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The Dopamine Agonist Bromocriptine Induces Hypotension by Venous and Arteriolar Dilation

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Summary: Acute bromocriptine administration reduced sitting and standing blood pressure and produced severe orthostatic hypotension in 12 normal subjects. Concomitantly, there was an increase in venous distensibility and basal blood flow, and a decrease in peripheral vascular resistance, as determined by forearm plethysmography. After administration of bromocriptine, plasma norepinephrine concentration decreased. Bromocriptine lowers blood pressure by dilating arterioles and veins, at least in part by means of dopaminergic inhibition of sympathetic nervous system activity. **Key Words:** Bromocriptine—Orthostatic hypotension—Venous and arteriolar dilation—Catecholamines—Plethysmography.

Bromocriptine, a dopamine agonist, lowers blood pressure in normal (1,2) and hypertensive man (3–5). Orthostatic hypotension is a debilitating side effect of bromocriptine that has limited its therapeutic usefulness in the treatment of patients with Parkinson's disease (6–9), prolactin secreting tumors, and acromegaly (10). The mechanism of the hypotensive action of bromocriptine is incompletely understood, but activation of dopamine receptors in the brain or the periphery could explain its ability to lower blood pressure (11–13). Dopamine receptors in the periphery are located primarily at three sites: sympathetic ganglia, sympathetic nerve terminals, and vascular smooth muscle (14–17). Stimulation of any of these sites causes a fall in arterial blood pressure through vasodilation and a reduction in peripheral vascular resistance (13,18). Dopamine dilates renal and mesenteric blood vessels (14,19), but it constricts forearm blood vessels in man (20). In experimental animals, the effect of bromocriptine on blood vessels has been variable depending on which vascular bed is examined (21–23) and the dose of bromocriptine used (24). In man, the precise hemodynamic and neuroendocrine mechanisms of bromocriptine's hypotension action have not been defined. This study was designed to evaluate these mechanisms systematically with concurrent measurements of blood pressure, peripheral vascular function, and circulating catecholamines in normal human subjects. The results indicate that bromocriptine lowers blood pressure by means of venous and arteriolar dilation associated with suppression of sympathetic nervous system activity.

METHODS

Twelve healthy subjects (five females and seven males; aged 23–33 years) were admitted to the University of Virginia Clinical Research Center. On day 1, placebo was administered at 1800, 2400, and 0600 h. On day 2, subjects received three doses of bromocriptine (2.5 mg) at similar 6-h intervals. Blood pressure and heart rate were monitored before each bromocriptine dose. A heparin lock was inserted in the right forearm each morning at 0700 h. Subjects remained supine until plethysmography was performed on the left forearm, approximately 1 h later. The protocol was approved by the Human Experimentation Committee, and prior patient consent was obtained.

For plethysmographic studies, subjects were in the basal post-absorptive state and avoided caffeine, nicotine, or venipuncture for at least 30 min prior to initiation of studies. Subjects were supine, with their heads elevated 15°, and wore light clothing. Studies were performed in a quiet, constant temperature room at 74–75°F (24°C). Duplicate measurements of blood pressure and heart rate were recorded in the right arm before and after

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each study. The left forearm was positioned at the level of the right atrium and was enclosed in a Plexiglas, single-chamber water plethysmograph (25). The temperature of the water in the plethysmograph was 32°C (89°F) (26). The height of the water was 23 cm above the upper surface of the left arm, assuring a local pressure sufficient to counterbalance natural venous pressure (27). To exclude the circulation of the hand, a pneumatic cuff at the wrist was inflated to suprasystolic levels during all measurements. Proximal blood pressure cuffs were placed over the brachial artery and slowly inflated. As the proximal cuff was inflated, blood pooled downstream and forearm volume increased. As forearm volume increased, the water level rose. The change in height was recorded and corresponded to a change in venous volume. The rate of change of height was also recorded and yielded an index of blood flow (25).

Venous distensibility was calculated at a distending pressure of 30 mm Hg using 5-mm stepwise increases of the proximal cuff. Three separate venous volume curves were generated; a 5-min equilibrium period was allowed between measurements with all cuffs deflated. The curves were reproducible and the average of the three curves was used and expressed as ml/100 ml forearm volume. An increase in venous volume indicates an increase in venous distensibility or venous dilation (25).

The initial slope of the volume record obtained after rapidly inflating the proximal cuff to 30 mm Hg was used as an index of basal blood flow and was expressed in ml/min/100 ml forearm volume. An increase in basal blood flow indicates arteriolar dilation (25).

Blood flow was measured during reactive hyperemia after 5 min of ischemia. Peak blood flow was recorded and expressed in ml/min/100 ml forearm volume. An increase in peak hyperemic blood flow indicates an increase in maximal dilating capacity of arterioles (25).

Blood pressure (mm Hg) and heart rate in beats per minute (bpm) were recorded before and after each plethysmographic study. The mean arterial pressure was calculated as the sum of the diastolic plus one-third of the pulse pressure and expressed in mm Hg. Forearm vascular resistance was calculated by dividing the mean arterial pressure by the basal blood flow and expressed in mm Hg/ml/min/100 ml forearm volume.

Blood for hormonal measurements was obtained through a heparin lock and centrifuged immediately at 0–4°C. The plasma was decanted and frozen at −70°C until assayed. For measurement of plasma catecholamines, two samples (15 min apart) were obtained in tubes containing EDTA (2 mg/ml), before and after plethysmographic studies. The average of all four values was used to calculate mean norepinephrine, epinephrine, and dopamine concentrations. Catecholamines were resolved by reverse-phase, high-performance liquid chromatography with electrochemical detection (28).

Blood for plasma renin activity (PRA) and plasma aldosterone concentration (PAC) was collected in EDTA-containing tubes. PRA was measured by the radioimmunoassay method described by Sealy et al. (29) and the PAC by the radioimmunoassay of Buhler et al. (30).

Statistical analysis was performed using Student's paired *t* test or a one-way analysis of variance. Changes were considered significant if the double tailed p values or the F values were less than 0.05. Data were expressed as mean ± 1 standard error (SE). The p values employed for systolic/diastolic blood pressures refer to the least significant change for either measurement.

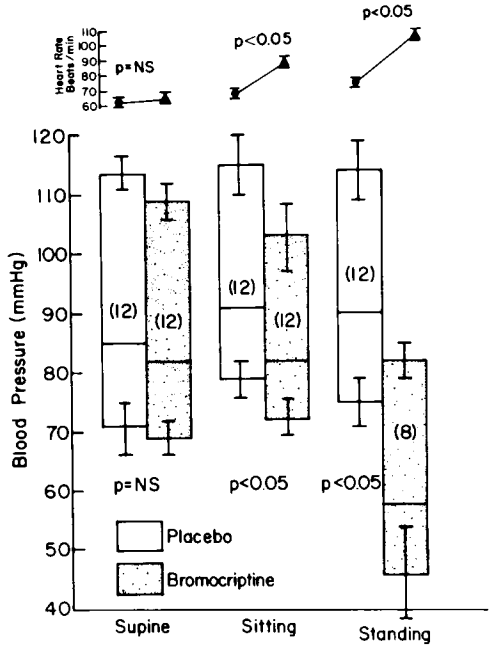

FIG. 1. Blood pressure response to bromocriptine. Mean ± SE; line within bars refers to mean arterial pressure (MAP). Number in parentheses = number of patients.

RESULTS

In Fig. 1, the blood pressure responses of the 12 subjects to bromocriptine is depicted. After treatment with bromocriptine, supine blood pressure did not change (113 ± 5/71 ± 3 vs. 109 ± 4/69 ± 3 mm Hg, respectively, $p > 0.05$). Supine heart rate was also unchanged (61 ± 2 vs. 64 ± 2 bpm, respectively, $p > 0.05$). However, when the subjects were in the sitting position, blood pressure fell from 115 ± 5/79 ± 3 to 103 ± 5/72 ± 4 mm Hg ($p < 0.05$), and heart rate rose from 67 ± 2 to 87 ± 5, respectively ($p < 0.05$). When the subjects were in the standing position, blood pressure also fell, from 114 ± 5/75 ± 4 to 82 ± 3/46 ± 8 mm Hg ($p < 0.05$), whereas heart rate rose from 76 ± 2 to 106 ± 4 bpm ($p < 0.05$).

A comparison of supine to sitting mean arterial pressure (MAP) on placebo revealed a rise in pressure from 85 ± 3 to 91 ± 3 mm Hg ($p < .05$), whereas those same values on bromocriptine exhibited no change (82 ± 3 vs. 82 ± 4 mm Hg, $p < 0.05$).

The effect of bromocriptine on orthostasis is shown in Fig. 2. The blood pressure and heart rate were recorded in eight subjects immediately after either 3 min of erect posture or the development of postural symptoms. A comparison of supine to

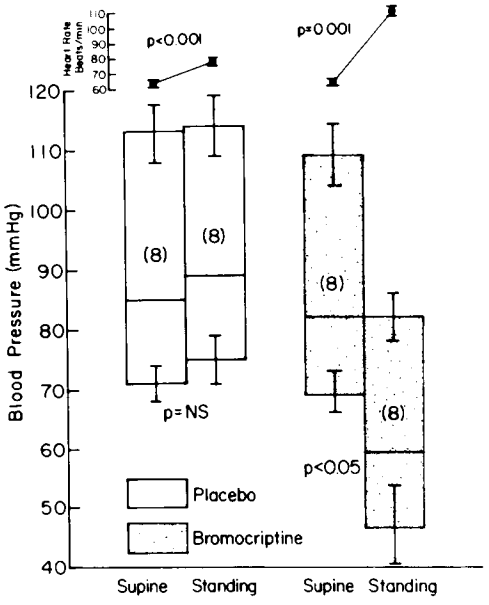

FIG. 2. Orthostatic blood pressure response to placebo and bromocriptine. Mean ± SE. Line within bars refers to mean arterial pressure (MAP). Number in parentheses = number of patients.

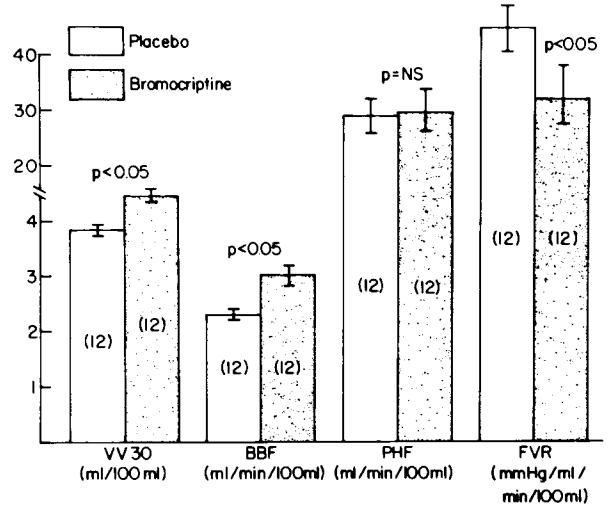

FIG. 3. Plethysmographic parameters before and after bromocriptine. VV, venous capacitance; BBF, basal blood flow; PHF, peak hyperemic flow; and forearm vascular resistance (FVR). Mean ± SE; number in parentheses = number of patients.

standing blood pressure with placebo revealed a slight rise in mean arterial pressure (MAP) (84 ± 4 to 90 ± 4 mm Hg, $p < 0.001$) and heart rate (65 ± 3 to 78 ± 3 bpm, $p < 0.001$). When bromocriptine was administered, there was a fall in MAP from 82 ± 2 to 58 ± 5 mm Hg ($p < 0.002$). Systolic blood pressure fell below 80 mm Hg in three subjects, one of whom developed syncope; when the subjects were standing, heart rate increased from 64 ± 2 to 106 ± 3 bpm ($p < 0.01$).

Changes in forearm venous and arteriolar tone after bromocriptine treatment are shown in Fig. 3. Venous distensibility increased from 3.96 ± 0.26 to 4.44 ± 0.30 ml/100 ml forearm volume ($p < 0.05$). Basal blood flow also increased, from 2.33 ± 0.27 to 3.01 ± 0.37 ml/min/100 ml forearm volume ($p < 0.05$), but there was no change in peak hyperemic blood flow (29.2 ± 3.3 vs. 29.7 ± 3.3 ml/min/100 ml forearm volume, $p > 0.05$). Forearm vascular resistance decreased from 41.7 ± 5 to 32.8 ± 3 mm Hg/ml/min/100 ml forearm volume ($p < 0.05$).

Plasma catecholamine responses to bromocriptine were obtained in six subjects and are depicted in Fig. 4. After treatment with bromocriptine, plasma norepinephrine concentrations fell from 154 ± 24 to 70 ± 8 pg/ml ($p = 0.001$) when the subjects were in the supine position. There was no change in plasma epinephrine concentration (80 ± 17 vs. 70 ± 17 pg/ml, $p = 0.34$). Plasma dopamine concentrations were <40 pg/ml in all samples obtained.

The suppression of serum prolactin concentration induced by bromocriptine, from 82 ± 1.0 to 3.9 ± 1.0 ng/ml ($p < 0.05$), is shown in Fig. 5.

Bromocriptine did not alter plasma renin activity (1.64 ± 0.4 vs. 2.24 ± 1.0 ng/ml/h, $p = 0.16$), nor did it change plasma aldosterone concentration (8.3 ± 1.4 vs. 23.9 ± 10.2 ng/ml, $p = 0.09$).

Side effects of bromocriptine

Most subjects developed nasal stuffiness, usually after the first dose of bromocriptine. Nine subjects developed nausea, usually after the second dose of bromocriptine. If subjects remained supine, nausea resolved or was minimized. No antiemetics were given, although bromocriptine was discontinued after the first dose in one subject because of severe nausea. All subjects tested developed orthostatic hypotension, which resolved slowly over 5–7 h with a combination of intravenous and oral hydra-

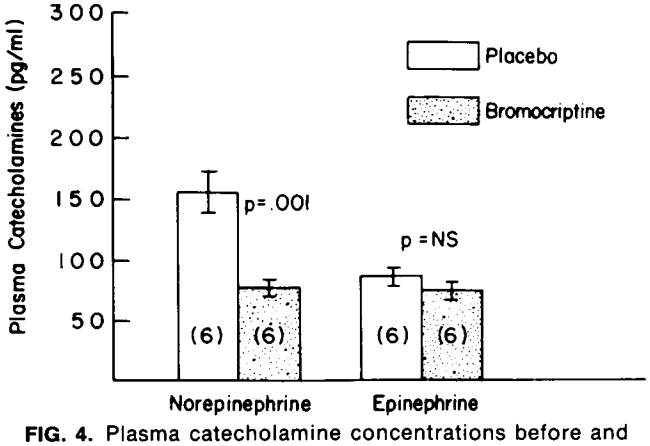

FIG. 4. Plasma catecholamine concentrations before and after bromocriptine administration. Mean ± SE; number in parentheses = number of patients.

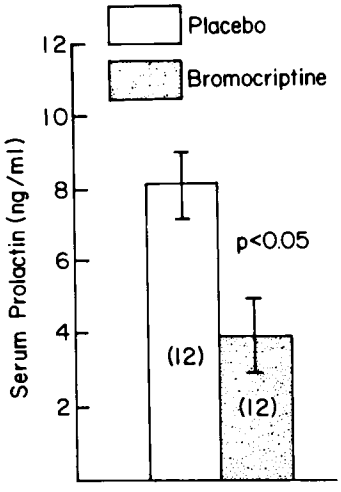

FIG. 5. Serum prolactin response to bromocriptine. Mean ± SE; number in parentheses = number of patients.

tion. Two subjects complained of mild headache which required no analgesics.

DISCUSSION

This study demonstrates in man for the first time that bromocriptine causes hypotension by means of reduction in peripheral venous and arteriolar tone. Bromocriptine did not influence blood pressure when the subjects were in the supine position. However, with the subject in the sitting and standing positions, bromocriptine produced consistent decrements in blood pressure; in addition, bromocriptine administration was associated with orthostatic hypotension. Thus, in placebo-treated subjects, blood pressure rose when the subjects changed from the supine to the standing position; with bromocriptine, that postural change produced a marked decrease in blood pressure. The hypotensive action of bromocriptine has been amply documented in normal (1,2) and hypertensive man (3–6), and in dogs (21,31,32), cats (24), and rats (33–35).

The heart rate response, on the other hand, has been variable. Many investigators have reported a decrease in heart rate with bromocriptine (8,21,24,32,36), while others have reported no change or a rise in heart rate (5,22,23,31,33). In our subjects, although heart rate increased as blood pressure fell, the degree of rise was insufficient to prevent severe orthostatic hypotension. The blunted heart rate response to assumption of erect position implies dysfunction of the normal baroreceptor reflex response. The increase in basal blood flow in our subjects signifies arteriolar dilation, which would be expected to decrease vascular resistance and lower blood pressure. The increase in venous distensibility demonstrates venous dilation, which would lead to venous pooling and account for the severe orthostatic decrease in blood pressure noted in our subjects.

In intact animals, bromocriptine may vasodilate or vasoconstrict, depending on the dose used and the vascular bed examined. Our data demonstrating vasodilation of forearm blood vessels are at variance with the data of Aellig (23) showing constriction of the veins of the human hand. Clark et al. (24), using intact dogs, have demonstrated constriction of renal and mesenteric arteries with low doses (6.25 and 12.5 μg/kg) and dilation with higher doses (25 μg/kg) of bromocriptine. Since systemic blood pressure and vascular resistance were reduced with all doses, it was assumed that other vascular beds dilated while the splanchnic beds constricted.

In isolated preparations, bromocriptine relaxed cerebral and peripheral blood vessels preconstricted with high potassium (37) (middle cerebral artery and central ear artery of rabbits) and with prostaglandin $F_2\alpha$ (38) (rabbit mesenteric artery). These isolated arterial segments are not devoid of sympathetic nerve terminals, and therefore do not distinguish between a pre- and postsynaptic action of bromocriptine. Thus, it seems likely that the hypotensive action of bromocriptine is related to its ability to vasodilate.

Does bromocriptine decrease vascular tone directly by activation of dopaminergic or adrenergic receptors on vascular smooth muscle cells or indirectly through inhibition of sympathetic nervous system activity? If bromocriptine were to cause vasodilation by a direct action on blood vessels alone, one would expect an increase in plasma norepinephrine concentration (39) as reported for minoxidil (40), phenoxybenzamine (41), nifedipine (42), and nitroprusside (43). In contrast, we demonstrate a decrease in plasma norepinephrine consistent with previous studies (2,5,34,36,44–47). An increase in plasma norepinephrine has not been reported, although Bybee et al. (47) have reported no change in norepinephrine following a single 2.5 mg dose of bromocriptine. Plasma epinephrine concentration is either unchanged, as reported here and by others (45,47), or decreased (2,44) following bromocriptine administration.

Ziegler et al. (36), using isolated rabbit ear arteries, reported inhibition by bromocriptine of vasoconstriction and norepinephrine release induced by electrical stimulation of sympathetic nerves. Bromocriptine did not affect vasoconstriction induced by exogenously perfused norepinephrine. Thus, bromocriptine appears to act not solely at vascular receptors by direct action, but indirectly through inhibition of sympathetic nerve activity.

Agonist activation of either dopamine or α_2-receptors on presynaptic membranes would lead to vasodilation and a decrease in circulating norepi-

nephrine concentration (18,48–51). Although there is evidence that bromocriptine can interact with α-receptors (21,32,52–54), several investigators have demonstrated in isolated vascular preparations that vasodilation by bromocriptine occurs despite α-adrenergic blockade with phenoxybenzamine (37,38). In intact normotensive animals, agents reported to inhibit the cardiovascular actions of bromocriptine include the dopamine antagonists: haloperidol (22,24), metoclopramide (22), sulpiride (22), pimozide (31), and the cholinergic ganglionic blocking agent, hexamethonium (31,32). In isolated vascular preparations, inhibition of bromocriptine-induced vasodilation has been reported for metoclopramide (38) and haloperidol (55). The antihypertensive action of bromocriptine was not affected by β-adrenergic blockade with propranolol (33,38,53), pindolol (38) or atenolol (38). Thus, although physiological interaction of bromocriptine and α-adrenergic receptors cannot be excluded, these factors as well as the blunted depressor activity in supine subjects (56) favor a primary action of bromocriptine on dopamine receptors. The presence of an intact sympathetic nervous system is necessary for full depressor or vasodilatory activity of bromocriptine (36,53). Whether bromocriptine acts on α- or dopamine-receptors in any given situation may depend on the local baseline adrenergic/cholinergic activity. Lokhandwala and Jandhyala (57) have postulated such a differential influence of dopamine. Under conditions of high basal sympathetic activity, dopamine suppresses sympathetic nervous system activity through activation of presynaptic inhibitory receptors, leading to a fall in blood pressure. Conversely, when sympathetic activity is depressed (e.g., with ganglionic blockade with hexamethonium) the vasodilator effect of dopamine is reversed and vasoconstriction ensues.

That bromocriptine can influence pituitary function is evident from the suppression of prolactin concentration reported here and by others (4,10,58). Bromocriptine has been reported to bind to brain tissue *in vitro* (59,60) and to lower norepinephrine concentration in CSF (36). Installation of bromocriptine into cerebral ventricles lowered heart rate in some cats (24), but had no effect in dogs (24). Also, the peripheral dopamine blocking agent domperidone was unable to prevent severe orthostatic hypotension in four subjects with Parkinson's disease (61). Thus, bromocriptine can exert a central nervous system action. Whether the hypotensive action of bromocriptine is related primarily to its central or peripheral nervous system activity remains to be elucidated.

In summary, we have demonstrated increases in venous distensibility and basal blood flow associated with a decrease in peripheral vascular resistance in normal subjects who developed orthostatic hypotension following the acute administration of bromocriptine. In these subjects, bromocriptine decreased circulating norepinephrine. These findings demonstrate that bromocriptine lowers blood pressure by dilating arterioles and veins. The orthostatic hypotension associated with bromocriptine treatment is caused by venous pooling. The concomitant suppression of circulating norepinephrine suggests that bromocriptine dilates arterioles and veins by its dopaminergic inhibition of sympathetic nervous system activity.

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