Failure to Demonstrate a Functional Connection Between the Adrenal Gland and Ventromedial Hypothalamic Nuclei with Regard to Control of Food Intake[1]

The studies of HETHERINGTON and RANSON[2–5], BROBECK[6,7] and others[8] have described the role of the ventromedial hypothalamic nuclei in the control of food intake. Ablations of these structures have been shown to result not only in hyperphagia and obesity when performed in mature rats, but also in stunting of growth[9,10] when lesions were placed in immature rats. Furthermore, lesions placed in the ventromedial hypothalamic nuclei of weanling female rats have been shown to result in adrenal atrophy[10].

Within the last few years, evidence has been accumulating[11–13] which suggests a functional relationship between the adrenal gland and the ventromedial hypothalamic nuclei. For example, HALASZ and SZENTAGOTHAI[11] have demonstrated that interference with adrenal function resulted in cellular changes in neurons of these hypothalamic structures. Since such an influence conceivably might affect one of the well-known functions of this nucleus, i.e. the control of spontaneous food intake, it was of interest to observe this parameter in rats bearing regenerating adrenals and ventromedial lesions.

The results reported here were derived from a study concerning the effect of ventromedial hypothalamic lesions on adrenal-regeneration hypertension[14]. The present note deals with observations on food intake of these animals from the time of operation at the age of 24 and 29 days, respectively, to the time of sacrifice (age 65 days). 119 weanling female rats of the Charles River CD strain were treated in the following manner: Group 1 served as intact controls; Group 2 was uninephrectomized and uniadrenalectomized and served as operated controls; Group 3 was subjected to right adreno-nephrectomy and contralateral adrenal enucleation[15] when 24 days old and received bilateral electrolytic lesions five days later; Group 4 received the hypothalamic lesions when 24 days old and was subjected to the enucleation procedure five days later; Group 5 was subjected to the enucleation procedure when 24 days old and Group 6 when 29 days old; Group 7 received ventromedial lesions at the age of 24 days and Group 8 at the age of 29 days; Group 9 was subjected to the enucleation procedure when 24 days old and received a unilateral lesion in the left ventromedial nucleus when 29 days old; Group 10 was treated identically except for the placement of the lesion in the right ventromedial nucleus. Group 11 received the left hypothalamic lesion when 24 days old and was enucleated five days later, and Group 12 was treated identically but for the placement of the unilateral lesion in the right ventromedial nucleus; Group 13 received the left lesion when 27 days old and Group 14 the right lesion when of the same age. The latter two groups were not subjected to the adrenal-enucleation procedure.

The hypothalamic lesions were placed with a modified Horsley-Clarke stereotaxic instrument using an enamel-coated NiCr electrode of 0.38 mm diameter and a direct anodal current of 1.5 mA that flowed for 12 sec. All rats were housed in individual cages in a room kept at 25.5°C. A synthetic diet (4.2 Cal/g) and 0.9% saline as drinking fluid were available ad libitum. The food intake data presented are means of continuous measurements throughout the experiment. The localization of the lesions was verified histologically, using the atlases of KRIEG[16] and DEGROOT[17].

The Table shows that interference with adrenal function as in adrenal enucleation (Groups 5 and 6) did not affect food intake when compared with intact (Group 1) and operated (Group 2) controls. Placement of bilateral ventromedial lesions (Groups 7 and 8) resulted in a slight increase of food intake which, however, was significant only in Group 7 ($p < 0.01$). When ventromedial lesions were placed in rats bearing regenerating adrenals (Group 3) food intake was not affected when compared with the controls (Groups 1 and 2), the adrenal-enucleated rats (Groups 5 and 6) and with rats with ventromedial lesions alone (Groups 7 and 8). Adrenal enucleation of rats with ventromedial lesions (Group 4), however, did result in a slight, but probably significant decrease of food intake

Group and operation	*N*	Food intake (g/day)	Terminal body weight (g)
1 Intact controls	10	12.6 ± 0.5[d] (a)	194 ± 8[d]
2 Uninephrectomized and uniadrenalectomized controls	8	14.4 ± 0.9	202 ± 10
3 AE[a] (24 d)–VMN[b] (29 d)	13	13.5 ± 1.0	205 ± 14
4 VMN (24 d)–AE (29 d)	7	12.2 ± 1.3 (b)	179 ± 17
5 AE (24 d)	10	13.3 ± 0.7	186 ± 7
6 AE (29 d)	13	13.3 ± 0.5	193 ± 5
7 VMN (24 d)	7	15.5 ± 0.6 (c)	209 ± 11
8 VMN (29 d)	11	15.0 ± 1.0 (d)	216 ± 14
9 AE (24 d)–VML[c] (29 d)	5	14.4 ± 0.7	210 ± 7
10 AE (24 d)–VMR[c] (29 d)	5	14.8 ± 0.5	212 ± 9
11 VML (24 d)–AE (29 d)	10	13.3 ± 0.5	192 ± 6
12 VMR (24 d)–AE (29 d)	9	13.9 ± 0.6	194 ± 7
13 VML (27d)	7	14.3 ± 0.7 (f)	209 ± 10
14 VMR (27 d)	4	12.8 ± 0.6 (e)	188 ± 9

[a] Adrenal-enucleated. [b] Ventromedial bilateral lesion. [c] Ventromedial lesion left and right, respectively (unilateral). [d] ± Mean S.E.M. (a) vs (c) = $p < 0.01$. (b) vs (c) = $p < 0.05$. (c) + (d) combined vs (e) = $p < 0.05$.

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($p < 0.05$) when compared with rats bearing ventromedial lesions (operated on day 24) but not when compared with rats operated somewhat later (Group 8). However, this decrease in food intake was not reflected in the body weight.

Placement of unilateral hypothalamic lesions in rats bearing regenerating adrenals (Groups 9 and 10), adrenal-enucleation in rats bearing unilateral ventromedial lesions (Groups 11 and 12) and placement of unilateral hypothalamic lesions alone (Groups 13 and 14) did not result in significant changes in food intake, either when compared within the unilateral groups (Group 9 through Group 14), or with controls (Groups 1 and 2) and rats with bilateral lesions and regenerating adrenals (Groups 3 to 6). However, rats with unilateral right lesions did show probably significant ($p < 0.05$) changes in food intake when compared with rats bearing bilateral ventromedial lesions (Groups 14 and pooled Groups 7 and 8 respectively).

HALASZ and SZENTAGOTHAI[11] have demonstrated that adrenalectomy resulted in swelling of cell nuclei of ventromedial neurons and that increased adrenal function, e.g. as under stress, lead to shrinkage of these cell nuclei. Furthermore, unilateral adrenalectomy resulted in swelling of cell nuclei in the contralateral ventromedial nucleus and shrinkage on the ipsilateral side. The authors suggested a nervous functional connection between the adrenal gland and the ventromedial nuclei, since interruption of the nervous connection between the adrenal and the celiac ganglion and the sympathetic chain induced exactly the same changes in nuclear size of the ventromedial nuclei as did adrenalectomy or adrenal cortical atrophy brought about by cortisone administration. They assumed that nervous information from the adrenal cortex, presumably from the capsular receptors described by KISS[13], must fairly directly reach the contralateral ventromedial nuclei. Further evidence for this concept came from the demonstration of a neurosecretory material in the ventromedial nuclei which could be shown after formol-pyridine fixation and Bielschowsky-Gross impregnation. This argyrophilic substance[12], which is very sparse in healthy cats and dogs, could be demonstrated in great abundance after adrenalectomy and following severe stress. This neurosecretory material is produced exactly at the anatomical site, the bilateral destruction of which brings about a significant decrease of adrenal weight. In our studies, too, decreased adrenal weight occurred in rats with ventromedial lesions. These and other findings will be reported elsewhere[14].

Our present findings suggest, however, that the influence of the adrenal gland on the ventromedial hypothalamic nucleus does not extend to the control of spontaneous food intake. The present results support the findings of KENNEDY[9] and BERNARDIS et al.[10], and BERNARDIS[18], that ventromedial lesions placed in weanling rats are not as hyperphagia-producing as when placed in adult rats. Very young, growing rats eat twice as much in relation to their body weight as do adults and release of the restraint on feeding behavior by placement of electrolytic lesions in the satiety center apparently cannot exceed the inherent hyperphagia of growth. These considerations might be cogently invoked in interpreting the lack of influence of the adrenal gland on food intake as shown in the present report[18].

Zusammenfassung. Die von HALASZ und SZENTAGOTHAI gezeigte funktionelle Beziehung der Nebennierenrinde mit dem N. ventromedialis hypothalami legte die Vermutung nahe, dass möglicherweise diese Kerne die Futteraufnahme kontrollieren und durch Nebennierenentkernung beeinflusst werden können. Nach unseren Ergebnissen bei jungen, weiblichen Ratten ist dies sicher nicht der Fall. Auch die erhöhte Futteraufnahme normaler Ratten, welche durch Läsionen in den ventromedialen Kernen hervorgerufen werden kann, blieb durch Enukleierung der Nebenniere unbeeinflusst.

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The Action of Epinephrectomy on the Toxicity of Neomycin

Under the framework of systematical research of neomycin, we have followed the action of epinephrectomy on its toxicity. The toxicity was tested in mice of a body weight of 16–18 g intravenously 24, 48 and 72 h following unilateral and bilateral epinephrectomy. The action of the epinephrectomy on the toxicity of neomycin has been compared with the action on the toxicity of other curareform substances, namely *d*-tubocurare and with a substance that, similarly to neomycin, lowers the ionized calcium in the blood, with ammonium oxalate and strychnine, the working mechanism of which differs thoroughly from that of curareform substances (central action)[1].

The toxicity in epinephrectomized mice has been acted upon by protamine, calcium chloride and hydrocortisone. The comparison was carried out by stating the toxicity of neomycin in normal mice with sham operation. Neomycin of 660 units/mg effectiveness (preparation Spofa, Czechoslovakia) was used. The results have been statistically evaluated by means of probit analysis, and a range of reliability of 95% probability has been established.

Results and discussion. We have found that bilateral epinephrectomy lowers the toxicity of neomycin, pro-

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