Experimental Hypertension and Hypotension
Induced by Hypothalamic Destruction in the Rat

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It has long been known that hypertension develops in certain cases of disorders in the central nervous system.\textsuperscript{1-5} Concerning this subject, however, few reports are available on the problem of localization as well as of mechanism.

The hypothalamus, which forms a nodal point of the limbic-forebrain-midbrain circuit, is concerned with the regulations of various visceral functions and complex behavioral and emotional reactions. Among these, the autonomic function, and the functions regulating thyroidal, adrenocortical and adrenomedullary secretions are considered to involve the cardiovascular system. Thus, we can infer that the disturbances of these hypothalamic functions might cause changes in the blood pressure level.

The present study was designed to observe the chronic effects of hypothalamic destruction on blood pressure, and to find the relation of the blood pressure changes to the sites of lesions responsible for them.

Material and Methods

About 100 Wistar rats of both sexes, 180 to 280g. in body weight, were used in this study. They were housed under normal conditions, some fed with stock diet, Oriental MNF, and others with Manitoba wheat mixed with cooked dried sardines, and seasoned with a little salt, and green vegetables. Both diets contained 0.3 per cent sodium. Animals were given tap water ad libitum.

After anesthesia using Na pentobarbital 30 mg/kg of body weight, the scalps were incised, parietal bones were drilled open, and bilateral hypothalamic lesions of various sizes were made by means of monopolar or concentric bipolar electrodes localized with the aid of stereotaxic apparatus model Tokyo-University-Noken, using currents of 10 to 40 V x 10 sec. The placements of electrodes were determined according to de Groot's atlas.\textsuperscript{6}

After operations, animals were kept alive and submitted to long term observations. Blood pressure was measured once a week over a period of three weeks before and over 10 weeks after the destruction by the modified tail-water plethysmographic methods.\textsuperscript{7} Moreover, at the same time, body weight, body temperature, electrocardiogram, changes in pupils and conditions of urine were recorded.

After 10 weeks of observation, animals were killed by decapitation. Immediately after autopsy, the pituitary, bilateral lobes of thyroid, bilateral adrenals and gonads were removed, cleaned of blood, fat and connective tissue, and weighed. The brain was fixed in 10\% formalin, embedded in celloidin, serially sectioned at 30\mu and stained with Nissl's technique to verify the sites of lesions.

\section*{Results}

Sustained rise or fall in blood pressure was observed following certain hypothalamic destruction.

Hypertension caused by hypothalamic destruction can be divided into the following three groups according to the sites and sizes of the lesions; that is, (1) hypertension following nearly total hypothalamic ablation, (2) hypertension following posterior hypothalamic lesions and (3) hypertension following anterior hypothalamic lesions.

Hypotension due to hypothalamic destruction can be divided into the following two groups according to the modus of the development; that is, (1) sustained stable hypotension that developed immediately after destruction and (2) unstable or gradually developing hypotension.

Table I shows the blood pressure levels,
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<th>Table I</th>
<th>Changes in Blood Pressure and Endocrine Organ Weights in Relation to</th>
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<tr>
<td><strong>animal No. and sexes</strong></td>
<td><strong>body weight (g)</strong></td>
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<td><strong>near total hypophalamic destruction</strong></td>
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<td><strong>posterior hypophalamic lesions</strong></td>
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<td><strong>sustained hypertension</strong></td>
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<td><strong>control</strong></td>
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*Japanese Circulation Journal Vol. 29, March 1965*
Statistical analyses were made according to Student’s small sample “t” test. Two shaded bars in each one column show the different extent of the lesions in both sides of the hypothalamus.

endocrine organ weights and the localizations of hypothalamic lesions in animals which developed hyper- or hypotension.

Hypertension following nearly total hypothalamectomy (Fig. 1): In one male rat (No. 019), sustained high blood pressure (maximum: 230 mm Hg, average: 198 mm Hg) developed after a normotensive interval of two weeks following destruction. Obesity, diabetes insipidus and transient glucosuria were the accompanying symptoms. At autopsy, adrenals were hypertrophied about 2.5 times in comparison with those of controls. Slight periarteritis nodosa was observed in a pancreatic artery. The hypothalamic lesion of this animal was extensive and almost all nuclei were affected except a large portion of arcuate nucleus, part of posterior hypothalamic area and part of lateral hypo-

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thalamic area (Table I).

Hypertension following posterior hypothalamic destruction (Fig. 2): Certain posterior hypothalamic lesions induced hypertension in 4 male rats, in one of which (No. 032, male) blood pressure rise occurred immediately after destruction, reaching as high as 198 mm Hg (average; 182 mm Hg). In this rat, adrenals showed an increase in weight. The area common to lesions in animals in this group was the posterior periventricular gray above the arcuate nucleus which was not severely injured (Table I).

Hypertension following anterior hypothalamic destruction (Fig. 3): In 6 animals (3 males, 3 females), mild hypertension developed following certain anterior hypothalamic destruction. In a typical case (No. 067, female), average blood pressure level of postoperative stage was 161 mm Hg (maximum; 174 mm Hg). In this group, adrenals showed a moderate increase in weight. Sites common to lesions in animals in this group were the anterior hypothalamic area and anterior periventricular gray (Table I).

Sustained stable hypertension following hypothalamic destruction (Fig. 4): In 7 male and 1 female rats, in which hypothalamic destruction involved a large portion of arcuate nucleus (Table I), this type of hypertension developed in association with various endocrine deficits. Above all, adrenal atrophy was noticed in every animal in this group and seemed to be essential for the development of hypertension of this type.

Unstable of gradually developing hypertension following hypothalamic destruction (Fig. 5): 11 rats (7 males 4 females) belong to this group. In some, blood pressure level was lowered immediately after destruction, but exhibited considerable fluctuation, sometimes returning to the limit of normal range. In others, first after some normotensive interval following destruction, hypertension developed gradually and became sustained. In this group, no definite change in endocrine organ weights was noticed. The localization common to lesions in this group was the anterodorsal part of the hypothalamus (Table I).

Hypothalamus-lesioned animals with blood pressure unchanged: 5 male animals with posterior hypothalamic lesions, 19 (14 males and 5 females) with anterior hypothalamic lesions, 12 (6 males and 6 females) with lesions in median hypothalamus, in which arcuate nuclei were not severely injured, and 3 (2 males and 1 female) with extensive lesions in the hypothalamus showed no blood pressure change.

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Transient rise or fall in blood pressure, however, was observed frequently. Some in this group exhibited considerable resemblance in sizes and sites of lesions to those in the animals in which sustained blood pressure changes developed. Lesions of some in this group (No. 032, 140, 121, 505, 048) are shown in Table I, but those of others omitted.

In addition, heat stagnation occurred easily in some animals with anterior hypothalamic lesions, especially extending to the pre-optic area, when they were exposed to a warm environment. But this seemed to be irrelevant to blood pressure rise in animals with anterior

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hypothalamic lesions, because blood pressure rise sometimes developed in the absence of heat stagnation, and vice versa. Also, changes of heart rates in ECG, mydriasis or miosis, observed in some animals, was independent on the blood pressure level.

**DISCUSSION**

It has long been stated that certain disorders in the central nervous system induce hypertension. For instance, glioma in the floor of the fourth ventricle,¹⁷ poliomyelitis,¹⁷,²⁰ acute encephalitis,⁴ and brain stem trauma⁵ have been referred to as such. Experimental procedures that have been reported to induce hypertension by the manipulations on the central nervous system, are as follows: (1) constriction of arteries supplying the head,⁸–¹² (2) injection of kaolin into cisterna magna¹³ or physiologically saline solution into subdural pace¹⁴¹⁵ and (3) so-called neurogenic hypertension caused by buffer nerve ablation¹⁶¹⁷ in which the afferent pathway from cardiovascular system to central nervous system is interrupted.

Besides, participation of the central nervous system in the maintenance of chronic renal hypertension has been suggested by many researchers¹⁸–²⁶. Few experimental studies, however, have informed us of the localization of the parts of the central nervous system which are responsible for the development of hypertension, when they go into dysfunction.

In the present study, we ascertained the development of hypertension and hypotension by means of hypothalamic destruction. As the obesity caused by hypothalamic destruction is called hypothalamic obesity,²¹ sustained blood pressure rise or fall following hypothalamic destruction shall be called hereafter as hypothalamic hyper- or hypotension, respectively.

Concerning the mechanisms of the development of hypothalamic hyper- and hypotension, the following two explanations might be plausible. First, purely neurological alterations following hypothalamic lesions, that is, the elimination of hypothalamic vasotonic or vasodilator influence, might be speculated as responsible for the development of hypothalamic hyper- or hypotension. According to Nauta,²² the hypothalamus is a nodal point in the limbic-forebrain-midbrain circuit. Impulses originating from the higher level such as the cortex, thalamus and limbic system relay in or pass through the hypothalamus and descend further through the midbrain reticular formation to the visceral motor nuclei of the lower brain stem and the spinal cord. Pitts, Larabee and Bronk²³ reported excellent data on the participation of the hypothalamus in the sympathetic discharge through the medullary center to the cardiovascular system. Baust and Katz²⁴ recorded a single unit activity from the posterior hypothalamus in 1961, and suggested that hypothalamic nerve cells in this area, influenced directly by the blood pressure level, might produce an inhibitory effect on the bulbar sympathetic center. These facts indicate the hypothalamus, whose discharges are transmitted to sympathetic motor neurons by mediation through medullary vasomotor center, exerts some influence on the regulation of cardiovascular system. The repeated observations that blood pressure is maintained at a normal level after low mesencephalic or pontile transection of the brain stem²⁵²⁶ suggest that any tonic influence of suprabulbar origin is of minor significance²⁷. This seems to be inconsistent with the speculation that the elimination of hypothalamic vasotonic or vasodepressor influence might be responsible for the development of hyper- or hypotension following hypothalamic destruction. Pressor or depressor effects, however, are obtainable also in the suprabulbar region by electrical stimulation²⁸–²¹. Thus, it is probable that the results obtained by transection experiment might merely mean that in the medullary level, pressor and depressor zones are arranged in such a simple manner that they can be separated by the common transection across the neuroaxis, but not so in the suprabulbar level. Thus, the possibility that hyper- or hypotension following hypothalamic destruction might be ascribed to neural mechanisms effected by the mediation of medullary vasomotor center, cannot be denied even on a theoretical basis.

The sites common to lesions were the anterior hypothalamic area and periventricular gray in the hypertensive animals with anterior hy-
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pithalamic lesions, and the periventricular gray in the ones with posterior lesions, while in the hypertensive rat with extensive lesions, both areas were involved. The majority of fibers connecting the limbic system with the lower brain structures pass through the anterior hypothalamic area, and the periventricular gray is regarded as the chief descending connection of the hypothalamic nuclei. Thus, it is highly probable that hypothalamic hypertension might be a result of the elimination of vasodilator influence on the medullary vasmotor center, originating from the hypothalamus or the higher brain structure, especially the limbic system, the descending fibers of which pass through the anterior hypothalamic area or periventricular gray.

Secondly, neuroendocrine alterations following hypothalamic lesions should be considered as a possible mechanism causing the development of hypothalamic hyper-or hypotension. The hypertensive rats in this study showed an increase in adrenal weight, suggesting the hyperactivity of pituitary-adrenal axis (although the hypertrophy secondary to hypertension cannot be entirely denied), while the rats with sustained stable hypotension showed a remarkable decrease. It was already reported that in the spontaneously hypertensive rats (OKAMOTO and AOYAMA), histological findings indicating hyperactivity of pituitary-adrenal or thyroid axis were ascertained to exist even in the prehypertensive stage.

As to the hypothalamic control of pituitary-adrenal axis, although the details of localization of ACTH field are yet controversial, ACTH activating role of median eminence seems to be established by the fact that the electrical stimulation of this region enhances ACTH output, as indicated by lymphopenia, eosinopenia, ascorbic acid depletion in the adrenal, increased plasma glucocorticoid and increased corticosteroids in adrenal venous effluent, and alteration of sudanophilic substances in adrenal cortex, and that the lesions in median eminence reduce adrenal reaction in response to stress. Many reports are available in favour of the assumption that the negative feedback control mechanism of corticoids exists in some parts of the hypothalamus, although the problem of localization remains unsettled. Besides, the limbic system and midbrain are stated to exert some influence on ACTH secretion, probably by the mediation through the hypothalamus to pituitary.

Glucocorticoids whose secretion are regulated in these ways by the hypothalamo-pituitary system are said to have hypertensive potentials, and in fact, their administration produces hypertension in the rat. Thus, it may justly be speculated that the development of hypothalamic hypertension is due to enhanced activity of pituitary-adrenal axis owing to the release of ACTH activating arcuate nucleus from inhibition of negative feedback receptors. We must take into account that the fibers effecting ACTH inhibition from limbic system are also involved in anterior hypothalamic lesions, and those from the midbrain reticular formation in posterior lesions.

In 1951, Heinbecker and Pfeifferberger reported the development of adrenal hyperplasia accompanied by hypertension and obesity (experimental Cushing’s syndrome according to them) by means of severance of afferent or efferent pathways to or from paraventricular nuclei in the dog. Although they clearly stated as pathogenetic findings the atrophy of paired paraventricular nuclei and preponderance of pituitary eosinophils, we could never recognize such findings in the hypertensive animals in the present study (detailed histological study on the endocrine organs of the animals reported here will be published soon). We also, however, confirmed the development of a syndrome which resembles Cushing’s syndrome in a hypothalamus-lesioned animal (No. 19), but it should be taken into consideration that obesity observed in hypothalamus-lesioned animal is not due to anabolic effect of steroid, but due to augmented appetite owing to involvement of ventromedial nucleus, and that glucocorticoids do not increase body weight in the rat, but rather reduce it when given in large doses.

If we presume neuroendocrine mechanism in the development of hypothalamic hypertension, it might be more convincing to ascribe it
to the enhanced pituitary-adrenal function owing to the release of arcuate nucleus from other areas than to accept Heinebecker et al's hypothesis\(^{(a)}\).

Mechanism of sustained stable hypotension caused by hypothalamic destruction involving arcuate nucleus may justly be ascribed to pituitary-adrenal inertia.

In 1961, Keller\(^{(b)}\) reported the development of hypotension in dogs with hypothalamic lesions, not accompanied by endocrine deficit, which he attributed to the disturbance of energy metabolism. In contrast with his rather topographically indefinite data, our results obtained by minute destructions indicate that the anterodorsal portion of the hypothalamus was responsible for the development. As to the mechanism of this type of hypotension, besides neural deficit, interference of regulatory mechanism of catecholamine secretion which is said to locate in some parts of the hypothalamus\(^{(c, d)}\) can be suggested.

Further detailed investigations are required as to the localization of sites responsible for the development of hypothalamic hyper- and hypotension, as well as as to the causating mechanism of them.

**Summary**

Certain bilateral hypothalamic electrolytic destruction caused sustained blood pressure rise or fall.

1) In one male rat, hypertension (maximum; 230 mm Hg, average; 198 ± 19 mm Hg) developed after extensive hypothalamic lesions involving almost all nuclei except a large portion of the arcuate nucleus and part of posterior and lateral area. In this case, adrenal weight was remarkably increased.

2) Posterior hypothalamic destruction induced hypertension in 4 rats. In a typical one, postoperative blood pressure level was 182 ± 10 mm Hg in average value (maximum; 198 mm Hg). Adrenal weight was also increased in this rat. The area common to lesions in this group was the posterior periventricular gray just above the arcuate nucleus and the adjacent part.

3) Anterior hypothalamic destruction resulted in mild hypertension in 6 animals. In a typical one, postoperative blood pressure level was 161 ± 9 mm Hg in average value (maximum; 174 mm Hg). The area common to lesions in this group was the anterior hypothalamic area, anterior periventricular gray and the adjacent part.

4) Stable hypotension, in association with decrease in adrenal weight, was observed in 8 animals with hypothalamic lesions affecting arcuate nucleus.

5) Lesions in the anterodorsal part of the hypothalamus were proved to cause hypotension, not accompanied by changes in endocrine organ weights (in 11 animals).

**Acknowledgement**

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**References**

11) Crandall, E.E., H.L. McCrorey, E.J. Sukowski and


