Effect of Adrenalectomy on Pressor Responsiveness to Angiotonin and Renin

By G. C. Salmoiraghi, M.D., and T. W. McCubbin, M.D.

Pressor response to injection of renin is reduced or abolished during adrenal insufficiency without concurrent change in response to angiotonin and other drugs. Selective loss of response to renin is considered to result from depletion of available renin-substrate by endogenous renin; when release of endogenous renin is precluded by nephrectomy, adrenalectomy does not cause diminution of response to renin. The increase in response to angiotonin and renin that follows nephrectomy is not prevented by adrenalectomy.

It has often been shown that adrenalectomy reduces arterial pressure in experimental renal hypertension and recent studies indicate that adrenalectomy may modify clinical essential hypertension. Participation of the adrenal glands in hypertensive diseases is also suggested by the observations (1) that the zona glomerulosa hypertrophies in renal hypertensive rats, (2) that sodium metabolism may be altered in essential hypertension, (3) that a synergism, or dependence, exists between the actions of adrenal steroids and kidney extracts containing renin in eliciting necrotizing arteriolitis, and (4) that adrenalectomy prevents vascular lesions in renal hypertensive rats.

Since the renin-angiotonin system remains one of the probable primary mechanisms of hypertension, the hypotensive effect of adrenalectomy might depend upon inhibition of, or interference with, this mechanism. Accordingly, the effect of adrenalectomy on cardiovascular responses to injected renin, angiotonin and other drugs has been measured and the more immediate causes of the observed changes investigated.

METHODS

Femoral arterial pressures of adult mongrel dogs were recorded on a smoked drum by a mercury manometer; heparin was used in the connecting tubing. Normal dogs were anesthetized with 30 mg. per kilogram of sodium pentobarbital intravenously; less anesthetic was required after adrenalectomy.

Test drugs were injected into a femoral vein and were: angiotonin (amount raising arterial pressure an average of 17 mm. Hg in 20 normal pentobarbitalized dogs); serotonin creatine sulfate (40 gamma as serotonin); histamine diphosphate (5 to 20 gamma); renin (amount raising arterial pressure an average of 30 mm. Hg in 20 normal pentobarbitalized dogs). Dosage was constant during each experiment.

From one to four days following control measurements of cardiovascular responsiveness, one adrenal gland was removed with aseptic technic through a retroperitoneal flank incision, and responsiveness remeasured two to five days later. The second adrenal was removed after another two to five days and responsiveness was measured 24 hours later and at intervals of one or more days until death; in a few dogs, the only test after adrenalectomy was at three to four days. Prophylactic penicillin was given after each test or surgical procedure.

No dog received supportive therapy; they were fed Purina dog chow and tap water ad libitum in addition to 1 pound of horse meat twice a week.

Gross and microscopic examination at autopsy verified removal of all adrenal tissue.

RESULTS

Adrenalectomy in Normal Dogs. Eight of 14 dogs died within two days following removal of the second adrenal gland. Five dogs survived for from three to five days and one survived for 10 days. Arterial pressures, measured during light pentobarbital anesthesia, fell slightly during the several days following removal of one adrenal; removal of the second adrenal was followed by progressive decline in arterial pressure until values were approximately 50 per cent of the respective normals 24 hours before death. The amount of pentobarbital...
CARDIOVASCULAR RESPONSES FOUR DAYS AFTER BILATERAL ADRENALECTOMY.

The cardiovascular responses four days after bilateral adrenalectomy are shown in Figure 1. The responses were measured after administration of various vasoactive substances: (1) angiotensin; (2) serotonin 100 gamma; (3) histamine 5 and 10 gamma; (4) noradrenaline 1.25, 2.5 and 5 gamma; (5) adrenaline 2.5, 5 and 10 gamma; (6) renin.

The required dose of light anesthesia became less during succeeding days after adrenalectomy. Cardiovascular responsiveness was not significantly altered following removal of one adrenal gland. Twenty-four hours after removal of the second adrenal, responses to renin were often increased and those to angiotensin were increased 5 to 28 mm Hg in five of six dogs. Responses to 1.25 and 2.5 gamma of noradrenaline and responses to 5 and 10 gamma of histamine were also increased in the majority of experiments while responses to 2.5, 5 and 10 gamma of adrenaline, 5 gamma of noradrenaline and 100 gamma of serotonin creatinine sulfate showed no consistent change from control values.

This variable increase in responsiveness 24 hours after bilateral adrenalectomy might have been due to denervation of a portion of the splanchnic bed, since surgery undoubtedly interrupted sympathetic vasomotor nerves. That this was the case seems indicated by experiments in which the paravertebral sympathetic chains were removed from T10 to L4 and the splanchnic nerves cut one or more weeks prior to bilateral adrenalectomy; the latter procedure then failed, in four of five dogs, to elicit an increased response to renin and angiotensin.

Two or more days after removal of the second adrenal renin response began to diminish,

Fig. 1. Cardiovascular responses four days after bilateral adrenalectomy. (1) angiotensin; (2) serotonin 100 gamma; (3) histamine 5 and 10 gamma; (4) noradrenaline 1.25, 2.5 and 5 gamma; (5) adrenaline 2.5, 5 and 10 gamma; (6) renin.

Fig. 2. Cardiovascular responses 3 days after bilateral nephrectomy and adrenalectomy. (1) angiotensin; (2) renin; (3) kymograph off.
ADRENALECTOMY AND PRESSOR RESPONSIVENESS

TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Initial Blood Pressure</th>
<th>Angiotonin</th>
<th>Renin</th>
<th>Serotonin SCS 100γ</th>
<th>Histamine 1.25γ</th>
<th>Histamine 2.5γ</th>
<th>Noradrenaline 5γ</th>
<th>Noradrenaline 10γ</th>
<th>Adrenaline 5γ</th>
<th>Adrenaline 10γ</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>162</td>
<td>+11</td>
<td>-11</td>
<td>-10</td>
<td>+14</td>
<td>+19</td>
<td>+21</td>
<td>+20</td>
<td>+24</td>
<td>+34</td>
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<tr>
<td>After unilateral adrenalectomy</td>
<td>156</td>
<td>+12</td>
<td>+17</td>
<td>-27</td>
<td>+12</td>
<td>+22</td>
<td>+35</td>
<td>+23</td>
<td>+32</td>
<td>+48</td>
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<tr>
<td>1 day</td>
<td>90</td>
<td>+34</td>
<td>+31</td>
<td>+6</td>
<td>-21</td>
<td>-26</td>
<td>+35</td>
<td>+34</td>
<td>+45</td>
<td>+63</td>
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<tr>
<td>4 days</td>
<td>68</td>
<td>+26</td>
<td>+7</td>
<td>-5</td>
<td>-21</td>
<td>+26</td>
<td>+40</td>
<td>+28</td>
<td>+35</td>
<td>+46</td>
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<tr>
<td>After unilateral nephrectomy and adrenalectomy</td>
<td>155</td>
<td>+16</td>
<td>+33</td>
<td>+5</td>
<td>-7</td>
<td>-26</td>
<td>+33</td>
<td>+59</td>
<td>+26</td>
<td>+53</td>
</tr>
<tr>
<td>After bilateral nephrectomy and adrenalectomy 3 days</td>
<td>85</td>
<td>+43</td>
<td>+78</td>
<td>+6</td>
<td>-4</td>
<td>-21</td>
<td>+26</td>
<td>+65</td>
<td>+22</td>
<td>+56</td>
</tr>
</tbody>
</table>

* All values are in mm. Hg.

while that to angiotonin was unchanged. Following the irregular increase 24 hours after removal of the second adrenal, responses to histamine, serotonin, noradrenaline and adrenaline showed no consistent further change during succeeding days. A representative experiment is shown in table 1a.

Paravertebral lumbar sympathectomy and splanchnicectomy did not influence the decrease in response to renin late after adrenalectomy.

During the collapse that shortly preceded death, response to all drugs was much impaired or even abolished.

Injection of renin during the repeated tests following adrenalectomy might have exhausted available renin substrate and resulted in the selective loss of response to renin. That this was not the case is indicated by three experiments in which the adrenal glands were removed in two stages and only one test made postoperatively, and this on the third or fourth day. Responses to renin were reduced to 13, 14 and 8 mm. Hg from respective control values of 27, 29 and 21 mm. Hg. Responses to angiotonin were, as in the previous series, largely unchanged.

Effect of Combined Adrenalectomy and Nephrectomy. Adrenalectomy was combined with nephrectomy in five dogs to determine whether adrenal insufficiency and/or operative trauma associated with adrenalectomy might have caused release of amounts of renin large enough to exhaust plasma renin-substrate. Control measurements were made four to seven days following removal of one adrenal and kidney. Three or four days after removal of the other adrenal and kidney, responses to both renin and angiotonin were strikingly increased. A representative experiment is shown in table 1b.

Arterial pressures declined less during succeeding days when nephrectomy accompanied adrenalectomy, and more pentobarbital was required to induce light anesthesia than when adrenalectomy was done alone. Survival time in the nephrectomized-adrenalectomized group, however, was approximately the same as in the adrenalectomized series (4, 4, 4, 3 and 5 days).

DISCUSSION

These experiments indicate that advanced adrenal insufficiency does not significantly impair responsiveness of the cardiovascular system to many injected vasoactive drugs unless animals are in terminal adrenal failure.

Adrenalectomy did, however, cause consistent reduction or even loss of response to injected renin, and this finding confirms most previous similar studies. Increase in response to renin with no concurrent loss of response to angiotonin suggests depletion of
renin substrate. It is probable that this was the case, for when endogenous renin was excluded by nephrectomy at the time of adrenalectomy, diminution of response to renin did not appear. Depletion of substrate could have depended upon greatly increased excretion of renin, or, lesser amounts of renin might have exhausted circulating substrate because of impaired hepatic replacement. Against the likelihood that adrenalectomy completely prevents formation of renin substrate by the liver is the evidence that plasma renin substrate levels return to normal after nephrectomy in adrenalectomized rats. Favoring an increased excretion of renin is the observation that diminution of plasma renin-substrate in experimental shock is prevented by nephrectomy, and it is known that adrenalectomy does not decrease renin content in kidneys.

The present experiments accord with those of Houssay and Dexter who found a positive correlation between plasma renin-substrate and response to renin in adrenalectomized dogs.

Care is necessary in evaluating changes in the cardiovascular reactivity following adrenalectomy, since the procedure denervates a portion of the splanchnic bed with resultant increase in responsiveness. These increased responses should probably be considered as the true controls.

The well-documented increase in response to angiotonin and renin after nephrectomy is not dependent upon the adrenal glands, since an increase occurred when adrenalectomy and nephrectomy were done simultaneously.

**Summary**

Pressor responsiveness to renin and angiotonin was increased in dogs 24 hours after bilateral adrenalectomy. This increase probably resulted from a denervation-sensitization due to interruption of sympathetic vasomotor pathways during operation; it was largely prevented by prior lumbar sympathectomy.

During adrenal insufficiency, pressor response to injected renin was decreased while responsiveness to angiotonin, serotonin, histamine, noradrenaline and adrenaline showed no significant change. Responsiveness to all drugs was diminished during terminal shock.

Diminution of response to injected renin after bilateral adrenalectomy did not occur if adrenalectomy was combined with nephrectomy. Selective loss of response to renin is considered to be due to exhaustion of available renin substrate.

Unilateral adrenalectomy did not significantly modify cardiovascular responsiveness. Adrenalectomy did not prevent the increased response to angiotonin and renin that occurs after nephrectomy.

**REFERENCES**


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