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Effects of Bromocryptine on Hormone and Blood Pressure Levels in the Spontaneously Hypertensive Rat[1] (40517)

J. P. MCMURTRY,[2] N. KAZAMA AND B. C. WEXLER

May Institute for Medical Research of the Jewish Hospital and Departments of Medicine and Pathology, University of Cincinnati College of Medicine, Cincinnati, Ohio 45229

Under certain conditions prolactin may act as a hypertensive agent, either directly affecting vascular reactivity (1, 2) or indirectly by altering vascular sensitivity to noradrenaline and angiotensin (1, 3). Clinical evidence relating prolactin to hypertension are contradictory. Stumpe *et al.* (4) have observed elevated prolactin levels in hypertensive males, whereas others report normal prolactin levels in hypertensive patients (5).

The spontaneously hypertensive rat (SHR) is a unique model for the investigation of essential hypertension as it may relate to man in that both neurogenic (6) and humoral mechanisms (7, 8) may be contributing factors to the development and maintenance of the hypertensive state. The dopamine agonist, 2 Br-α-ergocryptine (CB-154) has been used successfully to reduce hyperprolactinemia and blood pressure levels in patients with essential hypertension (4). The SHR rat has been reported to be hyperprolactinemic (9). We have investigated the effects of chronic CB-154 treatment on blood prolactin, corticosterone, aldosterone, and blood pressure levels in the SH rat to determine whether suppression of hypothalamic-pituitary release of prolactin would be reflected in reduction of adrenal steroids concomitant with reduction of blood pressure.

Materials and methods. The SH rats used in this experiment were descendants of the original Okamoto-Aoki Kyoto strain kindly provided by N.I.H. (Dr. C. Hansen). These animals were raised on a 12-hr light–dark cycle and were housed at a temperature of 26 ± 1° and humidity of 45–50%. Commercial rat chow (Purina) and tap water were available *ad libitum.*

Two days prior to the inception of chronic treatment with CB-154 (Sandoz Pharmaceuticals, East Hanover, NY), blood pressure was recorded by the Friedman-Freed microphonic manometer, indirect tail cuff method. On Day 1, a 1–2 ml heparinized blood sample was taken via cardiac puncture. Each animal was then injected s.c. daily for 21 days with CB-154, dissolved in 0.9% saline. Young, hypertensive rats, 90–100 days old (Group I) received 1.0 mg CB-154 daily (454 μg/100 g body wt for males and 574 μg/100 g body wt for females), whereas hypertensive older animals (18–24 months of age, Group II) received 1.5 mg/day (427 and 559 μg/100 g body wt for males and females respectively). Two days prior to the termination of the experiment, blood pressures were recorded again. On Day 22 blood samples were collected from all animals by decapitation, centrifuged, and stored at −20°. Blood samples were collected between 1500 to 1600 hr in young SHR when serum levels of prolactin, aldosterone, and corticosterone are known to be high, i.e., to evaluate the effectiveness of the CB-154 treatment. Blood samples were taken between 0900–1100 hr in the older rats, Group II, when the aforementioned are known to be elevated (to be published). Vaginal smears from female rats were used to record the stage of their estrous cycle.

Blood prolactin levels were determined by means of a double antibody radioimmunoassay (RIA) (10) using materials kindly provided by Dr. A. Parlow (NIAMDD). Corticosterone was measured by a modification of Murphy's method (11) and aldosterone by a modification of a RIA method previously described (12). Differences between means were statistically evaluated using Student's "t" test and analysis of variance (13).

Results. The effect of chronic CB-154 treat-

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[2] Send reprint requests to Dr. John P. McMurtry, May Institute for Medical Research, 421 Ridgeway Avenue, Cincinnati, Ohio 45229.

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ment on blood pressure in young, mildly hypertensive SH rats was equivocal (Table I). Blood pressure was significantly ($P < 0.05$) reduced in males, while blood pressure remained essentially unchanged in females. However, the decrease (6 mmHg) in blood pressure is of doubtful physiological significance. Mean body weights in both sexes were slightly reduced (10–15 g) following treatment (data not presented). Prolactin levels were significantly ($P < 0.001$) decreased in both sexes (Table I). Plasma corticosterone concentrations were also reduced in both sexes but not significantly. Paradoxically, plasma aldosterone levels did not change appreciably in females whereas in males aldosterone levels were significantly ($P < 0.02$) decreased, concomitant with a small, although significant, decrease in blood pressure. In the older male and female SHR, long-term treatment with CB-154 effectively reduced blood pressure ($P < 0.001$) (Table II). (The efficacy of CB-154 on blood pressure would appear to be related to age rather than dose as both Groups I and II received approximately equal amounts.) Similarly, prolactin concentrations were reduced in both sexes (Table II). Corticosterone levels were slightly below normal. Unlike the younger animals, aldosterone levels in the older SHR were unaffected by CB-154. It is noteworthy that the aldosterone levels (Table II) were greatly elevated in the older SH rats. Body weights in the older animals were not altered.

Discussion. It is evident from this study that administration of the dopaminergic antagonist, 2-bromoergocryptine, causes a marked decrease in the elevated prolactin and blood pressure levels of mature SH rats. It is not possible to ascertain from this study whether treatment with CB-154 affected prolactin secretion and blood pressure independently or whether the lowered blood prolactin caused the reduction in blood pressure. The prolactin-reducing action of CB-154 is rapid, i.e., within 30 to 60 min (14). Conversely, the anti-hypertensive effect of CB-154 was not evident until after 1–3 days of treatment (4).

It is well established that basal prolactin

TABLE I. BLOOD PRESSURE AND PLASMA LEVELS OF PROLACTIN, CORTICOSTERONE, AND ALDOSTERONE IN MALE AND FEMALE SH RATS (90–100 DAYS OF AGE) BEFORE AND AFTER TREATMENT (1 mg DAILY) WITH α-BROMOCRYPTINE.

		Pretreatment	Posttreatment	*P* value
Males	Blood pressure (mm Hg)	168.4 ± 2.0 (25)[a]	162.7 ± 1.0 (24)	.05
	Prolactin[b] (ng/ml)	92.0 ± 8.5 (30)	32.6 ± 2.5 (28)	.001
	Corticosterone[b] (μg/100 ml)	14.4 ± 1.5 (28)	11.9 ± 1.9 (28)	NS
	Aldosterone (ng/100 ml)	14.8 ± 2.7 (7)	8.8 ± 1.0 (26)	.02
Females	Blood pressure (mm Hg)	160.4 ± 1.7 (25)	157.3 ± 2.1 (15)	NS
	Prolactin[b] (ng/ml)	250.7 ± 49.4 (24)	44.9 ± 4.7 (19)	.001
	Corticosterone[b] (μg/100 ml)	32.5 ± 4.4 (18)	22.7 ± 2.8 (19)	NS
	Aldosterone[b] (ng/100 ml)	12.3 ± 1.2 (5)	11.4 ± 0.9 (17)	NS

[a] Mean ± SE. Number of observations/group in parentheses.
[b] All blood samples (pretreatment and posttreatment) were collected between 1500–1600 hr.

TABLE II. BLOOD PRESSURE AND PLASMA LEVELS OF PROLACTIN, CORTICOSTERONE, AND ALDOSTERONE IN MALE AND FEMALE SH RATS (18–24 MONTHS OF AGE) BEFORE AND AFTER TREATMENT (1.5 mg DAILY) WITH α-BROMOCRYPTINE.

		Pretreatment	Posttreatment	*P* value
Males	Blood pressure (mm Hg)	177.6 ± 5.2 (7)[a]	129.4 ± 3.6 (7)	.001
	Prolactin[b] (ng/ml)	52.6 ± 2.2 (10)	17.4 ± 4.4 (10)	.001
	Corticosterone[b] (μg/100 ml)	4.6 ± 0.9 (10)	3.2 ± 1.0 (9)	NS
	Aldosterone[b] (ng/100 ml)	56.2 ± 13.6 (4)	82.9 ± 24.6 (6)	NS
Females	Blood pressure (mm Hg)	187.4 ± 8.3 (10)	131.3 ± 7.2 (10)	.001
	Prolactin[b] (ng/ml)	125.8 ± 23.8 (8)	31.9 ± 2.6 (8)	.001
	Corticosterone[b] (μg/100 ml)	9.7 ± 1.4 (5)	5.6 ± 1.3 (5)	NS
	Aldosterone[b] (ng/100 ml)	40.8 ± 13.6 (3)	42.7 ± 7.8 (3)	NS

[a] Mean ± SE. Number of observations/group in parentheses.
[b] All blood samples (pretreatment and posttreatment) were collected between 0900–1100 hr.

secretion is under the control of the tuberoinfundibular dopaminergic system (15). Recent studies suggest that central dopaminergic mechanisms are an important regulator of blood pressure (16). Central catecholamine mechanisms in the central nervous system may play an important role in the regulation of blood pressure in man, and in the genetic hypertension of SH rats (17). Therefore, it is possible that the anti-hypertensive effect of bromoergocryptine was due to its elevation of central dopaminergic activity and depletion of hypothalamic stores of catecholamines (17), or the relaxation of peripheral vascular smooth muscle (18). Bromoergocryptine was most effective in lowering blood pressure in the older SH rats (Table II). Older rats have reduced brain catecholamine levels (19).

Corticosterone and aldosterone are known to be hypertensinogenic (20). Aldosterone levels were elevated in the older SHR. We have found that SHR are hyper-responsive to stress and produce greater quantities of corticosterone and aldosterone under both quiescent and stressful conditions as they grow older and their hypertension worsens (to be published). Corticosterone levels were only slightly reduced and aldosterone was unaffected by treatment with bromoergocryptine. The inter-relationship between reduced prolactin and blood pressure lowering with adrenal steroid secretion remains to be elucidated.

Summary. Treatment of young and old male and female SH rats with bromoergocryptine (21 days) significantly reduced blood prolactin concentrations. Blood pressure was slightly depressed in young male SH rats whereas in females blood pressure was unchanged. Hypertension was reduced (30%) to normotensive levels in old rats of both sexes. Corticosterone levels were slightly affected by treatment. A significant drop in aldosterone levels was noted in young male SH rats exclusively. The hypotensive action of bromocryptine (a dopamine agonist) is uncertain but may be related to changes in catecholamine levels or actions within the central nervous system.

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