Effect of Athyroid State on Vascular Reactivity and Arterial Pressure in Neurogenic and Renal Hypertensive Dogs

By JAMES W. McCUBBIN, M.D., and IRVINE H. PAGE, M.D.

Since vascular responsiveness to adrenaline, noradrenaline, renin and angiotonin is reduced by suppression of thyroidal function in normotensive dogs, it was a possibility that in neurogenic and renal hypertensive animals suppression of thyroidal function might be associated with decrease in arterial pressure. This possibility was not confirmed, hypertension persisting unaltered in both groups of hypertensive animals over long periods of observation. Changes in vascular reactivity were slight in comparison with those associated with the athyroid state in normotensive dogs.

IN THE preceding paper it was shown that complete suppression of thyroidal function in normal dogs sharply reduces vascular responsiveness to adrenaline, noradrenaline, renin and angiotonin. The renin-angiotonin renal pressor system has often been suggested as part of the mechanism of experimental renal hypertension. Adrenaline and noradrenaline are important mediators of the effector portion of the sympathetic nervous system and are, therefore, presumably involved in the mechanism of experimental neurogenic hypertension.

Arterial pressure might be lowered if responsiveness to substances participating intimately in the mechanism of a specific type of hypertension should be reduced. To this end, thyroid activity has been suppressed with radioactive iodine or thyroidectomy in neurogenic as well as renal hypertensive dogs. The latter group has been included despite previous observations that subtotal¹ or total² thyroidectomy has no effect on arterial pressure in dogs with renal hypertension. In view of the difficulty associated with permanent removal of all thyroid tissue³ it seemed worthwhile to confirm this observation through the use of radioactive iodine.

METHODS

Normal adult mongrel dogs were used in all experiments. Renal hypertension was induced by Page's method⁴ and chronic neurogenic hypertension elicited by section of the buffer nerves according to the technic described by Grimson.⁵ Blood pressures were measured twice weekly for the first two or three months of each experiment and once weekly thereafter. All pressures were taken in a soundproofed room and recorded from a mercury manometer, after direct puncture of the femoral artery with a 20 gage needle. Pulses were counted by palpation of the opposite femoral artery.

Vascular reactivity was measured according to the technic previously described.⁶ Test drugs were submaximal doses of adrenaline, noradrenaline and histamine and were kept the same for each animal for the duration of the experiment. Tetraethylammonium chloride (TEAC) was given in a dose of 5 mg. per kilogram. Reactivity was tested after the establishment of sustained hypertension and again several months after intravenous administration of radioactive iodine (¹³¹I)* or thyroidectomy. Fifteen to 20 millieuries of I¹³¹, given in a single dose, effectively abolished thyroidal function as judged by lack of cervical uptake of tracer doses given at intervals during the course of each experiment. Thyroidectomized dogs failed to show cervical uptake of tracer doses of I¹³¹.

RESULTS

A. Effect of Athyroidism on Experimental Neurogenic Hypertension

Five neurogenic hypertensive dogs were treated with I¹³¹ and thyroidectomy was done in another. As seen in table 1, suppression of thyroidal function had no significant effect on

* The radioactive iodine used in this investigation was supplied by Oak Ridge National Laboratory on authorization from the Isotopes Division, U. S. Atomic Energy Commission. We are grateful to Dr. Otto Glasser of the Cleveland Clinic for his assistance in measuring and handling this material.
arterial pressure over periods ranging from 4 to 17 months with an average of 11.5 months. It was not unusual, however, for arterial pressure to fall to normal or near normal levels during the first few days after administration of I\textsuperscript{131}. This brief hypotensive response was presumably associated with the thyroiditis that followed a large dose of I\textsuperscript{131}. Cardioacceleration, a prominent feature of experimental neurogenic hypertension, was less prominent several months after treatment with I\textsuperscript{131} (table 1).

Changes in vascular reactivity after suppression of thyroidal function were minor and equivocal (table 2) in contrast with those associated with athyroidism in normal animals.\textsuperscript{8} Pressor activity of adrenaline was more often increased than decreased. Noradrenaline responses were reduced in four dogs, unchanged in one and increased in another. Reactivity to histamine and tetraethylammonium chloride were largely unchanged, the enhanced responsiveness that occurs after buffer nerve section\textsuperscript{6} persisting in the athyroid state.

One athyroid neurogenic hypertensive dog received 1 Gm. per kilogram of desiccated thyroid (Parke, Davis USP)* daily for one month. Tested again at the end of this time, adrenaline responses had become entirely depressor. Noradrenaline and histamine responses were unchanged and tetraethylammonium chloride produced a smaller hypotensive response. Replacement therapy did not change arterial pressure or heart rate.

B. Effect of Athyroidism on Experimental Renal Hypertension

Four renal hypertensive dogs showed no significant change in arterial pressure during observation periods ranging between 5 and 10 months after treatment with I\textsuperscript{131} in two and thyroidectomy in two (table 3).

There was no definite change in reactivity to adrenaline, noradrenaline or histamine. Hypotensive responses to tetraethylammonium chloride were considerably increased in three dogs and were unchanged in the fourth (table 4).

Appearance of both groups of athyroid hypertensive animals was the same as that described for normal dogs following suppression

\* Desiccated thyroid was kindly supplied by Dr. Harry E. Carnes, Parke, Davis and Co.

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Table 1.—Arterial Pressure and Pulse Rate in Experimental Neurogenic Hypertension before and after Suppression of Thyroidal Function.

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control Values</th>
<th>After Suppression of Thyroidal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B. P. Pulse</td>
<td>Months B. P. Pulse</td>
</tr>
<tr>
<td>3197</td>
<td>225 185</td>
<td>10 220 140 I\textsuperscript{131}</td>
</tr>
<tr>
<td>2814</td>
<td>210 185</td>
<td>17 240 152 I\textsuperscript{131}</td>
</tr>
<tr>
<td>2807</td>
<td>205 174</td>
<td>17 225 140 I\textsuperscript{131}</td>
</tr>
<tr>
<td>2725</td>
<td>212 164</td>
<td>4 215 142 Thyroidectomy</td>
</tr>
<tr>
<td>2717</td>
<td>205 175</td>
<td>13 220 154 I\textsuperscript{131}</td>
</tr>
<tr>
<td>3191</td>
<td>242 176</td>
<td>8 215 142 I\textsuperscript{131}</td>
</tr>
</tbody>
</table>

Table 2.—Vascular Reactivity in Neurogenic Hypertensive Dogs before and after Suppression of Thyroidal Function.

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control Values</th>
<th>After Suppression of Thyroidal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B. P. Pulse</td>
<td>Months B. P. Pulse</td>
</tr>
<tr>
<td>3533</td>
<td>195 122</td>
<td>10 200 120 I\textsuperscript{131}</td>
</tr>
<tr>
<td>2601</td>
<td>210 110</td>
<td>8 200 104 Thyroidectomy</td>
</tr>
<tr>
<td>2700</td>
<td>195 108</td>
<td>7 190 98 Thyroidectomy</td>
</tr>
<tr>
<td>3539</td>
<td>190 150</td>
<td>5 225 154 I\textsuperscript{131}</td>
</tr>
</tbody>
</table>

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of thyroidal activity. Myxedema appeared in none.

**Table 4.—Vascular Reactivity in Renal Hypertensive Dogs before and after Suppression of Thyroidal Function.**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Adrenaline</th>
<th>Noradrenaline</th>
<th>Histamine</th>
<th>TEAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3533 control</td>
<td>+55</td>
<td>+40</td>
<td>-40</td>
<td>+5</td>
</tr>
<tr>
<td>2661 9 months after I(^{131})</td>
<td>+47</td>
<td>+32</td>
<td>-32</td>
<td>-93</td>
</tr>
<tr>
<td>3700 control</td>
<td>+26</td>
<td>+76</td>
<td>-71</td>
<td>+8</td>
</tr>
<tr>
<td>3539 6 months after I(^{131})</td>
<td>+51</td>
<td>+47</td>
<td>-50</td>
<td>-70</td>
</tr>
</tbody>
</table>

**Discussion**

Since reactivity to adrenaline, noradrenaline, renin and angiotonin decreased markedly in athyroid dogs,\(^3\) it seemed reasonable to assume that suppression of thyroidal activity might be of benefit in experimental hypertensions. This study has shown such an assumption to be unjustified. Hypertension persisted to the same or greater degree in both neurogenic and renal hypertensive dogs many months after complete suppression of thyroidal function with I\(^{131}\) or after thyroidectomy. On the other hand, it was expected that changes in vascular reactivity associated with athyroidism would occur to the same extent as in normal dogs. This was also not the case. In contrast to normal dogs, athyroidism was associated with only minor and equivocal alterations in vascular responsiveness. With the possible exception of noradrenaline responses which were more often decreased than not, reactivity in neurogenic hypertensive dogs was essentially unchanged. Three of four renal hypertensive dogs showed increased responsiveness to tetraethylammonium chloride as the only change in reactivity following appearance of athyroidism. With these exceptions, it appears that inherent in the mechanisms of both experimental neurogenic and renal hypertension is a tendency to stabilize vascular reactivity at a fixed level which eliminates the modifying effect of suppression of thyroidal function. Even so, reactivity to noradrenaline was sharply depressed in several athyroid neurogenic hypertensive dogs without modifying arterial pressure levels. Also, replacement therapy with desiccated thyroid resulted in complete inversion of adrenaline responses without modifying the hypertensive arterial pressure. It has been shown\(^6\) that neurogenic hypertension depends upon an intact sympathetic nervous system. If adrenaline and noradrenaline are the principal humoral mediators of sympathetic nerves, it is puzzling why diminishing reactivity to these drugs fails to lower arterial pressure in experimental neurogenic hypertension.

As an incidental observation, it was noted that pulse rate in neurogenic hypertensive dogs showed a definite tendency to slow several months after suppression of thyroidal function. Whether this was due to training or to absence of thyroidal function was not determined. The latter view is the more probable one since control periods lasted as long as three months. Despite slower rates, there was no associated fall in arterial pressure and this observation is in accord with a previous report\(^7\) demonstrating the minor role of cardioacceleration in chronic neurogenic hypertension in dogs.

**Summary and Conclusions**

Elimination of thyroidal function by thyroidectomy or treatment with I\(^{131}\) failed to modify arterial pressure levels in neurogenic and renal hypertensive dogs over periods of observation as long as 17 months in the neurogenic group and 10 months in the renal group. Slowing of pulse rate in neurogenic hypertensive dogs occurred several months after suppression of thyroidal function without accompanying decrease in arterial pressure.

Athyroidism was associated with only minor changes in vascular reactivity in both groups of hypertensive animals. These were less marked and not as consistently present as in the athyroid state in normotensive dogs.\(^3\) It is suggested that the mechanisms producing experimental neurogenic and renal hypertension
tend also to maintain vascular reactivity at a fixed level. Neurogenic hypertension persisted to the same degree, however, in the face of diminished reactivity to both adrenaline and noradrenaline.

REFERENCES
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