A STUDY OF ADRENAL REGENERATION HYPERTENSION:
EFFECT OF THE DELAYED ADRENAL ENUCLEATION
ON THE DEVELOPMENT OF HYPERTENSION
AND SALT APPETITE

RYOYU TAKEDA, SHIMPEI MORIMOTO,
SUSUMU MIYABO AND MOTOTAKA MURAKAMI

*Second Department of Internal Medicine, School of Medicine,
Kanazawa University, Kanazawa*

Morimoto (1962) has reported a detailed investigation on the hormonal milieu and sodium and water balance in Skelton's hypertension (Skelton, 1955), emphasizing the significance of excessive salt appetite following relative adrenocortical insufficiency, simulating acute loss of renal mass in the pathogenesis of hypertension. But he gave no definite information about the relation between the increase of salt intake and the time of adrenal enucleation. In this paper additional experiment in this regard is presented.

MATERIALS AND METHODS

Female Wistar rats weighing 80 to 90 g were divided into 4 groups and treated as follows.

Group 1: Being control group, no operation was performed and tap water was given for drinking.

Group 2: Unilateral nephroadrenalectomy with contralateral adrenal enucleation was performed and 1% saline solution was given for drinking.

Group 3: Unilateral nephroadrenalectomy was performed and 2 weeks later the contralateral adrenal was enucleated. For drinking 1% saline solution was given.

Group 4: Same operations as in group 3 were performed and 2% saline solution was given for drinking.

The animals were fed on rice and placed in separate cages to measure the consumption of drinking fluid. The blood pressure was measured at 1 or 2 week intervals by direct cannulation of the femoral artery with animals under pentobarbital soda anesthesia. At the end of the 7th week blood for the determination of plasma electrolytes was obtained by severing the femoral artery. The content of extractable renin was determined according to the method proposed by Tobian *et al.* (1959). At autopsy, the kidneys, hearts, and adrenals were weighed and fixed in formalin for histological examination.

RESULTS

As shown in Table 1, rise of blood pressure to higher than 130 mmHg was observed in group 2 in the 4th week, and the average values were 148.0 and 138.2 mmHg in the 6th and 7th week respectively. On the other hand, in groups 3 and 4 only one animal showed a pressure exceeding 130 mmHg after the adrenal enucleation. The renal content of extractable renin was lower than normal in groups 2 and 3, being 5.3 and 6.3 respectively in the 7th week. The average value of extractable renin in the 4th week was higher in group 2 than group 3, but there was too wide variation for the difference to be regarded significant.

Table 1. Blood pressure and extractable renin content in the kidneys

Group	Week	Average blood pressure (mmHg)	No. of rats	Extractable renin content in the kidneys (mmHg)	No. of rats
Group 1	1	104.0	3	33.5	7
	2	113.0	3		
	4	110.0	3		
	6	116.0	3		
Group 2	2	96.6	3	21.3 5.3	3 3
	3	115.3	3		
	4	135.0	3		
	6	148.0	3		
	7	138.2	5		
Group 3	2	109.3	3	11.6 6.3	5 3
	3	105.0	3		
	4	115.2	4		
	6	122.3	3		
	7	129.0	5		
Group 4	4	102.3	3		
	7	124.0	4		

As depicted in Figure 1, group 2 began to show excessive salt appetite in the 2nd week and then the daily consumption of saline solution increase gradually until the 7th week, while no excessive salt appetite such as was found in group 3. But when 2% saline solution was substituted for the 1% saline (group 4), the consumption of saline rose significantly, attaining to approximately two fold that of group 3. The levels of plasma sodium and potassium in groups 1, 2, and 3 were within normal range, but the animals of group 4 showed hypernatremia and hypopotassemia as shown in Table 2.

It can be noted from Figure 2 that the visceral masses measured in the 7th week indicated hypertrophy of the hearts and kidneys in all the three operated groups, but the adrenals were found to have returned to the normal weight. In group 4 increase of body-weight was greatly limited and hypertrophy of hearts

Fig. 1. The daily consumption of saline solution in uninephroadrenalectomized rats, bearing the regenerating adrenal in the other side

- Group 2
 ●.....● Group 3
 ●-.-● Group 4

Table 2. Plasma levels of sodium and potassium at the end of the 7th week

Group	1	2	3	4
No. of rats	6	8	5	4
Sodium (mEq/L)	140.3 +4.1	140.2 +2.3	140.9 +2.2	153.5 +8.7
potassium	4.03+0.26	4.08+0.30	4.46+0.44	3.70+0.55

and kidneys, and histological changes in cardiovascular system were more conspicuous in that group than in any other. Figure 3 shows the microscopic picture of myocarditis induced by the administration of 2% saline solution in a rat of group 4.

Fig. 2. The body-weight and visceral masses of each group at the end of the 7th week
The blank columns represent net weight and black columns
represent organ weight / 100 g of body-weight.

Fig. 3. The microscopic photograph showing myocarditis induced by the administration of 2% saline solution in a uninephroadrenalectomized rat bearing the regenerating adrenal in the other side

DISCUSSION

It is generally recognized that 3 major conditioning factors, unilateral nephro-adrenalectomy, contralateral adrenal enucleation, and the administration of salt, are necessary for the development of Skelton's hypertension. However, the operative mechanism responsible for the elevation of blood pressure remains unresolved. The early attempts (Grollman, 1957; Brogi and Fellegrino, 1959; Masson and Peron, 1958) to clarify the endocrine involvement of adrenal cortex in this hypertension were fruitless. Morimoto (1962) also failed to demonstrate a positive role of corticoids in the pathogenesis of hypertension. In his investigation he found that during adrenal regeneration there were no excessive amounts of plasma corticosterone or urinary aldosterone, significant unbalance of the steroid pattern, nor any hyperresponsiveness of the regenerating adrenal cortex to ACTH.

Compensatory hypertrophy of the remaining kidney within 1 week after the nephrectomy was a prominent finding, but as mentioned above its extractable renin showed a gradual decrease. Inasmuch as the decrease of extractable renin occurred irrespective of blood pressure in both groups 2 and 3, it seems likely to be consequent on the salt administration. Anyhow it is inconceivable that renin plays a primary role in the development of adrenal regeneration hypertension.

More definitive experiments are needed to explain the result reasonably that neither increase of salt intake nor significant rise of blood pressure are observed, if there is a 2-weeks-interval between the unilateral nephro-adrenalectomy and the contralateral adrenal enucleation. Is the production of elevated blood pressure ascribed to the difference of salt consumption? If the hypertensive potential of salt is important primary in Skelton's hypertension, it is strange that increasing the concentration of sodium chloride in the drinking fluid to 2% causes increase of salt intake and conspicuous lesions of cardiovascular system, but it does not materially raise the blood pressure. A possible explanation for these conflicting results might be involved in the circumstances that the animals forced to drink thick saline are in a state of salt intoxication.

As was pointed out by Morimoto (1962) the excessive salt appetite following relative adrenocortical insufficiency, simulating acute loss of renal mass is considered to be one of the initiating factors of Skelton's hypertension. But excessive salt appetite alone does not seem to lead to sustained hypertension if the animals fall into the state of salt intoxication as was observed in group 4.

SUMMARY

The relation between the salt intake and the time of adrenal enucleation in Skelton's hypertension was investigated.

Neither increase of salt nor elevation of the blood pressure into hypertensive range occurred, if there is a 2-weeks-interval between the uninephro-adrenalectomy and the contralateral adrenal enucleation.

Under the same procedure increasing the concentration of sodium chloride

in the drinking fluid to 2% caused increase of salt intake, but it brought the animals into the state of salt intoxication without hypertension.

The reasonable explanation for these results remains unresolved.

REFERENCES

- Brogi, M.P. and C. Fellegrino (1959). *J. Physiol. (London)* **146**, 165.
Grollman, A. The Endocrine Society 39th Meeting, New York, (1957).
Masson, G.M.C. and F.G. Peron (1958). *Endocrinology* **62**, 229.
Morimoto, S. (1962). *Folia Endocrinol. Japon.* **38**, 52. (In Japanese)
Skelton, F.R. (1955). *Proc. Soc. Exptl. Biol. Med.* **90**, 342.
Tobian, L., J. Janeczek and A. Tomboulia (1959). *Ibid.* **100**, 94.