptors have been identified in regions of brain that involve BP homeostasis.14 It is possible that the BP-lowering effect of Br may have been related to a reduction of sympathetic outflow. Other antihypertensive actions may have been important.

The Br reduced plasma NE and BP in the hypertensives in both supine and standing positions. However, the associated reduction in pulse rate was not significant. This disparity is similar to that found after alpha methyldopa treatment in both supine and standing positions11 and after clonidine in the upright position.16 Further, although plasma NE was reduced during isometric exercise there was no attenuation of the blood pressure response. Similar findings have been reported after reserpine,15 guanethidine,14 and a magnified BP response was found after propranolol,20 methyldopa,21 and clonidine.20 This phenomenon suggested that central suppression of sympathetic outflow may have enhanced responses to endogenous NE.20

The Br may have stimulated peripheral dopamine receptors in the kidney and contributed to the lowering of BP by increasing Na excretion. However, after the initial dose of Br there was a slight reduction in Na excretion, suggesting that natriuresis does not contribute to the acute antihypertensive effect of Br. During chronic Br therapy, Na excretion was increased slightly but the changes were not significant. The changes in the individual patients were inconsistent. Dopamine infusion in dogs increased BP and PRA,11 possibly by stimulating dopamine receptors in the kidney. Therefore, if Br exerted an agonist effect on peripheral dopamine receptors, one would expect to find increased PRA. There was, however, an insignificant reduction of PRA.

The BP reduction in this small group of patients with primary hypertension and raised plasma NE is thought to be related to suppression of central sympathetic tone. Previous findings of reduced NE in the cerebrospinal fluid of normotensive subjects and the lack of an antagonism by doxepine19 of the cardiovascular effects of Br combined with the minimal effects of Br on both Na+ and renin in our patients suggest to us that the hypotensive actions of Br were not related to effects on dopamine receptors in the kidney. It is possible, however, that other effects of the drug contributed to the BP lowering. Further investigations may establish the significance and site of the dopaminergic-noradrenergic interactions and their relevance to the pathogenesis of primary hypertension.

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