Effect of Ventromedial Hypothalamic Lesions on Development of Adrenal-Regeneration Hypertension in Weanling Female Rats

Regeneration of the adrenal cortex in the uninephrectomized rat given saline to drink is accompanied by the development of an acute form of hypertensive vascular disease[1]. When adrenal regeneration is prevented by hypophysectomy[2] or by administration of corticosterone[3] the hypertension fails to develop, thereby indicating the dependence of this form of hypertension on the functional integrity of the pituitary-adrenal axis. The physiologic function of this latter system is, in turn, dependent upon the hypothalamus, since placement of electrolytic lesions in the hypothalamus is followed by evidence of disturbed adrenocortical activity[4–6]. It seemed reasonable to suppose, therefore, that hypothalamic lesions might exert an influence on the development of adrenal-regeneration hypertension. Initial experiments demonstrated that placement of bilateral ventromedial lesions in young-adult animals inhibited the development of adrenal-regeneration hypertension[7] when the hyperphagia, which regularly occurs in adult rats after ablation of the ventromedial nuclei[5,8], was prevented by pair-feeding with sham-operated control animals. The present study was done to determine the influence of ventromedial nuclear ablation on adrenal-regeneration hypertension in weanling rats in which hyperphagia does not occur as a result of such hypothalamic lesions[8–10].

Materials and methods. Weanling female Charles River rats were uninephrectomized and uniadrenalectomized, divided into 4 groups and treated as follows: group 1 rats received no further treatment. Group 2 rats had bilateral electrolytic lesions placed in the ventromedial hypothalamus as described previously[7,11]. Group 3 rats had the left adrenal enucleated[12]. Group 4 rats had both left adrenal enucleation and electrolytic ablation of ventromedial nuclei performed 5 days apart. Adrenal enucleation was performed first in 17 rats whereas ventromedial lesions were placed first in 14 animals. All operations were done under ether anesthesia.

The animals were caged singly in a room kept at 22.5 °C with 12 h light and 12 h dark cycles. A synthetic diet (4.2 Cal/g, 0.8% NaCl) and 1% saline as drinking fluid were provided ad libitum. Food and saline intake were measured 3 days weekly and the total sodium consumption computed. Body weight and systolic blood pressure were measured[13] under light ether anesthesia at weekly intervals and at the end of the experiment.

After 6 weeks the rats were killed by decapitation, blood collected and plasma obtained for sodium and potassium determination by flame-photometry. Organs were removed, fixed in 10% formalin and weighed. Pituitaries were examined under a dissecting microscope for possible mechanical or thermal damage. The hypothalamic lesions were localized on cresyl violet-stained sections[14] and composite diagrams[15] constructed of the lesions common to the rats of each group (Figure 1).

Data was analyzed according to students t test. Differences between standard errors of the mean having a P value < 0.05 are considered significant and < 0.01 are considered highly significant.

Results. Terminal systolic blood pressure: Figure 2 shows that rats with hypothalamic lesions (group 2) had a significantly lower blood pressure ($P < 0.02$) than untreated controls (group 1) and that rats bearing regenerating adrenals (group 3) developed highly significant hypertension ($P < 0.01$). However, the presence of bilateral ventromedial lesions prevented to a highly significant

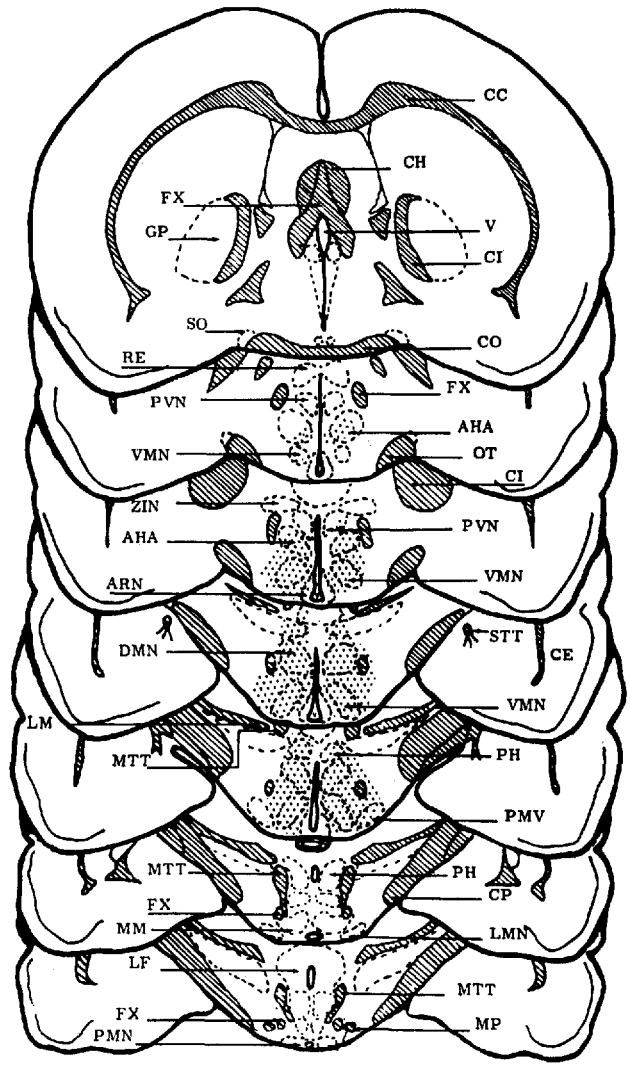

Fig. 1. Composite diagram depicting the characteristic localization of hypothalamic lesions in the rats of groups 2 and 4. The lesions are common to all rats of groups 2 and 4 and are depicted in stippling. Abbreviations for the pertinent anatomical structures indicated in the coronal section diagrams are as follows: GX, fornix; PVN, paraventricular nucleus; AHA, anterior hypothalamic area; VMN, ventromedial nucleus; ARN, arcuate nucleus; DMN, dorsomedial nucleus; PMV, ventral premamillary nucleus.

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Terminal body weights (g) and relative organ weights (mg/100 g body weight)

Group	No. of animals	Final body weight g	Heart mg%	Kidney mg%	Thymus mg%	Adrenal mg%
1	20	187 ± 5[a]	391 ± 9	732 ± 25	315 ± 18	19.1 ± 1.2
2	14	175 ± 8	404 ± 11	700 ± 17	305 ± 9	18.3 ± 0.8
3	37	193 ± 3	449 ± 12	768 ± 29	293 ± 11	17.5 ± 0.9
4	31	200 ± 8	405 ± 12	719 ± 38	228 ± 14	15.6 ± 1.1

[a] Standard error of the mean.

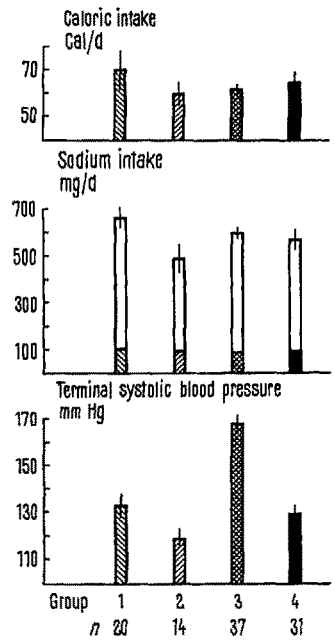

Fig. 2. Caloric intake, sodium intake and terminal systolic blood pressure. Group 1, controls; group 2, bilateral electrolytic lesions in the ventromedial hypothalamus; group 3, adrenal-enucleation; group 4, adrenal enucleation and ventromedial hypothalamic lesions. In the sodium intake graph the dietary sodium consumption is represented by the lower part of each bar and the sodium intake from the drinking fluid is shown as the open part of each bar. The vertical line at the top of the bars indicates the standard error of the mean.

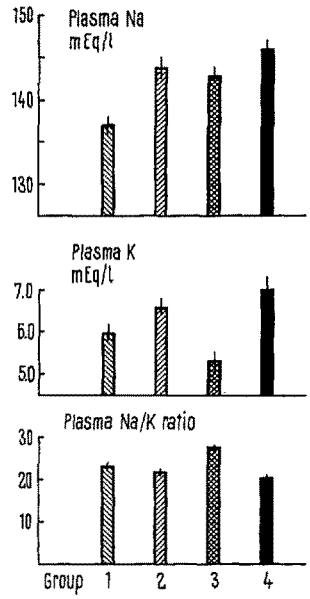

Fig. 3. Plasma sodium and potassium levels and plasma sodium and potassium ratios.

degree ($P < 0.001$) the elevation of blood pressure in the rats of group 4 which also bore regenerating adrenals.

Sodium consumption and caloric intake: sodium intake was slightly reduced ($P < 0.02$) in group 2 because of a smaller consumption of saline drinking solution. There was no significant difference in caloric consumption between any of the groups (Figure 2). Plasma sodium and potassium: plasma sodium levels in groups 2, 3 and 4 were very significantly higher ($P < 0.01$) than in group 1 (Figure 3). In contrast, plasma potassium was significantly higher ($P < 0.05$) than control levels in the rats with hypothalamic lesions (groups 2 and 4), and very significantly lower ($P < 0.01$) in the rats with adrenal-regeneration hypertension (group 3). The difference between the values for group 3 and group 4 was highly significant ($P < 0.01$). The plasma Na/K ratio was very significantly higher ($P < 0.01$) for group 3 than for any other group.

Body and organ weights: final body weight was slightly lower for group 2 rats than for other groups (Table). Significant cardiac hypertrophy ($P < 0.05$) occurred only in the rats with adrenal-regeneration hypertension (group 3). The difference between the heart weights of groups 3 and 4 was highly significant ($P < 0.01$). The weight of the kidney was largest in group 3 but differed significantly from other groups only in the case of group 2. The adrenal weight of rats with ventromedial lesions (group 2) was unchanged from control values (group 1) but the weight of the regenerated adrenal was significantly less ($P < 0.05$) in group 4 than in group 3. It is of interest, therefore, that significant ($P < 0.01$) thymic involution occurred only in group 4.

Discussion. The results of this experiment clearly support previously published observations in young-adult rats[7], that the development of adrenal regeneration hypertension is inhibited by placement of electrolytic lesions in the ventromedial nuclear region of the hypothalamus. How this is brought about remains a matter for speculation. It is apparent from both the present and previous experimental results that the hypotensive effect of ventromedial nuclear ablation cannot be explained by differences in either caloric or sodium chloride consumption, since these parameters were the same in rats which became hypertensive and in those which did not. However, this does not mean that the mechanism is unrelated to the electrolyte metabolic status of the lesioned animals. Elevated plasma potassium levels have been reported in

both adult and weanling rats with ventromedial lesions[16], and in the present experiment plasma sodium was elevated as well. In contrast, the rats bearing a regenerating adrenal had elevated plasma sodium and depressed plasma potassium levels. The net effect of these plasma electrolyte changes was an increased Na/K ratio in the rats with a regenerating adrenal (group 3) and a normal Na/K ratio in the rats with both a regenerating adrenal and ventromedial lesions (group 4).

Although these findings do not clarify the mechanism whereby ventromedial nuclear ablation affects the development of adrenal-regeneration hypertension, they do call to mind the reports of MENEELY, BALL and YOUMANS[17] and MENEELY and BALL[18] that administration of potassium chloride can ameliorate the hypertension which accompanies high sodium chloride consumption in the rat.

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Zusammenfassung. Ventromedial hypothalame Läsionen hemmen die NNR-Regenerations-Hypertonie. Dabei ist nicht eine Verschiebung in der Nahrungs- oder Elektrolyt-Aufnahme verantwortlich[19,20].

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[19] Acknowledgment: the authors wish to express their appreciation to Mr. M. BAHORSKY and Mrs. LUISE BOHACEK for their excellent technical assistance.
[20] This investigation was supported by U.S.P.H.S. Grant No. HE 06975 from the National Heart Institute and Training Grant No. 5T01-GM-1500 from the National Institute of General Medical Sciences.
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Eating and Drinking Induced by Cerebral-Ventricular Injections in Rats with Lesions in the Lateral Hypothalamus

Normal, satiated rats, when injected in the lateral ventricle of the brain with small quantities of pentobarbital sodium or 5% saline at 10 µl/min for 10 min, show a temporary eating response. Hyperphagic rats with lesions in the ventromedial area of the hypothalamus exhibit the same response to the pentobarbital sodium injection but do not eat following the 5% saline injection[1]. Drinking is caused by an injection of 2 or 5% saline at about 10 µl/min in the lateral ventricle of either normal or hyperphagic rats[1,2], apparently as a result of hypertonicity acting on osmoreceptors in the hypothalamus.

Rats suffering from aphagia and adipsia following lesions in the lateral hypothalamus often recover from these deficits in a few days or weeks if the animals are maintained by forced feeding and watering. RODGERS, EPSTEIN and TEITELBAUM[3] have presented rather conclusive evidence that the aphagia and adipsia are temporary motivational deficits and have described 4 stages of recovery. In stage I, the rats are both aphagic and adipsic. In stage II, the rats are anorexic and adipsic (e.g. the animals eat small quantities of wet, chocolate chip cookies). In stage III, the rats remain adipsic, but eat enough voluntarily to maintain their body weight. In stage IV, the animals drink water and eat normal laboratory food. These animals often still remain 'prandial drinkers' in that they drink only if receiving food.

In contrast to normal rats, rats with lesions in the lateral area who have then recovered from aphagia and adipsia do not respond to insulin-induced hypoglycemia by eating[4]. They lack many of the normal water regulation functions and will not drink to regulate body water following hyperthermia, increased serum osmolarity, or water deprivation[5]. They do not compensate for an induced sodium deficiency[5]; nor can they be induced to drink by intracranially administered carbachol[6].

We have studied, in rats recovering from lateral lesions, the responses to injections of pentobarbital sodium and 5% saline at 5 µl/min for about 4 min. We have not been able to induce aphagic rats to eat by intraventricular injections until they eat voluntarily, nor can they be induced to drink by intraventricular injections of a hypertonic solution until they drink voluntarily.

Female Charles River albino rats (220–270 g) were lesioned in the lateral area of the hypothalamus (stereotaxic coordinates of BERNARDIS and SKELTON[7] for the ventromedial nuclei with the substitution of 1.8–2.0 mm for the lateral coordinates). The rats were then cannulated in the lateral ventricle in a manner similar to that of MABEL, BAILE and MAYER[1]. The accuracy of this method of cannula placement was confirmed with the following tests: (1) histological location of Indian ink infused through the cannula; (2) elicitation of eating in normal rats infused with 65 mg/ml pentobarbital sodium at the rate of 5 µl/min; (3) elicitation of drinking in normal rats infused with 5% saline at 5 µl/min.

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