BROMOCRIPTINE-INDUCED MODULATION OF PLASMA ALDOSTERONE RESPONSE TO ACUTE STIMULATIONS

By

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ABSTRACT

The influence of the dopaminergic agent 2-bromoergocryptine on plasma aldosterone response to acute stimulations was assessed in 14 normal male volunteers. Without modifying basal plasma aldosterone levels or urinary aldosterone excretion, bromocriptine retarded and diminished significantly the plasma aldosterone response to angiotensin II or ACTH, but did not alter the response to upright posture. These results point to a bromocriptine-induced modulation of the plasma aldosterone response to direct stimulations at the adrenal level. The present work brings further evidence for an effect of the dopaminergic system on the physiological control of aldosterone.

Bromocriptine is well known to inhibit prolactin by its dopaminergic action (Del Pozo et al. 1973; Dray & Oakley 1976). It also lowers the levels of other hypophyseal hormones, e.g. growth hormone (Camanni et al. 1975; Liuzzi et al. 1974; Thorner et al. 1975; Tolis et al. 1975), ACTH (Benker et al. 1976; Lambert & Birkenhager 1976) and TSH (Miyai et al. 1974). Based upon these observations, the possibility for dopaminergic pathways to play a role in the regulation of certain hormonal agents exists.

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Reports on the influence of bromocriptine on aldosterone regulation are controversial. Edwards et al. (1975) found that prior treatment with bromocriptine blocked the rise of plasma aldosterone induced by volume depletion. Other investigators did not observe an effect of bromocriptine on the stimulation of aldosterone induced by the progressive rise of potassium between dialyses (Olgaard et al. 1976), by postural changes (Del Pozo et al. 1977) or by sodium deprivation (Semple & Mason 1978). These contradictory findings prompted the present study which was designed to evaluate the effect of bromocriptine administration on the response of the renin-angiotensin-aldosterone system to stimulation by upright posture, ACTH and angiotensin II (AII) in normal subjects.

**PROTOCOLS AND METHODS**

The study protocols were approved by the institutional Ethics Committee. Fourteen healthy male volunteers aged from 25 to 32 years gave their informed consent for the studies. They were on unrestricted sodium and potassium diet and continued their usual activity except during the tests.

**Bromocriptine treatment.** – 2.5 mg bromocriptine (Parlodel®, Sandoz) was administered orally every 12 h for 5 days.

Aldosterone excretion and urinary electrolytes were measured on the control day and on the third day of treatment. Plasma renin activity and plasma prolactin were measured on the control day and on the morning of the fourth day of treatment. Body weight and arterial blood pressure were controlled daily.

**Acute stimulation tests.** – They were performed during the morning hours starting between 7 and 8 a.m. with subjects recumbent for 12 h after an overnight fast. No food or fluid intake was allowed during the experimental period. The tests were done before and on day 4 of bromocriptine treatment for either the posture or the AII studies and on day 5 for ACTH study. Blood samples were drawn from an indwelling venous catheter for plasma aldosterone, cortisol, plasma renin activity and prolactin determination.

1. Upright posture (6 subjects): blood samples were drawn in recumbency and 10, 20, 30, 60 and 120 min after assumption of upright posture.

2. ACTH administration (8 subjects): blood samples were drawn at 0 min and 10, 20, 30, 60 and 120 min after one bolus injection of 0.5 mg β1-24 ACTH (Synacthen® Ciba).

3. AII infusion (6 subjects): from 0 to 60 min AII (Hypertensin®, Ciba) was infused at a rate of 7 ng/kg/min regardless of the rise of the diastolic blood pressure. From 60 to 120 min the infusion rate was adjusted, if necessary, until a minimal rise of the diastolic blood pressure of 20 mm Hg was reached. This corresponds to the mean rise observed in 18 controls studied with an identical protocol (Birkhäuser et al. 1973). Blood pressure was followed regularly by an auscultatory method. Blood samples were drawn at 0 min and 10, 20, 30, 60, 75, 90 and 120 min after the beginning of the AII infusion.
Table 1.
Effect of bromocriptine administration on body weight, blood pressure, urinary electrolytes and aldosterone, plasma prolactin and plasma renin activity (n = 14, mean ± SEM, paired t-test).

<table>
<thead>
<tr>
<th></th>
<th>n = 14 mean ± SEM</th>
<th>Body weight (kg)</th>
<th>mean arterial blood pressure (mm Hg) recumbent upright</th>
<th>Na⁺ excretion mEq./24 h</th>
<th>K⁺ excretion mEq./24 h</th>
<th>Aldosterone excretion µg/24 h</th>
<th>Plasma prolactin ng/ml</th>
<th>Plasma renin activity ng/ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control day</td>
<td></td>
<td>73.3 ± 1.73</td>
<td>84 ± 3.5 93 ± 2.1</td>
<td>186.6 ± 20.2</td>
<td>80.8 ± 7.2</td>
<td>7.7 ± 1.05</td>
<td>9.09 ± 1.06</td>
<td>1.91 ± 0.20</td>
</tr>
<tr>
<td>under bromocriptine administration</td>
<td></td>
<td>73.3 ± 1.65</td>
<td>84 ± 1.8 92 ± 1.7</td>
<td>178.1 ± 17.3</td>
<td>74.6 ± 7.6</td>
<td>7.6 ± 1.30</td>
<td>1.37 ± 0.19</td>
<td>1.50 ± 0.28</td>
</tr>
<tr>
<td>paired t-test</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>P &lt; 0.001</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
Analytical methods

Plasma aldosterone was measured by RIA (Underwood & Williams 1972) or by double isotope derivative (DID) method (Bojesen & Thuneberg 1967). The RIA method was previously evaluated in our laboratory by Gaillard et al. (1976). Plasma renin activity (Poulsen & Jorgensen 1974; Vallotton 1971), plasma prolactin (Kit C.E.A.-I.R.E.-SORIN, furnished by Eidg. Institut für Reaktorforschung, Switzerland), and urinary aldosterone (Langan et al. 1974) were determined by radioimmunoassays. Plasma cortisol was measured by a competition method (Leclercq et al. 1969). Electrolytes were measured by flame photometry. Statistical evaluation was done by paired or unpaired t-test. The results are reported as mean ± SEM.

RESULTS

Effect of bromocriptine treatment (Table 1).

After 3 days of bromocriptine administration no change in body weight, mean arterial blood pressure, urinary aldosterone and electrolytes occurred. There was a discrete but not significant decrease of mean plasma renin activity. Plasma prolactin values became suppressed in all subjects, decreasing from 9.09 ± 1.06 ng/ml to 1.37 ± 0.19 ng/ml ($P < 0.001$).

![Graph of plasma aldosterone and renin activity response to upright posture, before and on the 4th day of bromocriptine administration (n=6, mean ± SEM). The means in the 2 groups are not significantly different (paired t-test).](image-url)
Stimulation by upright posture (Fig. 1).

With upright posture, plasma aldosterone and renin activity increased significantly \((P < 0.05)\) and similarly in the untreated and treated subjects.

\textit{Stimulation by ACTH} (Fig. 2).

Plasma aldosterone increased significantly in both groups \((P < 0.01)\), but the increase was sluggish in the treated subjects, the difference of mean values being statistically significant at 10, 20, and 30 min when compared with controls. Cortisol increased similarly in both groups. Plasma renin activity decreased progressively and similarly from 2.16 \(\pm\) 0.28 to 1.73 \(\pm\) 0.24 in the untreated group and from 1.67 \(\pm\) 0.34 to 1.32 \(\pm\) 0.27 in the treated group (N.S.). Plasma prolactin levels remained suppressed.
Stimulation by A II (Fig. 3)

From 0 to 60 min, infusion of A II, at a rate of 7 ng/kg/min, induced a minimal 20 mm Hg increase in diastolic blood pressure, a sharp rise in plasma aldosterone and a decrease in plasma renin activity in the control group (n = 18) as previously published (Birkhäuser et al. 1973). In the bromocriptine treated subjects the aldosterone increase was very slow and significantly lower during the first 60 min ($P < 0.01$) when compared with the controls. In 3 out of 6 subjects the mean diastolic blood pressure increase was only 10–15 mm Hg. Plasma renin activity decreased to very low values.

From 60 to 120 min, plasma aldosterone remained constantly elevated in the control group. In the 3 treated subjects whose blood pressure had responded adequately to A II, plasma aldosterone remained lower than in the controls. In the 3 treated subjects whose blood pressure was only 10–15 mm Hg at 60 min, the dose of A II was increased to 10.5 ng/kg/min (one subject) and

![Graph](https://via.placeholder.com/150)

*Fig. 3.*

Plasma aldosterone and renin activity response to A II infusion in 6 subjects on the 4th day of bromocriptine administration. Shaded area: response in 18 untreated subjects receiving 7 ng/kg/min A II from 0 to 120 min (mean ± sem). The differences of the means between the 2 groups are highly significant at 10, 20, 30, 60 and 120 min ($P < 0.01$, unpaired t-test).
14 ng/kg/min (2 subjects) in order to achieve a 20 mm Hg blood pressure rise. At 120 min the mean aldosterone value was still significantly lower in the treated group \((P < 0.01)\), but in 2 of the subjects receiving a higher infusion rate (10.5 and 14 ng/kg/min A II, respectively) plasma aldosterone reached the values observed in the controls. Plasma renin activity stayed at low values. Plasma prolactin levels did not change.

**DISCUSSION**

*Edwards et al.* (1975), who observed, during bromocriptine administration, a lowered response of aldosterone to furosemide, postulated a dopaminergic modulation of the adrenal cortex response to volume depletion.

The present study investigates further, in normal subjects, the effect of bromocriptine on plasma aldosterone response to acute stimulation by A II or ACTH, two direct stimuli of the adrenal cortex, and by upright posture, an indirect stimulus acting through the renin-angiotensin system.

Under bromocriptine the basal plasma and urinary aldosterone values were unchanged. Mean plasma renin activity values decreased by 22 %, but this decrease was not statistically significant. The response to indirect stimuli such as posture (present study and *Del Pozo et al.* 1977) or sodium deprivation (*Semple & Mason* 1978) is not affected by bromocriptine treatment. The plasma aldosterone response to A II and ACTH administration was significantly retarded in the bromocriptine treated group (Figs. 2 and 3). The dopaminergic action of bromocriptine appears therefore to interfere only early on aldosterone as shown by the delayed response to the two direct stimuli studied. Two observations speak in favour of an effect at the adrenal level: the absence of correlation between plasma aldosterone and renin activity in bromocriptine treated subjects, which rules out a mediation by the renin-angiotensin system (*Edwards et al.* 1975) and the rise of plasma aldosterone obtained after metoclopramide, a dopamine-receptor blocking agent, in normal and in hypophysectomized subjects (*Norbiato et al.* 1977a,b) which speaks against a pituitary mediated action of bromocriptine. The latter observation does not eliminate a common central dopaminergic control of hormonal secretion influencing the adrenal cortex as well as the pituitary gland. Alternatively the possibility should be raised that prolactine exerts a permissive function for an adequate aldosterone response to ACTH or A II, and that its suppression results in an impairment of the responses. Our data do not permit to rule out this alternative explanation.

A central effect of bromocriptine on the factors regulating blood pressure is suggested by the finding that in hypertensive patients with high prolactin levels, bromocriptine suppressed prolactin and lowered blood pressure. This
hypotensive effect is much less pronounced in hypertensive patients with normal plasma prolactin (Stumpe et al. 1977) and was absent in our normotensive subjects.

The absence of a significant effect of bromocriptine on the aldosterone response to upright posture suggests that the alleged dopaminergic influence on aldosterone secretion can be overruled by other regulatory systems.

In conclusion, the lowered and delayed response of aldosterone to iv administration of A II or ACTH points to a modulating effect of bromocriptine at the adrenal level. To determine whether this dopaminergic effect is direct or indirect would require further studies such as with isolated adrenal gland.

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