Blood Pressure in Female and Male Rats Following Ventromedial Hypothalamic Lesions Placed at Four Different Ages.* (30648)

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Karplus and Kreidl(1) showed that stimulation of certain loci of the hypothalamus elicited changes in blood pressure. Subsequently, many workers(2,3,4,5,6,7,8) demonstrated that the hypothalamus is implicated in blood pressure homeostasis and that its influence is exerted over nervous pathways (9). Ablations in the anterior hypothalamus of the cat have been shown to release sympathetic centers and to result in a rise of blood pressure, whereas posterior lesions released the anterior parasympathetic hypothalamus and caused a fall in blood pressure (10). Furthermore, lesions in the posterior half of the hypothalamic gray matter of the dog, encroaching on the tuberal area, have been reported to result in a reduction of blood pressure(11).

With increasing knowledge of the role of the hypothalamus in both adenohypophyseal and neurohypophyseal function it became evident that blood pressure homeostasis might be influenced not only through purely nervous pathways but also by neuroendocrine mechanisms, particularly through adrenocorticotrophic hormone (ACTH) and the hypertensive effect of adrenocortical secretions(12, 13), or through growth hormone (STH) and its cardiovascular effects(13). In this vein one of the authors(14) has shown that young female rats with ventromedial hypothalamic lesions developed microsplanchnia, including atrophy of the adrenal glands. The present authors also have demonstrated(15) that blood pressure and adrenal weight were reduced by ventromedial lesions in otherwise intact rats and in rats bearing one regenerating adrenal, whereas adrenal enucleated rats without hypothalamic lesions developed hypertension(15,16).

The present investigation was undertaken to study the effect of ablation of ventromedial nuclei on blood pressure with respect to the following questions: a) are ventromedial lesions, when placed in older and more mature rats, as effective in reducing blood pressure or preventing its rise, as they are in weanling rats; b) is there a sex difference in the effect of such lesions; and c) can the blood pressure response following ventromedial nuclear ablation be related to certain somatic events known to affect blood pressure directly or indirectly.

Methods. Female and male Holtzman rats were divided into 8 groups each and treated as follows: Groups 1, 3, 5 and 7 received bilateral electrolytic lesions in the ventromedial hypothalamic area when 27 (26 for males), 59, 75 and 140 days old respectively. Groups 2, 4, 6 and 8 served as intact controls corresponding in age to the other groups. The lesions were placed with a stereotaxic instrument using an enamel-coated NiCr electrode of 0.38 mm diameter, from the bared tip of which an anodal current of 1.5 mA was allowed to flow for 12 seconds. The animals were accommodated in single cages in a room kept at 25°C with alternating periods of 12 hours light and 12 hours darkness and given a synthetic diet (4.2 Cal/g 0.8% NaCl) and tap water *ad libitum*. Blood pressure was measured prior to the operation and weekly thereafter, according to the microphonic method of Friedman and Freed(17) with the animals under light ether anesthesia. The rate of growth was quantitated by measuring body length. Food and water intake were measured for two days weekly and the sodium (Na) consumption computed from both food and water. After six weeks the animals were sacrificed and their organs were dissected, trimmed and weighed; only those results that are relevant to the discussion have been included in the tables. The hypothalamic blocks were treated in the usual manner, stained with cresyl violet(14) and the localization of the lesions determined with reference to the atlas of DeGroot(18).

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TABLE I. Body Weight, Body Length, Na Intake and Organ Weights of Female Rats with Ventromedial Lesions Placed at 4 Different Ages, and of Their Intact Controls.

Group (n)	Terminal: Body wt g	Terminal: Body wt % of controls	Terminal: Body length mm	Terminal: Body length % of controls	Avg Na intake (mg/day)	Organ wt (mg): Heart	Organ wt (mg): Kidneys	Organ wt (mg): Thymus	Organ wt (mg): Adrenals
1 (10)	231 ± 9*	+20	321 ± 5	−15	95 ± 9	630 ± 18	1433 ± 73	273 ± 21	40.4 ± 3.0
2 (12)	192 ± 5		377 ± 3		95 ± 3	676 ± 16	1610 ± 44	417 ± 25	63.0 ± 2.3
3 (4)	359 ± 28	+56	373 ± 6	− 6	145 ± 12	793 ± 62	1676 ± 62	329 ± 71	49.1 ± 6.0
4 (5)	230 ± 3		396 ± 4		104 ± 12	745 ± 25	1598 ± 59	342 ± 9	68.5 ± 3.9
5 (6)	390 ± 11	+69	378 ± 3	− 5	161 ± 9	856 ± 10	2092 ± 87	216 ± 25	60.9 ± 2.0
6 (7)	231 ± 4		399 ± 2		101 ± 12	747 ± 21	1706 ± 37	279 ± 28	72.7 ± 2.1
7 (5)	524 ± 19	+82	409 ± 3	+ .5	211 ± 13	1093 ± 19	2710 ± 207	223 ± 35	75.5 ± 2.0
8 (6)	288 ± 12		407 ± 4		112 ± 5	658 ± 25	1998 ± 72	180 ± 14	69.0 ± 3.6

* Mean ± S.E.M.

Results. Female rats. Fig. 1 shows the blood pressure levels of female rats with ventromedial lesions and of their appropriate intact controls. It is evident that rats with lesions placed at 27 days of age (Group 1) showed significantly lower values than did intact controls (Group 2). In contrast, rats with lesions placed at 59, 75 and 140 days of age (Groups 3, 5 and 7) did not show this effect.

Table I shows that the absolute organ weights of female rats with hypothalamic lesions were reduced when compared with their respective controls only in animals with lesions placed at the age of 27 days (Group 1) except for the adrenal glands which were significantly reduced in rats lesioned both at 27 and at 59 days of age (Group 3). Sodium intake was identical in female rats lesioned at 27 days of age (Group 1) when compared with their intact controls (Group 2), whereas rats with hypothalamic lesions placed at later ages (Groups 3, 5 and 7) showed significantly higher Na intake as a result of hypothalamic hyperphagia.

Body weights were significantly increased over controls in all rats with hypothalamic lesions, the greatest increase being in the rats lesioned at 140 days of age. On the other hand, growth retardation as reflected by body length was greatest in the rats lesioned at 27 days of age and was least in the oldest rats.

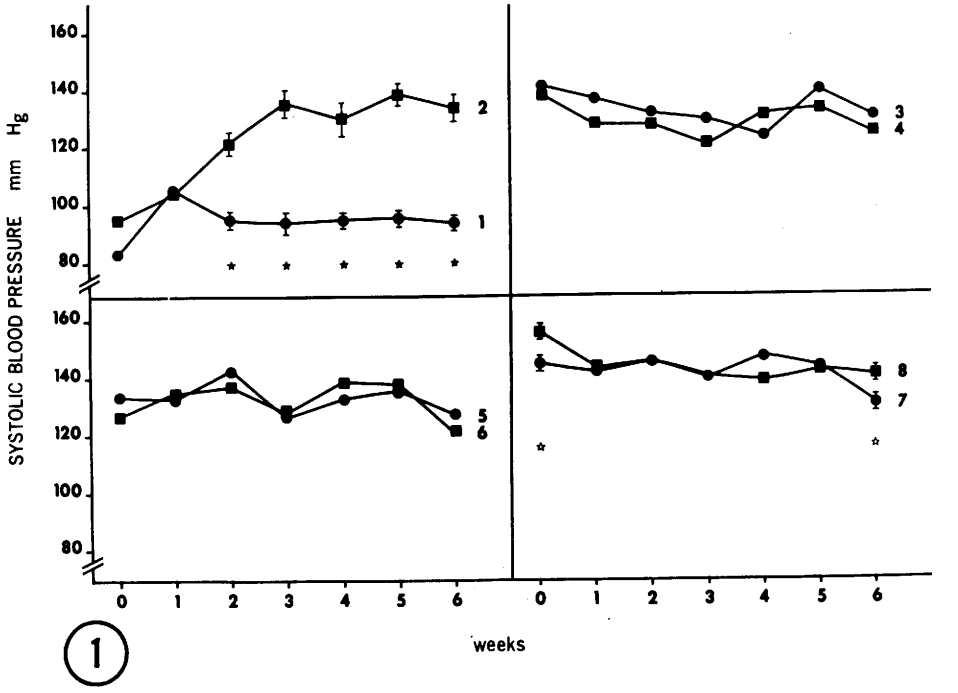
Male rats. Fig. 2 shows that rats with lesions placed at 26 days of age (Group 1) failed to develop a rise in blood pressure comparable to that of intact rats of the same age (Group 2). Animals with lesions placed at 59, 75 and 140 days of age (Groups 3, 5 and 7) showed blood pressures which did not significantly vary from those of corresponding controls (Groups 4, 6 and 8).

Table II shows that the absolute weights of heart, kidneys, thymus and adrenals were reduced in rats lesioned at 26 days of age (Group 1 *vs* Group 2). Thymus and adrenals also were significantly lighter in rats lesioned at 59 days of age (Group 3 *vs* Group 4). The sodium intake of rats operated upon at the age of 26 days (Group 1) was identical to that of the corresponding intact animals (Group 2). The sodium intake of the rats lesioned at the age of 59 and 75 days was greater than that of their intact controls but not significantly so, whereas rats with lesions placed at 140 days of age (Group 7) consumed significantly more sodium than did their controls (Group 8).

Except for those rats in which lesions had been placed at the age of 26 days, all rats with hypothalamic lesions showed greater final body weights than did their intact controls. Body length was reduced most in rats lesioned at the age of 26 days, and least in rats operated on when 140 days old.

Discussion. The present results show that interference with autonomic function early in life as produced by lesions in the ventromedial hypothalamus prevents the rise of blood pressure which normally occurs in the first few weeks of life. The mechanism whereby this is brought about is not clearly understood.

It is known that administration of sodium in excessive amounts over sufficiently long



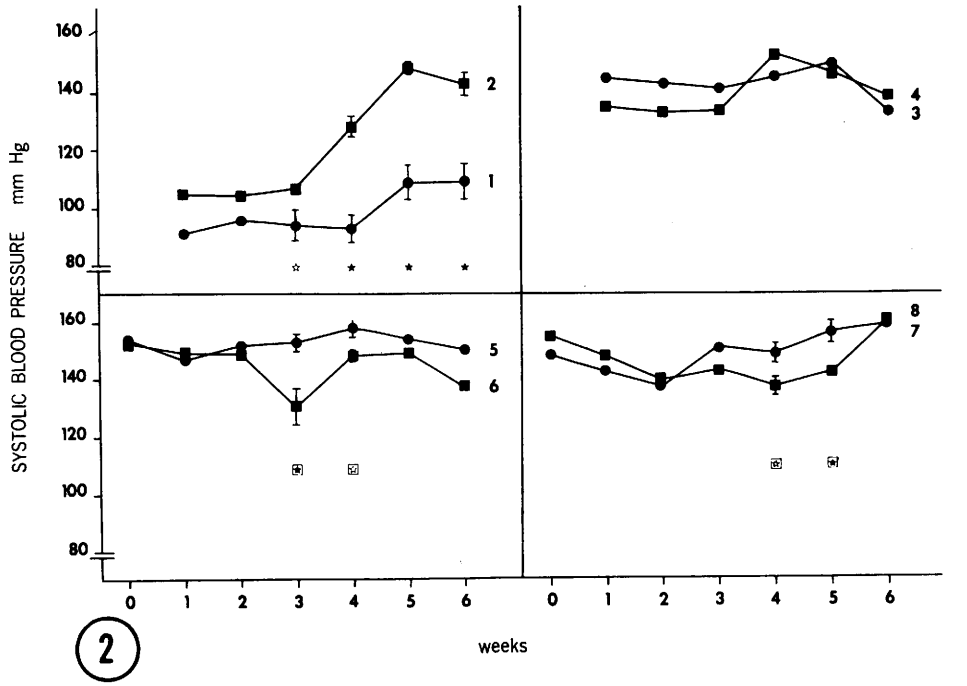


FIG. 1. Systolic blood pressure in female rats with ventromedial lesions placed at 27 days of age (Group 1), at 59 days of age (Group 3), at 75 days of age (Group 5), at 140 days of age (Group 7) and of their corresponding controls (Groups 2, 4, 6 and 8). Figure to the right of each curve denotes group number; dots represent rats with hypothalamic lesions, squares de-

TABLE II. Body Weight, Body Length, Na Intake and Organ Weights of Male Rats with Ventromedial Lesions Placed at 4 Different Ages and of Their Intact Controls.

Group (n)	Body wt g	Body wt % of controls	Body length mm	Body length % of controls	Avg Na intake (mg/day)	Organ wt (mg) Heart	Kidneys	Thymus	Adrenals
1 (6)	261 ± 18*	+ 1.9	343 ± 6	−9.5	135 ± 10	730 ± 34	1728 ± 125	342 ± 35	40.0 ± .33
2 (6)	266 ± 10		379 ± 13		136 ± 12	877 ± 32	2097 ± 69	578 ± 38	51.3 ± 2.40
3 (8)	432 ± 12	+26.7	404 ± 3	−6.5	192 ± 13	1032 ± 22	2588 ± 76	284 ± 38	47.5 ± 2.10
4 (6)	341 ± 7		432 ± 4		185 ± 5	1055 ± 70	2530 ± 56	404 ± 31	59.7 ± 2.49
5 (9)	454 ± 11	+15.8	427 ± 2	−5.3	209 ± 13	1114 ± 18	2630 ± 79	227 ± 22	50.1 ± 2.40
6 (4)	392 ± 8		451 ± 2		182 ± 20	1154 ± 42	2836 ± 78	312 ± 33	51.6 ± 1.84
7 (11)	629 ± 13	+29.4	461 ± 1	− .6	260 ± 15	1340 ± 17	3320 ± 103	237 ± 14	57.6 ± .93
8 (6)	486 ± 11		464 ± 2		195 ± 11	1302 ± 22	3154 ± 108	288 ± 27	60.7 ± 2.08

* Mean ± S.E.M.

periods results in an elevation of blood pressure(19). It is evident from the present data that those groups of rats that showed hyperphagia and thus increased sodium intake also showed blood pressures in the range of their intact controls. Only those animals that did not show increased food intake failed to attain the blood pressure levels observed in the controls. It is conceivable that the increased sodium intake in the older animals was sufficiently hypertensinogenic to overcome the hypotensive effect of the hypothalamic lesions, through whatever mechanism this latter effect was mediated.

The significantly depressed adrenal weights in these animals and the role which the adrenal glands play in blood pressure homeostasis and the pathogenesis of hypertensive disease (13,16) in this species suggest that decreased adrenal function may have contributed to the observed effects on blood pressure. On the other hand, adrenal weights also were reduced in rats lesioned at the age of 59 days, yet the blood pressure of these animals was not different from that of the controls. This may mean that other endocrine factors such as growth hormone are involved. The data on the rats lesioned at 140 days of age, *i.e.*, during adulthood, point in this direction, inasmuch as these animals showed the least retardation of body length and their adrenal weights were not different from those of their intact controls. Bernardis and Brownie(20), using plasma inorganic phosphorus as an indicator of growth hormone activity found that in intact male and female rats this parameter was significantly lower in 140-day-old animals than in 26-day-old rats. Furthermore, it was shown many years ago(21) that rats with ventromedial lesions are stunted, and work by the present authors(15) has shown that adrenal regeneration hypertension does not develop in female weanling rats with lesions in the ventromedial nuclei. These animals also were stunted.

Thus, it is very likely that the attainment of normal blood pressure levels in weanling rats is prevented by hypothalamic ventromedial lesions by interference with the finer neuroendocrine regulation of pituitary function. In older animals increased sodium intake, conditioned by hypothalamic hyperphagia might alleviate the hypotensinogenic effect of ventromedial lesions and thus permit normal blood pressure levels to be maintained.

Summary. 1. Ventromedial hypothalamic lesions placed in female and male rats at the

pict intact controls. Standard errors of the mean are indicated only where significant differences were found. Open asterisks depict $p < 0.05$, solid asterisks designate $p < 0.001$.

FIG. 2. Systolic blood pressure in male rats with ventromedial lesions placed at 26 days of age (Group 1), at 59 days of age (Group 3), at 75 days of age (Group 5), at 140 days of age (Group 7) and of their corresponding controls (Groups 2, 4, 6 and 8). Figure to the right of each curve denotes group number; dots represent rats with hypothalamic lesions, squares depict intact controls. Standard errors of mean are indicated only where significant differences were found. Open asterisks depict $p < 0.05$, open asterisks in square denote $p < 0.02$, solid asterisks in square designate $p < 0.01$, and solid asterisks represent $p < 0.001$.

age of 27 and 26 days respectively, prevented the rise of blood pressure normally observed in intact rats of this age; lesions placed at the age of 59, 75 and 140 days did not show this effect. 2. Rats that had been lesioned at 59, 75 and 140 days of age ingested more sodium than their respective intact controls; this was more pronounced in the female rats than in the male animals. 3. The increased sodium intake due to hypothalamic hyperphagia may be responsible for the alleviation of the hypotensive effect of the lesions resulting from neuroendocrine deficiencies. 4. The fact that ventromedial lesions prevented blood pressure and adrenal weight from attaining magnitudes appropriate for intact controls in weanling rats only, *i.e.*, during a phase of most active growth, suggests that the lesions interfered with the finer neuroendocrine regulation of adrenocorticotrophic hormone and perhaps growth hormone.

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Mycoplasma Isolates from Primary Cell Cultures and Human Diploid Cell Strains.* (30649)

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Contamination of tissue cultures with mycoplasmas has been well documented(1-8). The presence of cytopathic effects and the influence on cell growth by these organisms have varied from negligible or none(3,5,6,8-10) to retardation of growth(11) and widespread cytopathic effects(12-17). With the exception of one recent report(14) mycoplasmas found in uninoculated tissue cultures

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