Estrogen Inhibition of Corticoid Hypertension in Chickens

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WITH THE TECHNICAL ASSISTANCE OF P. JOHNSON AND A. ELLIS

Estrogens tend to lower the blood pressure of cockerels. Estrogen-treated cockerels and estrogen-secreting hens are immune to the chronic pressor effects of desoxycorticosterone acetate (DCA) and cortisone.

Both desoxycorticosterone acetate (DCA) and cortisone effect moderate hypertension in cockerels. The present studies demonstrate that estrogen-treated cockerels and estrogen-secreting hens are immune to this corticoid-induced blood pressure elevation.

METHODS

The experimental designs and technics were generally in accord with the standardized procedures of the department. Four series of experiments were accomplished varying in duration from five to nine weeks and utilizing a total of 95 chickens (table 1). In three series (BC 20, BC 31A and BC 31B), cockerels were utilized, and the effects of exogenous estrogens on corticoid hypertension assessed. In one series (BC 29), mature, gonadally active, egg laying hens were utilized, to determine whether desoxycorticosterone acetate would induce increased blood pressure in the presence of endogenous estrogen secretion. In two series (BC 29 and 31A), 1 per cent sodium chloride was incorporated in the feed, to increase the hypertensive effect of desoxycorticosterone acetate. In two series (BC 20 and 31A), a cholesterol-supplemented mash was fed, since it was desired concomitantly to study atherogenesis.

Blood pressure was determined on the unanesthetized quiescent bird, kept lying on its side on an animal board. A sciatic artery was isolated by blunt dissection and cannulated under direct visualization with a 20 gage needle, precautions being taken to eliminate blood loss. A Lilly electromanometer and Sanborn direct-writing twin Visocardiettes were used to obtain and record blood pressure.

Unanesthetized birds were bled via a wing vein. The blood was immediately heparinized, centrifuged, and the plasma removed. Plasma sodium and potassium concentrations were determined with a Beckman flame photometer.

RESULTS

Blood Pressures. In three series of experiments with cockerels, estrogens consistently inhibited the pressor response to corticoids (table 2). Estrogens were equally effective in preventing the hypertensive action of desoxycorticosterone acetate, desoxycorticosterone acetate plus sodium chloride and cortisone. Estrogen administration tended generally to induce blood pressure levels lower than controls. In mature, gonadally active, egg laying hens, desoxycorticosterone acetate plus sodium chloride failed to effect a pressor response (table 3).

Plasma Electrolytes. Both groups of egg-laying hens exhibited levels of plasma potassium significantly lower than those of cockerels (series BC 29, table 4). In cockerels, desoxycorticosterone alone, estrogens alone, and desoxycorticosterone plus sodium chloride all produced significant moderate hypopotassemia. The combination of estrogens plus corticoid consistently induced more marked hypopotassemia. Plasma sodium levels were unaltered by the experimental regimens, except for two groups: In series BC 31A, desoxycorticosterone acetate plus sodium chloride plus estrogens (group 4) effected hypernatremia, whereas in
TABLE 1.—Experimental Regimens

<table>
<thead>
<tr>
<th>Series and Sex</th>
<th>Group</th>
<th>Number of Birds</th>
<th>Chick Age During Experiment (weeks)</th>
<th>Diet</th>
<th>Hormone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC20†♂</td>
<td>1</td>
<td>6</td>
<td>12-19</td>
<td>1 CO†</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6</td>
<td>12-19</td>
<td>1 CO</td>
<td>Estrogens</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>12-19</td>
<td>1 CO</td>
<td>DCA + Estrogens</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6</td>
<td>12-19</td>
<td>1 CO</td>
<td>Cortisone + Estrogens</td>
</tr>
<tr>
<td>BC20†♀</td>
<td>1</td>
<td>5</td>
<td>22-31</td>
<td>PM + 1% NaCl</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>22-31</td>
<td>PM + 1% NaCl</td>
<td>DCA</td>
</tr>
<tr>
<td>BC31A†♂</td>
<td>1</td>
<td>8</td>
<td>9-16</td>
<td>PM</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6</td>
<td>9-16</td>
<td>1 CO</td>
<td>Estrogens</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11</td>
<td>9-16</td>
<td>1 CO + 1% NaCl</td>
<td>DCA</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
<td>9-16</td>
<td>1 CO + 1% NaCl</td>
<td>DCA + Estrogens</td>
</tr>
<tr>
<td>BC31B†♀</td>
<td>7</td>
<td>6</td>
<td>14-20</td>
<td>PM</td>
<td>DCA</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>5</td>
<td>14-20</td>
<td>PM</td>
<td>DCA + Estrogens</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>7</td>
<td>14-20</td>
<td>PM</td>
<td>Cortisone</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8</td>
<td>14-20</td>
<td>PM</td>
<td>Cortisone + Estrogens</td>
</tr>
</tbody>
</table>

* Hormone dosages were:
- Estrogens (mixed conjugated equine estrogens)—minimum of 20 mg./chick/day in the drinking water.
- DCA (desoxycorticosterone acetate in oil)—1 to 5 mg./chick/day parenterally.
- Cortisone (saline suspension)—2 to 20 mg./chick/day parenterally.
† 1 CO is chick starter mash plus 1% cholesterol and 5% cottonseed oil. PM is plain (unsupplemented) chick starter mash.

series BC 31B, desoxycorticosterone plus estrogens (group 8) induced hyponatremia, both in association with marked hypopotassemia.

Other findings. All groups given estrogens, desoxycorticosterone acetate, desoxycorticosterone acetate plus sodium chloride, or estrogens plus corticoid tended to exhibit moderate polydipsia. Exhibition of corticoid or estrogens plus corticoid had little or no consistent effect on feed intake, growth or development; all birds, irrespective of hormone regimen, were well nourished and well developed.

DISCUSSION

These experiments conclusively demonstrate that estrogen-treated cockerels and estrogen-secreting hens are significantly resistant to the chronic pressor influences of corticoids. They indicate that estrogens specifically inhibit corticoid-induced hypertension in chickens. They further suggest that estrogens tend generally to lower blood pressure in this avian species.

Review of the literature reveals a paucity of previous work on the effects of estrogens on blood pressure homeostasis. It is known that the systolic blood pressure of roosters is 15 to 25 per cent higher than that of hens. In Series BC32 hatched 2 to 3 weeks after Series BC31B control cockerels (substituting on plain mash and tap water ad lib.) exhibited these blood pressure findings: Systolic 138 ± 6.6 (range 114-150); diastolic 123 ± 6.4 (range 103-140).

TABLE 2.—Blood Pressures of Cockerels

<table>
<thead>
<tr>
<th>Series</th>
<th>Group</th>
<th>Age (wks.)</th>
<th>Regimen</th>
<th>Systolic Pressure (mm. Hg)</th>
<th>Diastolic Pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC20</td>
<td>1</td>
<td>10</td>
<td>1 CO Control</td>
<td>149 ± 3.2*</td>
<td>140-162</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
<td>1 CO Estrogens</td>
<td>142 ± 3.3</td>
<td>134-156</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>10</td>
<td>1 CO DCA + Estrogens</td>
<td>150 ± 3.4</td>
<td>136-160</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
<td>1 CO Cortisone + Estrogens</td>
<td>132 ± 6.7</td>
<td>116-162</td>
</tr>
<tr>
<td>BC31A</td>
<td>1</td>
<td>14</td>
<td>PM Control</td>
<td>142 ± 4.9</td>
<td>125-152</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>14</td>
<td>1 CO Estrogens</td>
<td>137 ± 4.7</td>
<td>115 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>14</td>
<td>1 CO NaCl-DCA</td>
<td>133 ± 2.9</td>
<td>103-147</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>14</td>
<td>1 CO NaCl-DCA + Estrogens</td>
<td>130 ± 3.3</td>
<td>111 ± 2.8</td>
</tr>
<tr>
<td>BC31B</td>
<td>7</td>
<td>20</td>
<td>DCA</td>
<td>161 ± 5.5</td>
<td>149-170</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>20</td>
<td>DCA + Estrogens</td>
<td>128 ± 3.7</td>
<td>109 ± 4.2</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>20</td>
<td>Cortisone</td>
<td>164 ± 4.5</td>
<td>148-173</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>20</td>
<td>Cortisone + Estrogens</td>
<td>132 ± 6.9</td>
<td>115-138</td>
</tr>
</tbody>
</table>

* Standard error (S.E.) of the mean.

S.D. = \( \sqrt{\frac{(X_i - \bar{X})^2}{N - 1}} \)

S.E. = \( \frac{S.D.}{\sqrt{N}} \)

† These are mean blood pressures.
‡ Range.
§ In Series BC32 hatched 2 to 3 weeks after Series BC31B control cockerels (substituting on plain mash and tap water ad lib.) exhibited these blood pressure findings: Systolic 138 ± 6.6 (range 114-150); diastolic 123 ± 6.4 (range 103-140).
TABLE 3.—Blood Pressures of Hens (Series BC29)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (weeks)</th>
<th>Regimen</th>
<th>Systolic Pressure (mm. Hg)</th>
<th>Diastolic Pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22*</td>
<td>PM</td>
<td>151 ± 5.81</td>
<td>119 ± 3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>135-170§</td>
<td>110-130</td>
</tr>
<tr>
<td>2</td>
<td>22*</td>
<td>PM</td>
<td>144 ± 2.5</td>
<td>122 ± 5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>135-150</td>
<td>106-138</td>
</tr>
<tr>
<td>1</td>
<td>31†</td>
<td>PM + 1% NaCl</td>
<td>160 ± 6.3</td>
<td>120 ± 3.1</td>
</tr>
<tr>
<td>2</td>
<td>31†</td>
<td>PM + 1% NaCl + DCA</td>
<td>155 ± 7.0</td>
<td>127 ± 4.7</td>
</tr>
</tbody>
</table>

* Data prior to institution of experimental regimen.
† Nine weeks on experimental regimen.
§ Standard error of the mean.

TABLE 4.—Plasma Electrolyte Concentrations

<table>
<thead>
<tr>
<th>Series and Sex</th>
<th>Group</th>
<th>Regimen</th>
<th>Plasma Na (mEq./L.)</th>
<th>Plasma K (mEq./L.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC29</td>
<td>1</td>
<td>PM + 1% NaCl</td>
<td>156.4 ± 1.3</td>
<td>2.63 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>PM + 1% NaCl + DCA</td>
<td>155.5 ± 2.0</td>
<td>2.34-2.92</td>
</tr>
<tr>
<td>BC31A</td>
<td>1</td>
<td>PM Control</td>
<td>157.2 ± 0.8</td>
<td>4.96 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 CO + Estrogens</td>
<td>156.0-159.2</td>
<td>4.04-5.74</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 CO + NaCl - DCA</td>
<td>155.0-159.2</td>
<td>4.04-4.12</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 CO + NaCl - DCA + Estrogens</td>
<td>156.3 ± 1.4</td>
<td>3.69 ± 0.12</td>
</tr>
<tr>
<td>BC31B</td>
<td>7</td>
<td>PM + DCA</td>
<td>161.6 ± 1.5</td>
<td>4.26 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>PM + DCA + Estrogens</td>
<td>157.0-156.6</td>
<td>3.56-4.78</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>PM + Cortisone</td>
<td>159.0 ± 4.1</td>
<td>3.49 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>PM + Cortisone + Estrogens</td>
<td>132.6-162.0</td>
<td>3.32-4.22</td>
</tr>
</tbody>
</table>

* Standard error of the mean.

Data on the influence of estrogens on blood pressure of rats are contradictory. It was reported,12,14 that estradiol and diethylstilbestrol may induce hypertension in this species. More recently, data were published demonstrating that pregnancy does not inhibit the hypertension developing in rats treated with antiplacenta serum plus desoxycorticosterone acetate.16 In another study, it was found that rats given estradiol plus desoxycorticosterone acetate frequently fail to develop the usual desoxycorticosterone acetate hypertension.17 This was interpreted as a non-specific response, attributable to general debility ensuing with the hormone combination. In view of our observations, further studies in the rat are definitely indicated.

At present, little is known concerning the mechanisms of estrogen effects on cardiovascular homeostasis. Estrogens are known to influence protein, lipid and calcium metabolism, with resultant alterations of plasma levels of various hormones.
of these substances. Estrogens also suppress the secretion of anterior pituitary hormones and inhibit injury-induced connective tissue proliferation. Further, they induce acute vasodilatation in rabbit, rat and man. Additional work is necessary to elucidate the relationship, if any, between these estrogen actions and estrogen inhibition of corticoid hypertension.

In the present experiments, estrogen inhibition of corticoid hypertension was invariably associated with significant lowering of plasma potassium levels. In view of other data relating altered water-electrolyte metabolism to the pathogenesis of hypertension, and demonstrating antihypertensive effects of both sodium and potassium depletion in rats, dogs, chicks and man, further work is essential to determine whether the concomitant effects of estrogens on water-electrolyte metabolism and on blood pressure homeostasis have any cause-and-effect inter-relationship.

From recent studies, it is clear that a significant sex difference exists in incidence of human hypertension. Hypertension is more common in young men than in young women; after the age of 40, the reverse is true, hypertension being more common in females. It is common knowledge that the female climacteric is “normally” associated with vasomotor instability, characterized by hot flushes and fluctuations in blood pressure. The older medical literature distinguishes a “menopausal hypertension,” presumably developing immediately after artificial or natural menopause. The actuality of this entity has been seriously challenged by more recent studies. However, several contemporary classifiers identify endocrine types of hypertension, including a type or types in females associated with significant folliculoid-corticoid dysfunction. Therapeutic trials of estrogens in hypertension, particularly in menopausal women, have yielded contradictory results, with the bulk of workers reporting little or no positive response.

Our demonstration of the ability of estrogens to inhibit experimental corticoid-induced hypertension, together with numerous observations on the influences of estrogens on cardiovascular function of man and animals, inevitably provokes the speculative questions: Does the natural endogenous estrogen secretion tend to protect premenopausal woman against hypertension? Is there any role for estrogens in the therapy of human hypertension? Neither of these questions can be answered with finality at present. Both problems merit further exploration.

**Summary**

1. Estrogens tend to lower blood pressure of cockerels.
2. Both estrogen-treated cockerels and estrogen-secreting hens are specifically protected against hypertension induced by desoxycorticosterone acetate, desoxycorticosterone acetate plus sodium chloride, and cortisone.
3. Mature egg-laying hens exhibit low potassium levels.
4. Estrogen inhibition of corticoid hypertension is associated in both cockerels and hens with decreased concentrations of plasma potassium.

**Sumario Español**

1. Los estrógenos tienden a reducir la presión arterial en gallipollos.
2. Los gallipollos tratados con estrogenu y gallinas produciendo estrógeno son específicamente protegidas contra la hipertensión inducida por acetato de desoxicorticosterona, acetato de desoxycorticosterona más cloruro de sodio y cortisona.
3. Gallinas adultas ponedoras de huevos exhiben niveles bajos de potasio.
4. La inhibición de la hipertensión corticoide por el estrógeno está asociada en ambos gallipollos y gallinas con concentraciones bajas de potasio en el plasma.

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ESTROGEN INHIBITION OF CORTICOID HYPERTENSION

Mr. A. Ellis accomplished the sodium and potassium flame photometric analyses. Messrs. G. Crowley and C. Jones also rendered excellent technical assistance.

REFERENCES


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