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BRIEF COMMUNICATION

Effect of Acute Administration of Bromocriptine on Isoproterenol- and Angiotensin II-Induced Water Intake in Estrogen-Treated Rats[1]

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FREGLY, M. J. *Effect of acute administration of bromocriptine on isoproterenol- and angiotensin II-induced water intake in estrogen-treated rats.* PHARMACOL BIOCHEM BEHAV 26(2) 431–434, 1987.— Chronic administration of an estrogenic agent is well known to attenuate the drinking response of rats to treatment with a variety of dipsogenic agents, and to increase plasma concentration of prolactin. Treatment with prolactin is also known to reduce the drinking response to administration of the dipsogenic agent, isoproterenol. Hence, a possibility existed that the antidipsogenic effect of chronic treatment with estrogen was mediated by an increased plasma prolactin concentration. Since bromocriptine, a dopaminergic agonist, is known to reduce plasma prolactin concentration in estrogen-treated rats, it was administered (1.0 mg/kg, IP) 15 min prior to treatment with either isoproterenol (25 μg/kg, SC) or angiotensin II (200 μg/kg, SC). The results suggest that the antidipsogenic effect of chronic treatment of rats with estradiol benzoate (30.4 and 45.7 μg/kg/day) can be reversed, at least partially, by acute administration of bromocriptine.

Angiotensin-induced drinking Isoproterenol-induced drinking Bromocriptine Dopamine receptor agonist Estradiol benzoate Antidipsogenic effect of estrogen

CHRONIC administration of estradiol benzoate to rats is accompanied by a reduced drinking response to administration of angiotensin II, isoproterenol, pilocarpine, and dehydration [6–8]. Estrogenic compounds are also well known to inhibit central production of the prolactin release-inhibiting hormone, dopamine [3,4]. Hence, chronic treatment with estrogenic steroids is accompanied by an increase in blood concentration and rate of secretion of prolactin [10]. Since implantation of a prolactin secreting tumor into rats has also been shown to reduce the drinking response to administration of isoproterenol [14], the possibility existed that the antidipsogenic effect of chronic treatment with estrogen was induced secondarily by an increase in the secretion of prolactin. The dopaminergic agonist, bromocriptine, has been shown to reduce plasma concentration of prolactin [15]. Hence, the effect of this compound on the drinking responses of estrogen-treated rats to acute administration of isoproterenol and angiotensin II was tested.

METHOD

Twenty-four female rats of the Blue Spruce Farms (Sprague Dawley) strain weighing initially from 230 to 260 g were used. They were kept 3 per cage in a room maintained at 25±1°C and illuminated from 0700 to 1900 hr. All rats were provided with Purina Laboratory Chow and tap water ad lib.

Sixteen of the rats were anesthetized with ether and implanted between the shoulder blades with Silastic® tubes containing crystalline estradiol benzoate as described earlier [1, 5, 16]. Eight of the rats were implanted with tubes (No. 602-265) 5 mm in length while the remaining rats were implanted with tubes 10 mm in length.

Three weeks after implantation of the tubes containing estradiol benzoate, the drinking response to acute administration of isoproterenol was tested. At 0900 hr all rats were weighed, administered isoproterenol, the beta-adrenoceptor agonist (25 μg/kg, SC), and placed alone into a stainless steel metabolic cage. No food was allowed during the experiment. Immediately after injection, each rat was given a preweighed bottle of tap water (26°C) in a container consisting of an infant nursing bottle with a cast aluminum spout [18]. Water intakes were then measured at 0.5 and 1.0 hr after treatment by weighing each bottle on a torsion balance.

At the beginning of the fourth week each group was di-

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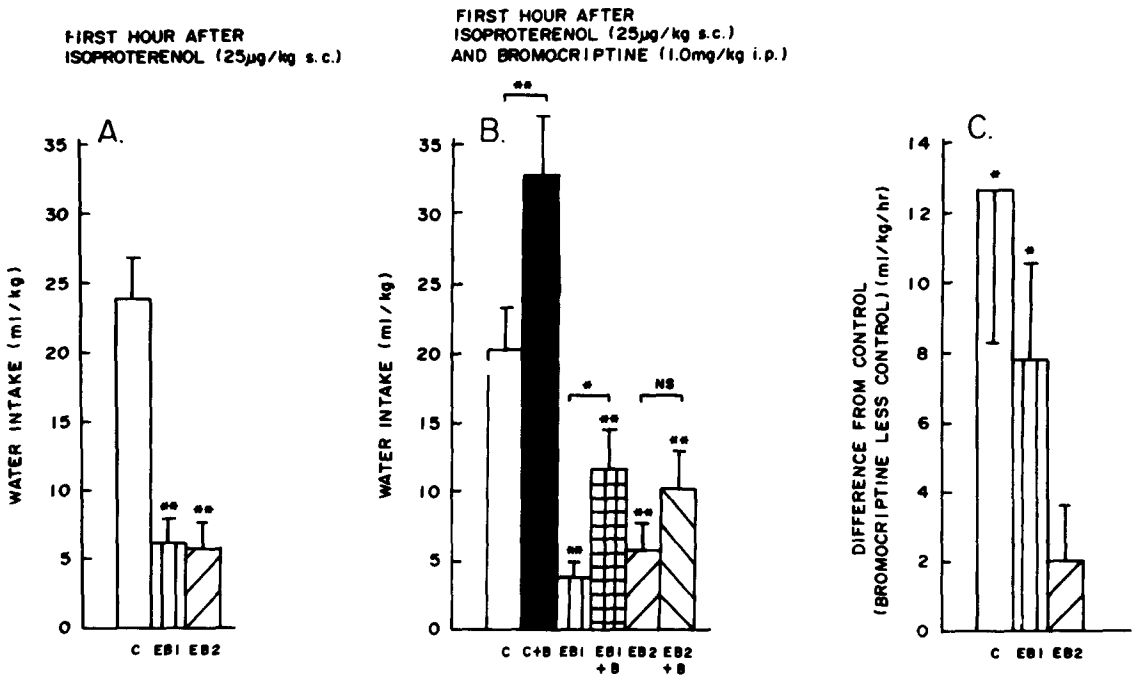

FIG. 1. Effect of administration of isoproterenol (25 μg/kg, SC) and bromocriptine (1.0 mg/kg, IP) on water intake of rats. Left panel shows the effect of isoproterenol administered alone on water intake. The second panel shows the effect of isoproterenol alone or isoproterenol in combination with bromocriptine on water intakes of the three groups. The right panel shows the difference in water intake of each group after bromocriptine and isoproterenol from that induced by isoproterenol alone. One standard error is set off at each mean. *$p<0.05$; **$p<0.01$, NS=not significant. EB1 and EB2 designate groups treated with 7.6 and 11.8 μg estradiol benzoate/day, respectively. B designates the groups treated with bromocriptine.

vided in half and the above experiment was repeated with the exception that half of the group received bromocriptine, the dopaminergic agonist, at 1.0 mg/kg, IP 15 min prior to administration of isoproterenol. The remaining half of each group received a similar volume of the vehicle used to dissolve the bromocriptine. At the end of the fourth week, the experiment was repeated with the groups switched, i.e., the groups receiving bromocriptine now received the vehicle used to solubilize bromocriptine.

At the beginning of the sixth week, a study similar to that described above for isoproterenol was carried out excepting that angiotensin II (200 μg/kg, SC) was used as the dipsogenic agent. At the end of the sixth week, the experiment was repeated with the groups switched as described above.

Statistical analysis of the data was carried out by either a one- or two-way analysis of variance where appropriate [20]. The difference between individual means was determined using the Neuman Keuls post hoc test [12]. Significance was set at the 95% confidence limit.

RESULTS

Water intakes induced by isoproterenol after three weeks of treatment with estradiol benzoate are shown in Fig. 1A. Since water intakes one hr after treatment were only slightly greater than those after 0.5 hr, only the one hr intakes are shown. The drinking response to administration of 25 μg isoproterenol/kg, SC was significantly attenuated in the two estrogen-treated groups, but to about the same extent (Fig. 1A).

When bromocriptine was administered in combination with isoproterenol (Fig. 1B), water intakes of all groups increased, but only those of the control group and the group treated with the lower dose of estradiol benzoate were increased significantly. The water intakes of each rat within each group were compared with and without bromocriptine by a one-tailed t-test. Bromocriptine was again shown to increase significantly the change in water intake of the control group and the group treated with the lower dose of estradiol benzoate, but not the group treated with the higher dose (Fig. 1C).

Water intakes of both estradiol benzoate-treated groups administered angiotensin II SC were less than that of the control group throughout the 2 hr study (Fig. 2). However, intakes of the estrogen-treated groups were significantly less only during the first and second hr. When bromocriptine was administered in combination with angiotensin II (Fig. 2), only the water intake of the control group was increased significantly ($p<0.05$) during the first half hr (Fig. 2, left panel). After 1.0 hr, water intakes of both the control group and the group receiving the lower dose of estradiol benzoate were increased significantly ($p<0.01$) above their control levels. During the second hr, water intakes of all groups were increased significantly by bromocriptine.

The Silastic® tubes were removed at the end of the experiment. Calculation of the dose of estradiol benzoate received by the rats showed the 7.6±0.9 and 11.8±1.4 μg/day (30.4

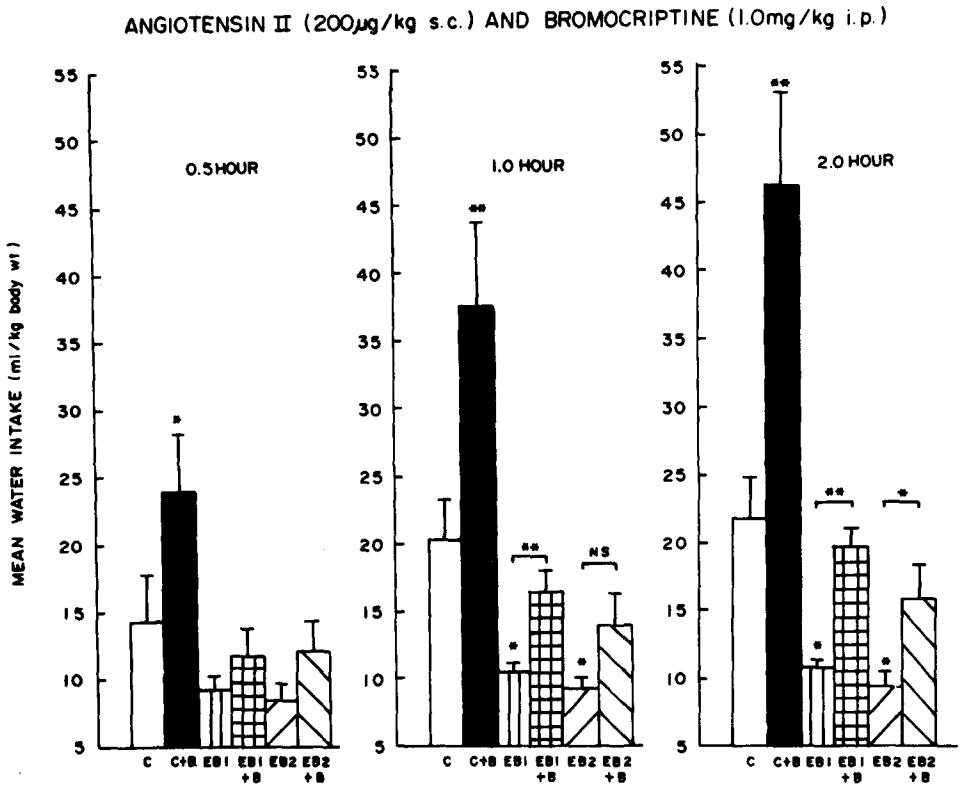

FIG. 2. Effect of administration of angiotensin II (200 μg/kg, SC) and bromocriptine (1.0 mg/kg, IP) on water intake of control and estrogen-treated rats during the 2 hr of the experiment. One standard error is set off at each mean. *$p<0.05$; **$p<0.01$, NS=not significant. EB1 and EB2 designate groups treated with 7.6 and 11.8 μg estradiol benzoate/day, respectively. B designates the groups treated with bromocriptine.

and 45.7 μg/kg/day) were released from the 5 and 10 mm Silastic® tubes, respectively.

DISCUSSION

Prolactin secretion is regulated in part at least by dopamine, the most established prolactin release-inhibiting hormone [19] which acts directly on specific dopaminergic receptors in the anterior pituitary [2, 10, 11]. A large body of experimental evidence supports the fact that estrogenic agents reduce the content of dopamine in the median eminence and striatum of the brain [3, 4, 9, 10, 13]. Others have shown that chronic administration of estradiol benzoate reduces the number of dopamine binding sites in the anterior pituitary gland [11]. Still other studies report that prolactin secretion is increased in vivo in estrogen-treated rats [17] and in vitro in anterior pituitary cells from rats treated chronically with estradiol benzoate [17]. It is thus significant that the antidipsogenic effect of chronic treatment of rats with estradiol benzoate can be reversed, at least partially, by acute administration of the dopaminergic agonist, bromocriptine. This suggests, but does not prove, that excessive secretion of prolactin plays a role.

Kaufman *et al.* [15] observed a syndrome of polydipsia, polyuria, and decreased urine osmolality without a change in food intake in male rats made chronically hyperprolactinemic by implanting anterior pituitary glands beneath the renal capsule. This syndrome is similar to that of estradiol-treated rats reported from this laboratory [1]. Katovich and Simpkins [14] made rats hyperprolactinemic by subcutaneous implantation of a prolactin-secreting adenoma. They also reported a polydipsia and a decreased dipsogenic responsiveness to administration of isoproterenol. However, hyperprolactinemia did not affect the drinking response to administration of angiotensin II. In this latter respect, their results do not agree with those obtained in estrogen-treated rats. The dichotomy between the drinking responses to isoproterenol and angiotensin II in the hyperprolactinemic rats was explained by the authors as the result of an effect of prolactin on beta-adrenergic responsiveness rather than a generalized antidipsogenic effect. In spite of this difference between hyperprolactinemic and estrogen-treated rats, it now seems reasonable to suggest that at least a portion of the effects of estrogenic agents on fluid turnover in rats may be attributed to the increased prolactin secretion accompanying chronic administration of an estrogenic agent.

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