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PRESSOR RESPONSIVENESS TO ANGIOTENSIN AND NOREPINEPHRINE IN THE HYPOTHYROID RAT A POSSIBLE MECHANISM FOR THE REVERSAL OF EXPERIMENTAL HYPERTENSION IN THE RAT BY HYPOTHYROIDISM

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Pressor Responsiveness to Angiotensin and Norepinephrine in the Hypothyroid Rat: A possible Mechanism for the Reversal of Experimental Hypertension in the Rat by Hypothyroidism

F. John Gennari

Submitted to the Faculty of Yale University School of Medicine as partial fulfillment of the requirements for the degree of Doctor of Medicine.

From the Department of Internal Medicine

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Introduction

A relationship between thyroid function and the production and maintenance of experimental hypertension in the rat has been demonstrated by many investigators. Braun-Menendez (1) first showed that thyroidectomy or thiouracil administration in the rat reversed or prevented renal ischemic hypertension. Since that time, Salgado (2) has shown that experimental hypothyroidism prevented the hypertension produced by desoxycorticosterone (DOC) administration, and Chappell et. al. (3) reversed or prevented adrenal regeneration hypertension by propylthiouracil (PTU) administration. Recently, Fregly (4,5,6) has shown that PTU administration or I^{131} treatment also prevents or reverses renal ischemic hypertension, and that PTU administration has the same effect on the hypertension produced by a high salt diet.

The question that naturally arises is what is the mechanism of this phenomenon. In seeking a common denominator for the effect of thyroid suppression on so many forms of experimental hypertension, one wonders whether vascular reactivity to pressor hormones and its relation to thyroid function plays a role. Hyperthyroidism in man and in the dog has been shown to increase cardiovascular responsiveness to norepinephrine and epinephrine (7,8,9). Conversely, Page and McCubbin demonstrated a decreased pressor responsiveness in hypothyroid dogs to norepineprine, epinephrine, and angiotonin (10). However, they were unable to reverse renal ischemic hypertension in the dog by thyroid ablation (11).

The purpose of this study, then, is to investigate the pressor response to angiotensin and norepinephrine in the hypothyroid rat, a model which has been demonstrated to reverse experimental hypertension.

Method

A colony of 30 male Sprague Dawley rats was maintained on regular Purina laboratory chow in a temperature controlled environment (72° F.). The rats were weighed twice weekly, and blood pressure determinations were made at least once weekly throughout the course of the study. Blood pressure measurements were done in the unanesthetized rat according to the technique of Friedman and Freed (12), modified by Fregly (13). The figure obtained for the systolic pressure in each rat is the mid-point of 3 consecutive blood pressure recordings within a 10 mm. Hg range, after stabilization of the rat in the restraining cage.

After three weeks of baseline blood pressure and weight determinations, 12 rats were chosen for I^{131} treatment. This group included 4 rats in which angiotensin response measurements had been carried out, according to the method described below, prior to treatment. The other 8 were randomly chosen from the colony. Each of these 12 rats was given 850 microcuries (uc.) NaI^{131} intraperitoneally. The rats were then isolated for 8 days, after which time they were returned to the same environment as the control animals for the remainder of the experiment.

Norepinephrine and synthetic angiotensin II were used for the pressor assays and were diluted to the desired concentration in a normal saline solution, to which 100 units of heparin per cc. had been added. With angiotensin only, polyvinylpyrrolidone, 1 mg. per cc., was also added to the injection solution to minimize losses due to adsorption. The pressor agents were injected intravenously through a #24 needle in the tail vein of the unanesthetized rat, according to the technique of

Cotlove (14). Figure 1 is a photograph of a rat in the restraining holder, with the tail pressure cuff, microphone, and intravenous needle in place.

Pressor response measurements were always carried out in both a control and an I^{131} treated rat on the same day. Pressor response to a control solution of heparin-saline was also measured in each rat.

The pressor response to angiotensin was measured from 3 to 5 weeks after I^{131} treatment in the following manner. Two doses, 30 mug. (millimicrograms) and 60 mug., were tested in each rat. After stabilization of the rat in the restraining holder, and following 2 identical blood pressure determinations at 30 second intervals, the test dose was injected rapidly intravenously, and the blood pressure measured at 20 second intervals until it returned to pre-injection levels. The difference between the pre-injection blood pressure and the peak systolic pressure following injection was defined as the pressor response. At least two injections of each dose level of angiotensin were carried out in each rat, except for rat #13.

Pressor response to norepinephrine was measured at 6 weeks after I^{131} treatment in the same manner as angiotensin except that the first blood pressure measurement was taken at 10 seconds after injection. Two dose levels, 120 mug. and 240 mug. were tested, and at least 3 injections of each dose were carried out in each rat.

Thyroid function in the I^{131} treated rats was assessed only incidentally during the course of the experiment, by means of bi-weekly weight determinations.

At the termination of the experiment, 8 weeks after I^{131} treatment, all of the treated rats were sacrificed, blood was collected for plasma PBI (protein bound iodine) determination, and the thyroid remnants were removed for microscopic examination. Five control animals were sacrificed and treated in the same manner for comparison. Plasma PBI's were done according to the dialysis technique of Seligson (15). Hematoxylin and eosin stains of sections of thyroid tissues were prepared.

Statistical analysis of all results for significance was carried out by means of the unpaired 't' test.

Results

1. Weight

The mean weights of the control and I^{131} treated rats throughout the course of the experiment are shown in figure 2. During the 3 week baseline period, the average weight in the colony increased from 170 gms. to 251 gms., in a normal growth pattern. The average weight of the 12 rats chosen for I^{131} treatment was 250.3 gms. and the average weight of the 18 controls was 252.7 gms. Following treatment, both groups continued to gain until 3 weeks after treatment. From this point on, the treated rats showed an essentially flat growth curve, in sharp contrast to the control group. The difference in weight was statistically significant from 26 days after treatment to the time of sacrifice.

2. Plasma PBI's and Thyroid Histology

Plasma PBI's were done on 11 I^{131} treated rats and 5 control rats at the time of sacrifice. The individual results are shown in Table 1. The mean PBI of the 5 control rats, 2.9 ug.%, is somewhat lower than the mean PBI in the normal rat obtained by Taurog and Chaikoff (16). However, the technique used here is different, and is known to give slightly lower levels in humans (15). The mean PBI of the 11 I^{131} treated rats, 0.74 ug.%, is significantly lower, and the highest value obtained in these rats was 1.2 ug.%. These values are in agreement with the results obtained by Feller et al. (17) after the administration of 875 uc. I^{131} to rats.

Microscopic examination of the thyroid sections of the 11 I^{131} treated rats showed disorganized architecture, fibrosis, and complete obliteration of the gland in some instances. In no histological section was colloid seen. The thyroid sections of the 5 control rats revealed normal thyroid tissue in all cases. By these two criteria and by the flat growth curve, the I^{131} treated rats were demonstrated to be hypothyroid.

3. Blood Pressure

The average weekly blood pressures of the control and hypothyroid rats are shown in Figure 3. The increase in blood pressure observed during the baseline study is thought to be due to the fact that the rats were rapidly growing during this time, and passed from a young to an adult pressure.

The average blood pressure of the control group during the 7 week experimental period was 148. This agrees with the average control blood pressure obtained by Fregly (13) in Sprague-Dawley rats, using the same technique.

The mean blood pressure of the I^{131} treated rats fell to a low point of 129, two weeks after treatment. This occurred quite consistently, as 11 of the 12 treated rats showed a significant decrease in blood pressure at this point. This was followed by a gradual increase in the average pressure to 143 at seven weeks after treatment, which was, however, still significantly lower than the control blood pressure. The decrease in blood pressure was significant from 10 days after treatment to the end of the study.

4. Pressor Responsiveness

Control

Two-thirds of the rats tested with one or more injections of heparin-saline solution alone demonstrated no pressor response. In the remaining third, responses of 5-10 mm. Hg were sporadically observed. These elevations were considered to be within the range of error of the technique used for blood pressure measurement, and pressor activity of the heparin-saline vehicle was considered as nil.

Angiotensin

Pressor responsiveness to angiotensin was measured in 15 control and 10 hypothyroid rats. The 15 control rats included 4 that were later treated with radioactive iodine. The typical response curve to both doses of angiotensin in a control and a hypothyroid rat is shown in Figure 4. The duration of response was 60 to 80 seconds with a peak rise in blood pressure occurring at the measurement taken 20 seconds after injection in all the rats tested. Thus, the duration of response to angiotensin in the hypothyroid rat was not found to be measurably altered by this technique. However, as can be seen from the individual case in Figure 4, the peak response to both doses of angiotensin was significantly decreased in the hypothyroid rat. Because more test injections of angiotensin were carried out in some rats than in others, the average pressor response to both doses was calculated for each rat. These individual averages and the number of pressor injections carried out at each dose level of angiotensin in every rat tested are shown in Table 2. The final computation of the mean pressor response to angiotensin in both the control and hypothyroid rats is the mean of these individual averages. These results are summarized in Table 3 and Figure 6. The hypothyroid rats showed a significantly ($p < .001$) decreased pressor response to both 30 and 60 mug. of angiotensin.

Table 4 shows the results of 3 rats tested for pressor responsiveness to angiotensin before and 3 weeks after I^{131} treatment. (The fourth rat, #13, died before pressor response after I^{131} treatment could be tested.) Two of the three rats show a distinct decrease in responsiveness at both dose levels, and the third shows a decreased pressor response at the 60 mug. angiotensin level. This group is too small to deal with statistically, but the results in this study, in which the rats acted as their

own control, are in agreement with the results of the larger study discussed above.

Norepinephrine

Pressor responsiveness to norepinephrine was measured in 8 control and 7 hypothyroid rats. Figure 5 illustrates a typical response to 120 and 240 mug. in a control and a hypothyroid rat. The peak response occurred at the measurement taken 10 seconds after injection, and the duration of response was 30-50 seconds in all the rats tested. There was no measurable alteration in duration of response in the hypothyroid rats, but again, a decreased pressor response to both dose levels of norepinephrine was observed. The average pressor response and the number of injections carried out at each dose level in every rat tested are shown in Table 5. The data were handled in the same manner as the data for angiotensin. The mean pressor responses of the 8 control and the 7 hypothyroid rats to 120 and 240 mug. of norepinephrine are shown in Table 6 and in Figure 6. The decrease in pressor responsiveness in the hypothyroid rats was significant at both dose levels ($p < .03$, $p < .001$).

5. Pressor Response as % Change in Blood Pressure

Because of the significantly lower basal blood pressure in the hypothyroid rats, the pressor responses to both angiotensin and norepinephrine were also calculated as the percentage of the pre-injection blood pressure in each rat. The mean pressor responses of the control and hypothyroid rats to both angiotensin and norepinephrine calculated by this method, are shown in Table 7. As can be seen, the hypothyroid rats still show a significantly decreased ($p < .001$) pressor response to both doses of angiotensin and to the higher dose of norepinephrine. The mean hypothyroid response to 120 mug. of norepinephrine, though still lower than the mean control response, is only borderline significant ($p < .06$).

Discussion

Radioactive iodine induced hypothyroidism in the rat has been demonstrated to result in a decreased basal blood pressure and a decreased pressor responsiveness to both norepinephrine and angiotensin II. Hypothyroidism was demonstrated in all the irradiated rats tested for pressor responsiveness by means of plasma PBI and thyroid histology at the time of sacrifice.

Feller et al. (17) measured plasma PBI and iodine content of the thyroid gland, and studied thyroid histology in 200 to 300 gram rats, at selected intervals after the intraperitoneal injection of 875 uc. I^{131}. In all the rats so treated, the PBI fell to less than 1.0 ug. %, thyroid gland iodine content fell to 0.36 ug., and thyroid histology revealed only rare thyroid epithelial cells still intact, at eight days after treatment. Thus, complete histological and functional destruction of the thyroid gland was demonstrated to occur one week after treatment. Fregly (6), again irradiating 200-300 gram rats with 875 uc. I^{131}, showed them all to be hypothyroid by means of colonic cooling rate, radioactive iodine uptake, and thyroid histology, at intervals up to six months after treatment. On the basis of these two studies, it was safe to assume that thyroid function had been disrupted within two weeks after I^{131} treatment, since hypothyroidism was demonstrated at the time of sacrifice, eight weeks after irradiation.

The growth pattern of the 12 rats treated with I^{131} (Figure 2) was characterized by a three week period of normal weight gain followed by a complete cessation of weight gain for the remainder of the study. This resulted in a final mean weight of 310 grams for the hypothyroid rats as opposed to 390 grams for the control rats. Complete absence of weight gain has been repeatedly observed

following the onset of propylthiouracil treatment in the growing rat (4,5,18). This occurs immediately, without any time interval of normal growth. Thyroidectomy has also been shown to lead to a decrease in weight gain in growing rats (2,19), but not as striking as that which follows propylthiouracil treatment. In the one other study in which weight was followed after I^{131} treatment in the rat (6), no difference in growth pattern was observed in the treated rats. However, both the control and hypothyroid rats were operatively made renal ischemic in that study, so that no real comparison is possible. The cessation of growth at three weeks after radiothyroidectomy observed in the present study is probably a manifestation of hypothyroidism. Whether the three week lag before the appearance of this manifestation is related to the technique used for the production of hypothyroidism remains to be determined.

Hypothyroidism in the rat did not lead to hair loss or change in hair texture, noticeable edema, or any behavioral changes in this study. This is in agreement with previous investigations on the hypothyroid rat (1-6). It is of interest to note that this is in contrast to the dog, which has been demonstrated to show the classical signs of increased hair coarseness, hair loss, thickened and edematous skin, and apathy and listlessness (10).

A striking finding was the fall in basal blood pressure in the hypothyroid rats to 129 mm. Hg at two weeks after I^{131} treatment, before any significant weight difference appeared (Figure 3). The blood pressure in these rats remained significantly lower than the control blood pressure for the duration of the study. Fregly (4) observed the same phenomenon after propylthiouracil administration in the rat. In his study, the basal blood

pressure fell to a low point three weeks after the onset of treatment, and it remained significantly lower than the mean control blood pressure throughout a seven week period of observation. As was noted above, no behavioral differences were observed in the hypothyroid rats. Thus it appears unlikely that the decreased blood pressure was secondary to a decreased state of excitement in the experimental situation in the hypothyroid rats.

Another factor that must be considered as a possible cause of decreased basal blood pressure in the hypothyroid rat is adrenal cortical insufficiency. Thyroidectomy and thiouracil treatment in rats has been demonstrated to lead to a decrease in adrenal weight by many investigators (19,20,21). On the other hand, Gabrilove and Soffer (22) demonstrated that propylthiouracil administration in rats for periods up to six weeks did not alter the adrenal response to ACTH or epinephrine, as measured by the change in ascorbic acid content, in spite of the fact that adrenal weight was reduced. Finally Fregly (18) demonstrated no decrease in adrenal weight or cholesterol content following prolonged propylthiouracil administration in the rat. There have been no studies of adrenal weight or function following I^{131} treatment in the rat. From the evidence presented here, involution of the adrenal seems to occur following thyroidectomy or thiouracil administration. Whether this is reflected in a decrease in adrenal function is not known. With propylthiouracil, no real impairment of adrenal function seems to occur. From this information it is impossible to predict adrenal cortical function in the I^{131} treated rat. However, since a decrease in basal blood pressure occurs following propylthiouracil administration, where there appears to be no adrenal insufficiency, it seems unlikely that the adrenal plays a role in the hypotension following I^{131} treatment.

The onset of decreased pressor responsiveness to the humoral agents involved in blood pressure control in the rat, as thyroid hormone disappears from the circulation, could also explain the relative hypotension observed in the hypothyroid rat. Since a decrease in basal blood pressure has not been noted in man or in the dog in the hypothyroid state, one might wonder if blood pressure regulation in the rat was more reliant on arteriolar responsiveness to norepinephrine and angiotensin than either the dog or man. From the available evidence, no conclusions as to the mechanism of decreased basal blood pressure in the hypothyroid rat can be made.

The problem of evaluating pressor responsiveness in the intact rat in this study was complicated by the fact that the blood pressure of the hypothyroid rats was significantly lower than that of the controls at the time of testing (see Figure 3). During the angiotensin response measurements, the mean hypothyroid blood pressure ranged from 134 to 139, while the average control pressure was 149 mm. Hg. Likewise, during the norepinephrine measurements, the mean hypothyroid blood pressure was 142 mm. Hg and the control blood pressure was around 153 mm. Hg.

In-vitro studies with aortic strips have demonstrated that responsiveness to norepinephrine is related to the amount of stretch force applied to the strip at the time of norepinephrine infusion (23,24). With increasing stretch applied to the aortic strip, its contractile response to norepinephrine is increased. On the basis of these studies, one might expect that at higher blood pressures, when an increased stretch force is acting on the arterial tree, an increased contractile response will follow the injection of a pressor agent. Conversely at a lower blood pressure, a decreased contractile response might be expected to occur after pressor injection, yielding a smaller increase in blood pressure as measured in the intact animal.

This hypothesis would be an argument against the results obtained here being a true reflection of any direct effect of hypothyroidism on vascular responsiveness. However, in contrast with this hypothesis, Phelan et al. (25) have demonstrated a different relationship between pre-injection blood pressure and pressor response in the intact rat. Giving norepinephrine intravenously to 50 control rats with blood pressures ranging from 90 to 150 mm. Hg and 50 inbred hypertensive rats with pressures from 110 to 180 mm. Hg, they found no relationship between the pre-injection blood pressure and pressor response. With angiotensin, in fact, they found exactly the opposite relationship. In both control and hypertensive rats, they found that the response to a standard dose of angiotensin decreased as the pre-injection blood pressure increased ($p < .01$). On the basis of this study, the decreased pressor responsiveness to angiotensin observed here, inspite of the decreased pre-injection blood pressure, is even more striking evidence that thyroid function is an important factor in pressor responsiveness.

In order to minimize the difference in basal blood pressure in calculating pressor response, the data, originally presented in terms of absolute elevation in mm. Hg (Figure 6) following pressor stimulation, was recalculated in terms of percentage change in blood pressure (Table 7). Thus, a 25 mm. Hg response at a pre-injection blood pressure of 125 mm. Hg would be considered as identical to a 30 mm. Hg response at a blood pressure of 150. By this method of calculation, responsiveness was still found to be significantly decreased in the hypothyroid rats, except for the response to 120 mug. of norepinephrine. These data demonstrate that difference in blood pressure was not an important factor in the decreased responsiveness observed in the hypothyroid rats.

Pressor response to norepinephrine in the hypothyroid dog was studied by Page and McCubbin (10) in 12 dogs made hypothyroid by either thyroidectomy, I^{131} treatment, or propylthiouracil administration. They demonstrated a reduction by one-half of the pressor response to intravenous norepinephrine. A semi-pure preparation of angiotensin was also tested in several of the hypothyroid dogs, and pressor response to this was also noted to be markedly reduced, although no figures were given. These results are in agreement with the findings in the hypothyroid rat presented here. The reduction in pressor responsiveness to norepinephrine in the hypothyroid rat is almost identical, quantitatively, to that observed in the hypothyroid dog. The results obtained here with synthetic angiotensin in the rat confirm the findings in the dog. Schneckloth et al. (7) measured pressor response to intravenous norepinephrine in one hypothyroid patient before starting treatment. The response observed was lower than that of the control subjects in his study, but euthyroid responses that low had been observed. More interestingly, the pressor response of this patient increased when thyroid therapy was instituted. Page and McCubbin (10) were unable to reverse the decreased pressor response in 4 hypothyroid dogs by the administration of thyroid extract , although all the other signs of hypothyroidism were reversed. No attempt was made in the present study to reverse the decreased pressor response with thyroid hormone. There have been no other studies on pressor responsiveness in the hypothyroid rat.

What, then, are the possible mechanisms by which disruption of thyroid function leads to a decrease in pressor responsiveness? Since we are dealing with the intact rat in this study, we must consider whether the effects of hypothyroidism on other organ systems could

conceivably lead to the decreased responsiveness of the vascular system observed here. As was mentioned above, adrenal involution may possibly occur in the hypothyroid rat. We can discard adrenal involution as playing a role in decreased pressor responsiveness, however, since several studies have shown there to be no alteration in pressor response to norepinephrine in the adrenalectomized dog (26), and no alteration in pressor response to angiotensin in adrenalectomized dogs or rats (26,27, 28). Hypophysectomy in the dog was also demonstrated to have no effect on the pressor response to angiotensin or epinephrine (27). The parathyroid glands have been shown to be undamaged histologically or functionally following treatment by this dosage of I^{131} in the rat (29). From these findings we can rule out the importance of any effect of hypothyroidism on the pituitary, adrenal, or parathyroid gland in playing a role in decreased vascular responsiveness.

At least two hypotheses can be advanced to explain the decreased pressor response observed in the hypothyroid rat: 1)The pressor substances are more rapidly destroyed before reaching their site of action, and 2)the arteriolar wall is less sensitive to the pressor action of these substances. As evidence for the first hypothesis, Spinks and Burn (30) have demonstrated an increased mono-amine oxidase activity in liver slices from hypothyroid rats. Increased mono-amine oxidase activity has also been found to occur in jejunal biopsy specimens from an untreated hypothyroid patient (31). An increased production of mono-amine oxidase in the hypothyroid rat could lead to increased breakdown of norepinephrine before it reached its site of action. Angiotensin, however, is not inactivated by this enzyme. Preliminary studies have revealed no increase in angiotensinase activity in the plasma of

hypothyroid rats. On the other hand, there has been no direct evidence demonstrating decreased sensitivity of isolated blood vessel wall in hypothyroidism. This type of study would clarify the question of whether or not arterial sensitivity to angiotensin and norepinephrine is reduced in hypothyroidism.

A possible mechanism for decreased vascular sensitivity to norepinephrine and angiotensin in the hypothyroid rat is suggested by the work of Fregly et al. (32,33). They have shown that propylthiouracil or methimazole treated rats prefer 0.15 N saline to water when offered both. This effect appears to be independent of the pituitary or adrenal gland, as hypophysectomized or adrenalectomized rats made hypothyroid consumed significantly more saline than their respective controls. Furthermore, studying salt metabolism in propylthiouracil treated rats, they found that rats so treated excreted slightly more sodium than they ingested, but not a significant amount. However, when put on a sodium deficient diet, the propylthiouracil treated rats would go quickly into negative sodium balance, excreting 2-3 times the amount of sodium excreted by controls under the same conditions, and they would die within three weeks unless salt was returned to the diet. Whether this decreased ability to retain sodium is secondary to a diuretic-like action of propylthiouracil, or whether it is a manifestation of hypothyroidism in the rat remains to be determined. These findings indicate that the hypothyroid rat, at least following goitrogen treatment, could become sodium depleted. Salt depletion, induced by chlorthiazide in the euthyroid dog, has been demonstrated to lead to a decreased pressor responsiveness to both norepinephrine and angiotensin (34). This hypothesis is, of course, pure speculation

at present. It is impossible from the available evidence on salt metabolism or mono-amine oxidase activity in hypothyroidism to say which if either, plays a role in the decreased responsiveness to pressor agents in the hypothyroid rat.

Finally, we must consider whether decreased responsiveness to pressor agents in the hypothyroid rat is an etiological factor in the reversal of experimental hypertension by hypothyroidism. Various studies in the intact rat have demonstrated an increased pressor response to norepinephrine and epinephrine in renal ischemic hypertension (35) and in DOC hypertension (36,37). Increased pressor responsiveness to angiotensin was also found to occur in DOC hypertension (36). On the other hand, Masson, Page, and Corcoran (38) found no significant increase in responsiveness to epinephrine, angiotensin, or renin in DOC hypertension, again testing for blood pressure response in the intact rat. However, a slight increase in pressor response to all three agents was noted in the hypertensive rats. In isolated aortic strips from both DOC and renal ischemic hypertensive rats, Mallov (39), and Redleaf and Tobian (40) found no increased responsiveness to pressor agents. More recently, however, Gordon and Nogueira (24) demonstrated a significantly increased response to norepinephrine in aortic strips from renal hypertensive rats, when they increased the pre-infusion stretch force on the aortic strips. Plotting pre-infusion stretch force against contractile response to norepinephrine, they found that the hypertensive aortas would give a maximum response at a higher stretch force than the controls (44 grams as opposed to 39 grams). Even at 39 grams stretch force, however, the contractile response of the hypertensive aortas was significantly greater than the control response. They concluded that

previous in-vitro studies had not used enough stretch force prior to norepinephrine infusion to achieve the maximum response needed to perceive any response difference in the hypertensive aortas. This last study, I think, is strong evidence in support of increased vascular responsiveness in experimental hypertension in the rat. If increased vascular responsiveness were an etiological factor in hypertension in the rat, then the reversal of this following disruption of thyroid function would explain the reversal of the experimantal hypertension. This remains to be proven.

Another interesting finding in all four types of experimental hypertension reversed by hypothyroidism in the rat is an increased sodium content in the aortic wall (41). Coupled with this finding, the renal hypertensive rat has been demonstrated to have a significant aversion for saline solutions (42,43). The onset of goitrogen treatment or thyroidectomy, besides reversing the experimental hypertension in these rats, also reverses their aversion to saline solutions (43). In fact the hypothyroid renal ischemic rat prefers saline to water, in sharp contrast to the euthyroid hypertensive controls.

Perhaps, then, the state of pressor responsiveness in the rat is only a reflection of the sodium content of the vessel walls. The excess accumulation of sodium in the blood vessel wall in the hypertensive rat which leads to increased contractility, might be prevented or reversed in hypothyroidism because of sodium wasting. Thus, the hypothyroid rat would be unable to accumulate sodium in its blood vessel walls, or to maintain an accumulation that has been built up by the hypertensive process. Bilateral adrenalectomy has been demonstrated

to reverse experimental hypertension in the rat (42,44) and here sodium wasting is known to occur. This hypothesis is pure speculation, and much experimental work needs to be done before the mechanism of the reversal of hypertension by hypothyroidism can be discovered.

Summary

In the rat, hypothyroidism is known to reverse experimental hypertension. In an attempt to study the mechanism of this phenomenon, 12 rats were made hypothyroid by radioactive iodine treatment, and pressor responsiveness to norepinephrine and angiotensin II was examined. The hypothyroid rats were found to have a significantly decreased pressor response to both pressor agents as compared to control rats. Hypothyroidism also resulted in a decreased basal blood pressure in the experimental rats, which was significant from two weeks after I^{131} treatment to the end of the study. Possible mechanisms for these findings, and possible mechanisms for the reversal of experimental hypertension in the rat by hypothyroidism are discussed.

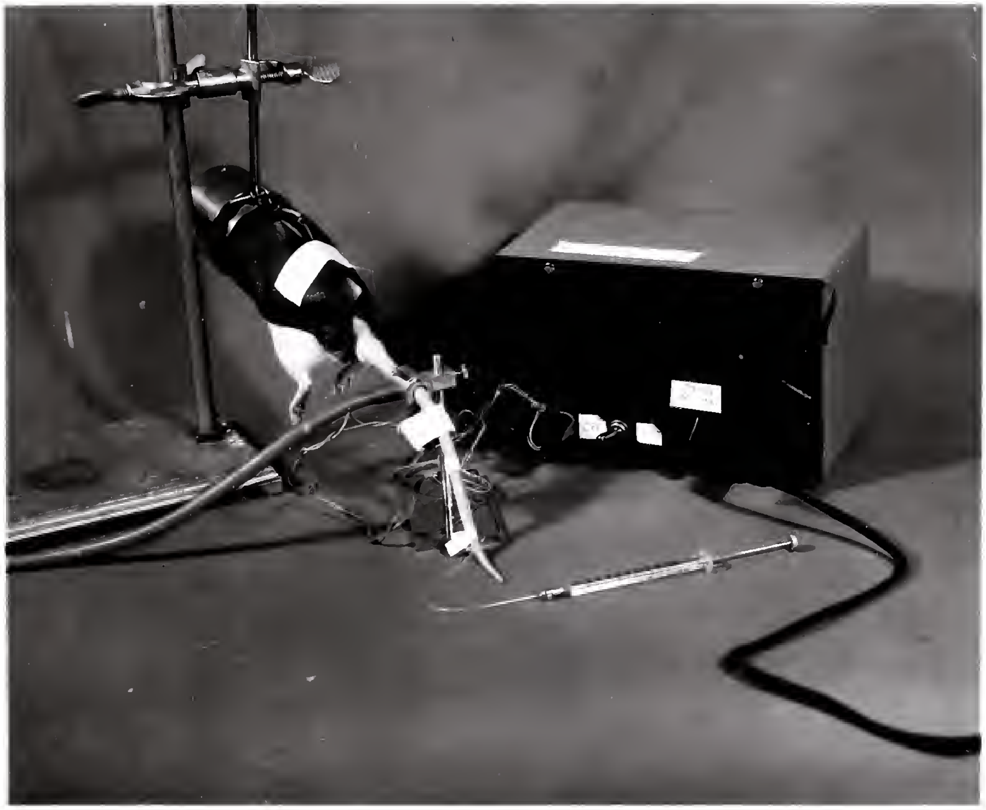

Figure 1: Photograph of rat in restraining holder with pressure cuff, microphone for amplification of arterial pulse, and intravenous needle in place on tail. This is the apparatus used for pressor response measurements.

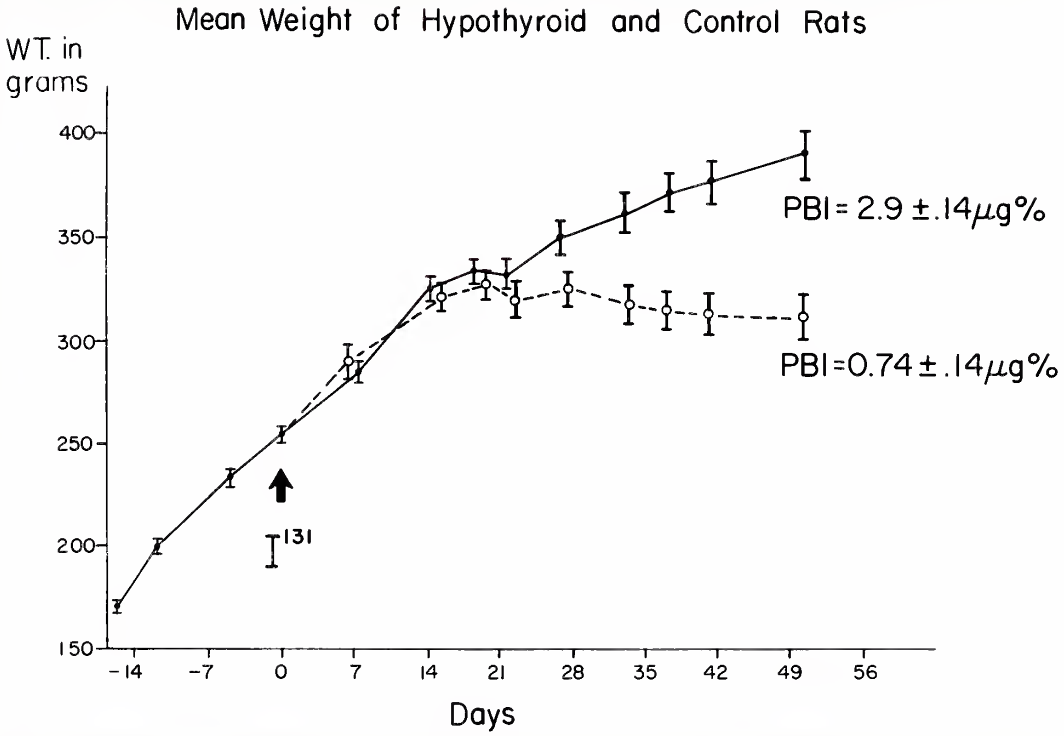

Figure 2: Mean weight of hypothyroid rats (dotted line), and control rats (solid line) during the course of the study, and the mean PBI of each group at the time of sacrifice. Vertical bars indicate ± the standard error of the mean in this and subsequent graphs.

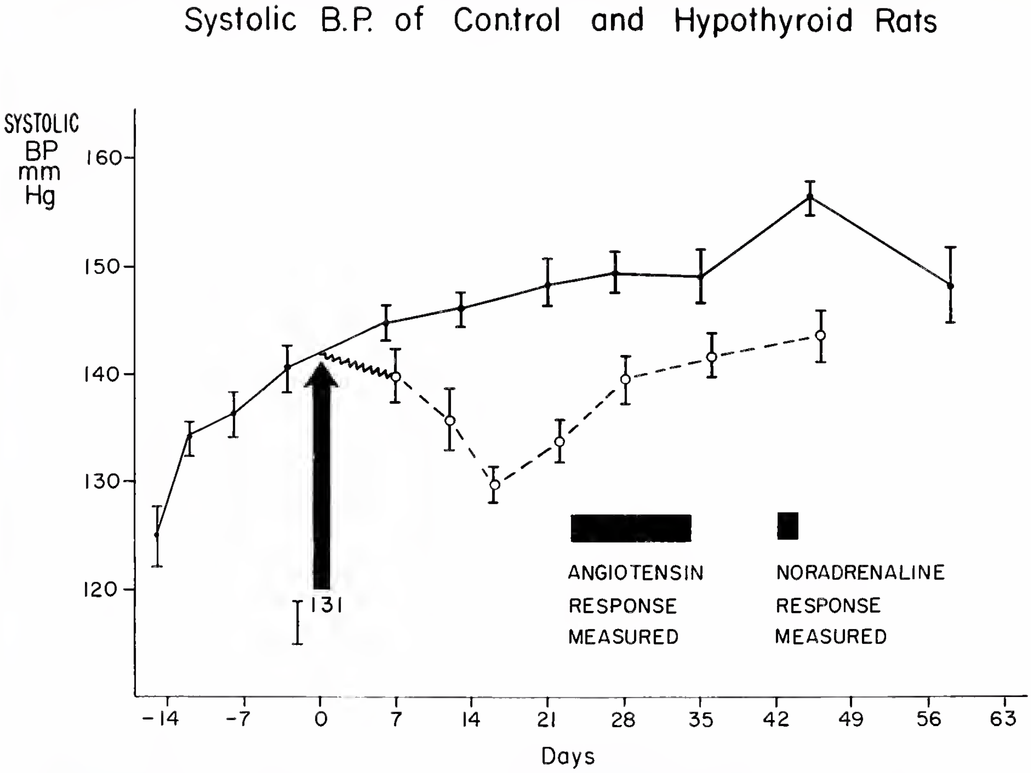

Figure 3: Mean systolic blood pressure of hypothyroid rats (dotted line) and control rats (solid line) during the course of the study. Solid bars indicate the time periods during which response measurements to the pressor agents were carried out.

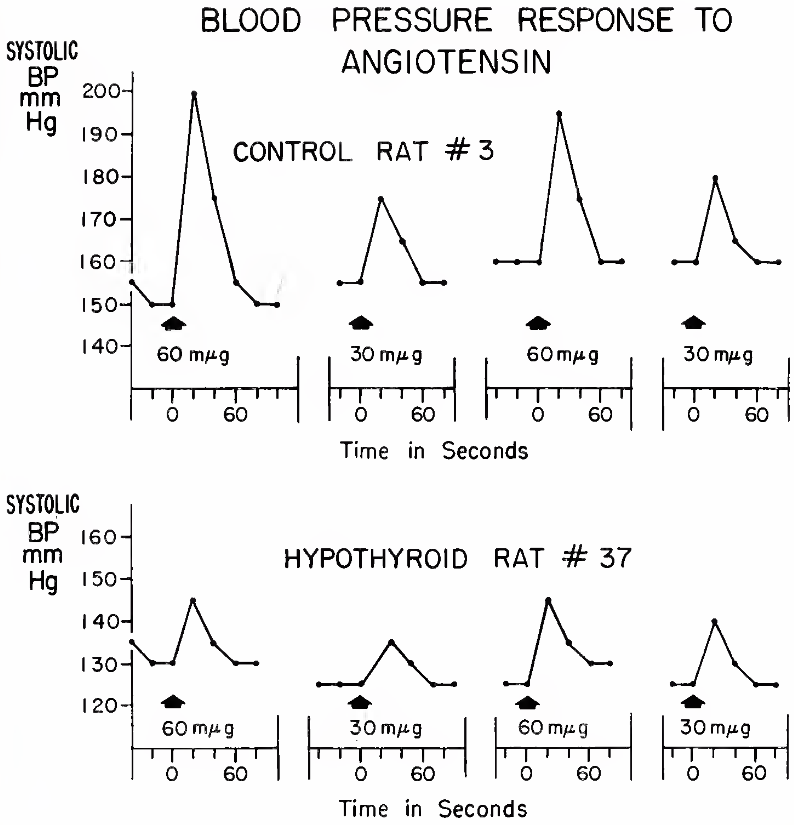

Figure 4: Blood pressure response to angiotensin in a control rat (above) and a hypothyroid rat (below).

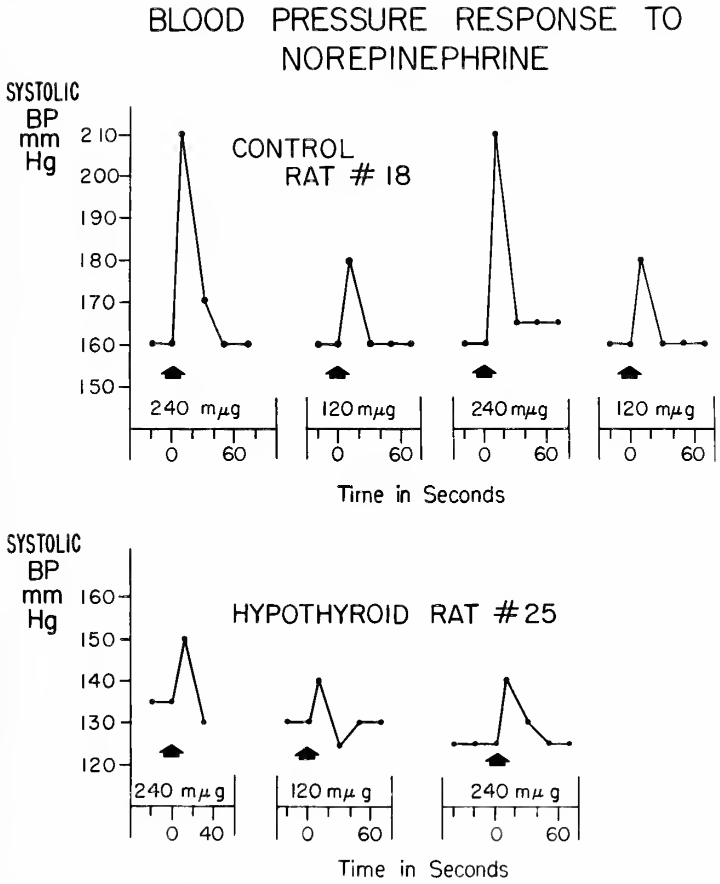

Figure 5: Blood pressure response to norepinephrine in a control rat (above) and a hypothyroid rat (below).

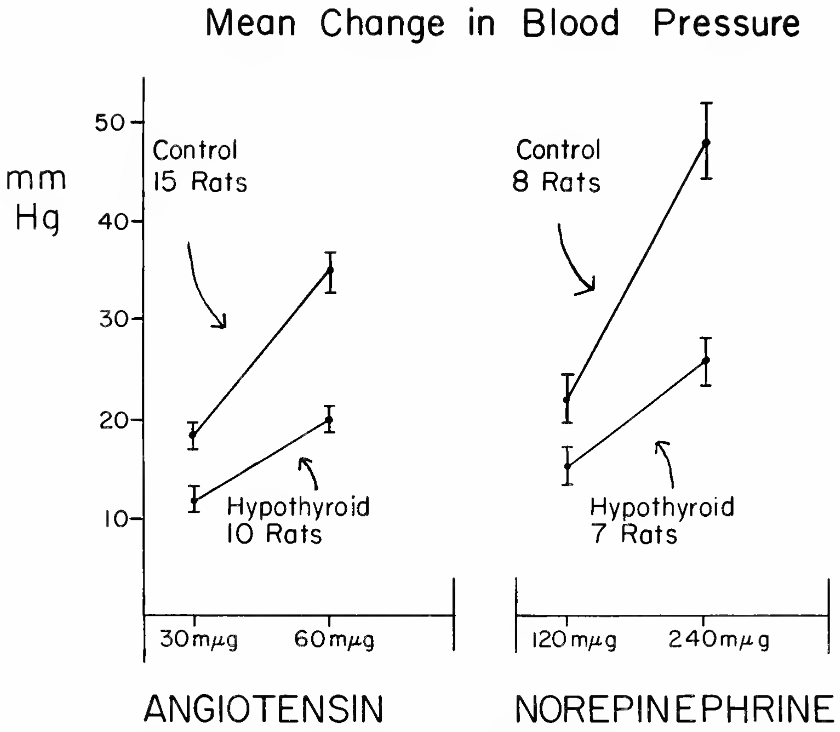

Figure 6: Mean rise in blood pressure following the intravenous injection of angiotensin (left) and norepinephrine (right) in the control and hypothyroid rats.

Table 1

Plasma PBI

Hypothyroid		Control	
Rat #	PBI	Rat #	PBI
#4	0.6 ug.%	#33	2.9 ug.%
#7	1.2	#35	3.1
#10	0.2	#28	2.5
#21	1.2	#29	2.6
#25	0.5	#26	3.2
#37	1.1		
#38	0.4		
#40	0.4		
#45	0.1		
#47	1.2		
#52	1.2		
Mean	0.74 ± .14 ug.%	Mean	2.9 ± .14 ug.%

Table 2

Angiotensin

Individual average pressor response and number of test injections carried out at each level.

A. Control

Rat #	Av. Pressor Response 30 mug.	Av. Pressor Response 60 mug.	No. of Injections 30 mug.	No. of Injections 60 mug.
#13	15mm. Hg	50mm. Hg	1	2
#45	15	32	2	2
#37	22	42	3	2
#47	17	40	2	3
#30	18	34	5	5
#28	13	29	5	6
#47	11	21	4	6
#33	20	27	2	2
#29	25	45	2	3
#6	16	34	4	4
#18	13	33	3	3
#26	17	25	2	3
#35	27	40	3	3
#3	18	40	3	3
#32	23	40	3	3

B. Hypothyroid

Rat #	Av. Pressor Response 30 mug.	Av. Pressor Response 60 mug.	No. of Injections 30 mug.	No. of Injections 60 mug.
#45	15	26	3	4
#37	14	22	7	8
#47	9	16	6	4
#4	5	16	4	4
#25	10	20	2	3
#21	12	17	4	4
#40	12	16	3	4
#7	14	23	5	5
#38	10	16	3	5
#52	15	22	3	4

Table 3

Angiotensin
Mean Pressor Response

		30 mug.	60 mug.
Control	15 rats	18 ± 1.1 mm. Hg	35 ± 2.0 mm. Hg
Hypothyroid	10 rats	12 ± 1.0 mm. Hg	20 ± 1.2 mm. Hg
	p	$< .001$	$< .001$

Table 4

Angiotensin
Self Control Comparison

Rat #		30 mug.	60 mug.
#37	before I^{131}	22 mm. Hg	42 mm. Hg
	after	14	22
#47	before I^{131}	17	40
	after	9	16
#45	before I^{131}	15	32
	after	15	26

Table 5

Norepinephrine

Individual average pressor response and number of test injections carried out at each level.

Rat #	Av. Pressor Response 120 mug.	Av. Pressor Response 240 mug.	No. of Injections 120 mug.	No. of Injections 240 mug.
A. Control				
#18	22 mm. Hg	50 mm. Hg	3	3
#26	23	57	3	3
#29	17	48	3	3
#35	14	32	5	5
#3	22	48	3	3
#6	27	63	3	3
#33	32	50	3	3
#32	18	34	3	4
B. Hypothyroid				
#7	17	33	3	3
#4	20	32	5	3
#25	7	17	3	4
#21	10	21	3	4
#40	17	25	3	3
#37	18	26	3	4
#45	13	30	3	3

Table 6

Norepinephrine

Mean Pressor Response

	120 mug.	240 mug.
Control 8 rats	22 ± 2.0 mm. Hg	48 ± 3.7 mm. Hg
Hypothyroid 7 rats	15 ± 1.8 mm. Hg	26 ± 2.2 mm. Hg
p	$< .03$	$< .001$

Table 7

Pressor Response as % Change in Blood Pressure

Angiotensin

	30 mug.	60 mug.
Control	12.2%	24.4%
Hypothyroid	8.4%	13.9%
p	$< .001$	$< .001$

Norepinephrine

	120 mug.	240 mug.
Control	13.0%	30.6%
Hypothyroid	10.1%	18.5%
p	$< .06$	$< .001$

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