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Hypothalamic Neurosecretory Nuclei and Nucleus Habenularis of Epithalamus in Essential Hypertension

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Summary. A morphometric study of the supraoptic and paraventricular nuclei in patients with essential hypertension revealed morphological manifestations of functional hypertrophy of the neurons of these nuclei which indicate an increased functional activity of the hypothalamo-hypophyseal neurosecretory system in this pathology. This may be interpreted as a reflection of the functional overloading of the distal part of the nephrons and collecting tubules due to the depression of proximal reabsorption with absolute or relative insufficiency of the function of the counter-current concentrating multiplier of the renal medulla. In patients with essential hypertension morphological signs of functional hypertrophy were observed in the nucleus habenularis of the epithalamus.

Numerous experimental morphological studies have demonstrated an increase secretory activity of the hypothalamo-hypophyseal neurosecretory system (HHNS) in different types of arterial hypertension (Aros and Ertl, 1961; Fukushima, 1968; Postnov *et al.*, 1970).
Similar studies performed on human autopsy material in cases of essential hypertension produced rather ambiguous results, and it is difficult to interpret the state of the HHNS during this disease on their basis (Wehrle, 1950; Bogdanovich, 1964; Grintsevich, 1968). This may be due to the fact that either the study was based on the evaluation of the secretory activity of the neurons by their content of the neurosecretory material by the moment of death (Bogdanovich, 1964) that reflects the total sum of the effects directly due to death (agony, cardiogenic shock, stress, etc.), or that the autopsy material employed was procured from patients with the terminal stage of hypertension having severe dystrophic changes in the cerebral vessels and brain tissue (Grintsevich, 1968). No data are available on the state of the nucleus habenularis of the epithalamus in human hypertension, although the functional relationship between this formation and the regulation of sodium metabolism has been established in several investigations (Szentagothai *et al.*, 1962; Faure *et al.*, 1965) warrants such a study.

In the present investigation autopsy material was used for studying the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus, as well as the nucleus habenularis of the epithalamus of patients with essential hypertension who died suddenly and of normal individuals who died of various irrelevant causes.

The assessment of the functional activity of the mentioned nuclei was based on the mean diameter of the neuronal nuclei and the mean diameter of the neurons, which are more stable parameters than a quantitative evaluation of the neurosecretory material and the phases of the neurosecretory cycle in the neurons.

Material and Methods

The matter of 28 autopsies was used in the study. All cases were divided into 2 groups (Table 1 and 2).

Table 1. Autopsy data on essential hypertension and control patients

Group	No. of cases (male + female)	Age (years)	Weight			
			Heart (g)	kidneys (g) (both, decapsulated)	adrenals (mg)	pituitary gland (mg)
Control	12 (9m + 3f)	16–59 (48)[a]	316 ± 7.7	260 ± 14.0	10.2 ± 0.5	574 ± 45
Essential hypertension	16 (13m + 3f)	31–64 (42)	476 ± 22	328 ± 15	16.1 ± 1.2	674 ± 44
P			0.001	0.001	0.001	NS[b]

[a] Mean value.
[b] NS = not significant.

The first group included 16 patients with essential hypertension (13 males and 3 females), aged 31 to 64 years, who died suddenly in the course of a few minutes to 4 hours due to acute coronary insufficiency, or due to brain hemorrhage. One third of these patients had not been subjected to antihypertensive therapy, the rest of them received Rauwolfia and Dibazole nonsystematically. The data on the duration of the hypertension and on the level of the arterial pressure by the time of the last attack, as well as, for some cases, their range of changes are presented in Table 2. The autopsy of all these cases demonstrated myocardial hypertrophy (heart weight of 375 to 710 g), with no macroscopic manifestations of nephrosclerosis noted (kidney weight of 290 to 370 g). A careful study of the autopsy matter excluded the presence of any processes, capable of producing symptomatic hypertension in these patients (tumors of the adrenal, pituitary or thyroid glands, occlusion of renal arteries).

The second (control) group consisted of 12 normal individuals (9 males and 3 females), aged 16, 23 years and from 31 to 59 years, who died in the course of a few minutes to 4 hours due to various types of mechanical trauma.

All autopsies were made within 6 hours after death.

At autopsy the diencephalon was removed and fixed in Bouin's fluid for 24 hours, then the block of hypothalamus with the paraventricular and supraoptic nuclei, and the block of epithalamus with the pineal gland were excised. The excised parts were again fixed in Bouin's fluid for 24 hours, embedded in paraffin, and the blocks were cut into series of frontal sections 10 μ thick. Every 20th section was used for the study. The sections were stained with chrome-hematoxylin phloxine and paraldehyd-fuchsin according to Gomori.

In every case 300 neurons of the supraoptic and paraventricular nuclei and 200 neurons of the nucleus habenularis were subjected to a morphometric analysis on the sections stained with chrome-hematoxylin phloxine. The mean diameters of the neurone and of its nucleus were determined by means of a screw ocular micrometer by measuring the greater and lesser diameters and calculating the mean value for every single neuron.

These measurements permitted to obtain the mean values of the diameters of the neurons and their nuclei in the PVN and SON and of the diameter of the neuronal nucleus in the n. habenularis in each group (Table 2), as well as to plot a diagram (spectrum) of the distribution of the neurons according to their mean nucleus diameter (Figs. 1, 2, 3).

Besides, the volume of the supraoptic nucleus (its right half) was measured in all cases using the method of diphasic planimetry according to Kesarev (1964).

Results

Table 2 shows that in cases of essential hypertension, in contrast to the control group, the neurons and their nuclei are enlarged in the n. supraopticus and n. paraventricularis of the hypothalamus; a statistically significant enlargement of the diameter of the neuronal nuclei is also observed in the n. habenularis of the epithalamus in this hypertension (the mean diameter of the neurons has not been measured in this nucleus).

From the diagram (spectrum) for the n. supraopticus (Fig. 1) may be seen that the patients with essential hypertension have a higher percentage of neurons with larger nuclei, which manifests itself in the spectrum by a shift of the peak to the right-hand side. In essential hypertension the prevailing mean diameter of the neuronal nuclei in the SON is 11–13 μ, while in the control group neuronal nuclei of a 10–11 μ diameter prevail.

The measurement of the volume of the supraoptic nucleus revealed its enlargement in essential hypertension as compared with the control group (Fig. 2; Table 2).

In patients with essential hypertension a relative increase of the number of neurons with large nuclei is observed in the n. paraventricularis, which is reflected in the spectrum by a shift of the peak to the right-hand side (Fig. 3).

In the n. habenularis of the epithalamus in essential hypertension a distinct shift of the peak to the right-hand side (Fig. 4) is seen in the spectrum, which indicates an increase of the percentage of neurons with large nuclei.

The study of the distribution of the neurosecretory material in the neurons of the supraoptic and paraventricular nuclei revealed an enlargement of the perikaryon in essential hypertension. A part of the neurons had an increased amount of the neurosecretory material, while some neurons had, an empty and enlarged perikaryon. In the axons and the neurosecretory tracts between these nuclei and the neurohypophysis, as well as in the neurohypophysis itself, the amount of the neurosecretory material was insignificant. The capillary network of these nuclei was dilated, the contours of the capillaries were more distinct due to some thickening of their basal membrane.

No Gomori-positive substance was found in the cytoplasm of the neurons of the nucleus habenularis when stained with paraldehydfuchsin.

Discussion

An enlargement of the neuron nuclei size in the secretory nuclei of the hypothalamus (with the exception, of course, of the swelling of the neuronal nuclei in cases of acute effects) is considered to be a reliable sign of a hypertrophy of the neurons caused by a prolonged period of their increased functional activity (Eichner, 1951; Szentagothai *et al.*, 1962; Palkovits and Fischer, 1968).

Table 2. Data of the morphometric study of the diencephalon

N.N.	Sex	Age (years)	Duration of disease (years)	Blood pressure (mm Hg)	Diagnosis, cause of the death
a) Control group					
1.	♂	16	—	—	Mechanical trauma
2.	♀	59	—	—	,,
3.	♂	33	—	—	,,
4.	♂	32	—	—	,,
5.	♀	31	—	—	,,
6.	♂	40	—	—	,,
7.	♂	41	—	—	,,
8.	♂	23	—	—	,,
9.	♂	46	—	—	,,
10.	♂	48	—	—	,,
11.	♀	52	—	—	,,
12.	♂	35	—	—	,,
Mean values					
b) Essential hypertension					
1.	♂	48	6	170/110–220/120	Cerebral haemorrhage
2.	♂	40	5	170/90 –190/110	Acute coronary insufficiency
3.	♂	64	12	180/110–230/130	,,
4.	♂	59	14	170/110–220/130	,,
5.	♂	37	6	170/110–180/140	,,
6.	♂	36	2	170/100	,,
7.	♂	62	20	180/100–220/130	,,
8.	♂	54	10	160/100	,,
9.	♂	46	10	180/120–220/140	,,
10.	♀	45	23	200/100–250/130	Cerebral haemorrhage
11.	♂	59	8	180/100–200/100	Acute coronary insufficiency
12.	♀	47	7	180/120–250/150	,,
13.	♂	31	2	160/120	,,
14.	♀	47	5	160/110–220/130	Cerebral haemorrhage
15.	♂	44	—	160/110–220/130	Acute coronary insufficiency
16.	♂	48	5	170/100	,,
Mean values					
P					

At the same time it is obvious that an enlargement of the neuron may be caused by a retention of the neurosecretory material, when its excretion is reduced. Therefore, the mean diameter of a neuron may be used as a criterion of its hypertrophy only when combined with the neuron nucleus size and, naturally, if no significant retention of the neurosecretory material is observed.

A similar evaluation should be also applied to the volume of the neurosecretory nucleus as a whole (in this case, to the volume of the supraoptic nucleus). Its nuclei in essential hypertension and in the control group

Nucleus supraopticus		Volume of nucleus supra-opticus (mm^3)	Nucleus paraventricularis		N. habenularis. Mean diameter of neuronal nuclei (μ)
Mean diameter of neurone (μ)	Mean diameter of neuronal nucleus (μ)		Mean diameter of neurone (μ)	Mean diameter of neuronal nucleus (μ)	
17.0	11.2	4.8	14.7	9.4	7.0
21.7	11.9	4.7	19.9	11.4	7.5
21.9	11.4	4.4	16.8	10.2	6.8
19.0	10.0	4.5	16.9	9.4	7.6
17.8	9.3	4.8	16.0	9.2	7.1
16.4	9.5	4.3	16.0	9.6	7.0
18.1	10.7	5.3	17.3	9.4	6.9
18.6	9.7	4.3	17.5	9.6	6.6
20.3	10.4	—	17.2	8.9	6.3
18.3	10.1	5.3	16.1	8.8	6.9
18.2	10.3	4.0	15.9	9.3	6.9
18.3	9.2	4.3	16.6	9.0	6.9
18.8 ± 0.5	10.3 ± 0.2	4.5 ± 0.1	16.7 ± 0.4	9.5 ± 0.2	6.6 ± 0.09
24.8	12.6	9.8	21.5	12.2	8.7
25.7	12.4	—	20.3	11.4	8.2
23.6	12.3	7.4	22.9	12.2	9.0
19.9	11.0	—	20.0	11.0	8.0
21.0	11.2	4.3	18.9	10.8	7.9
19.5	10.5	6.9	18.2	9.9	6.1
22.1	12.7	6.3	21.2	11.9	8.4
20.6	11.8	8.3	20.8	11.6	8.2
22.5	11.7	6.3	21.9	11.0	7.6
20.3	11.4	7.3	20.8	11.4	7.8
19.7	11.2	7.7	19.1	10.4	7.1
20.4	11.7	5.4	21.0	11.9	7.9
19.5	10.3	4.3	20.0	10.8	7.2
25.1	12.1	5.9	18.6	10.5	7.9
19.9	9.9	5.9	18.5	10.2	6.5
19.6	11.0	6.4	17.2	10.4	7.0
21.5 ± 0.5	11.5 ± 0.2	6.6 ± 0.4	20.2 ± 0.4	11.1 ± 0.1	7.7 ± 0.2
0.001	0.001	0.001	0.001	0.001	0.001

enlargement may be due to both the actual hypertrophy of its neurons, and, partially, to the vascularization and the degree of blood filling of the vessels.

On this basis, it is possible to interpret with sufficient grounds the data of the morphometric study of the supraoptic and paraventricular nuclei in patients with essential hypertension as a proof of a chronic increased functional activity of hypothalamo-hypophyseal neurosecretory system. The observed enlargement of the neurons and their nuclei in the n. paraventricularis and n. supraopticus in such

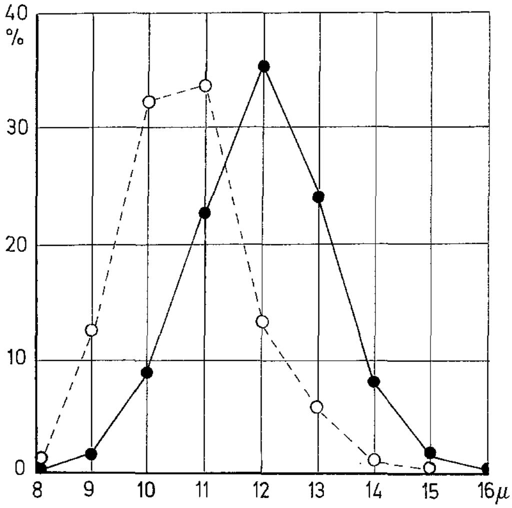

Fig. 1. Spectrum of sizes of neuronal nuclei in n. supraopticus of hypothalamus. Solid line—essential hypertension (mean values of 16 cases); dotted line—control groups (12 cases)

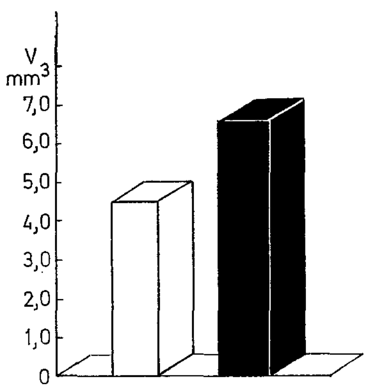

Fig. 2. Volume of n. supraopticus in essential hypertension (black column), and in the control group (white column)

patients, as well as the enlargement of the volume of the supraoptic nucleus, as a whole, characterizes the actual hypertrophy of the proximal part of the HHNS. Our general conclusion proceeding from these data does not agree with those of Wehrle (1950), Bogdanovich (1964) and Grintsevich (1968), who did not demonstrate the activation of the HHNS function as a sign typical for essential hypertension.

An enlargement of diameter of the neuronal nuclei in the n. habenularis in the same patients seems also to be an objective integral indication of the chronic activation of its function.

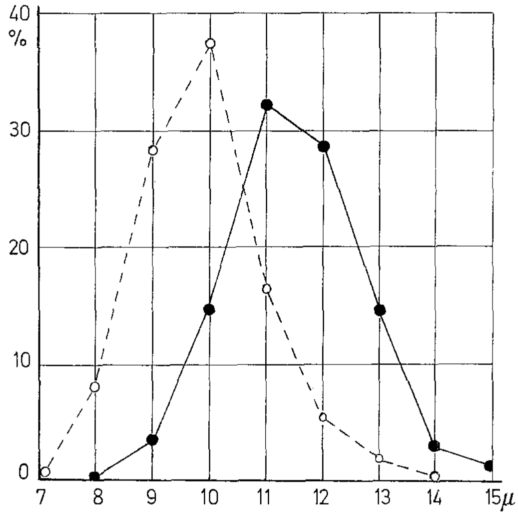

Fig. 3. Spectrum of sizes of neuronal nuclei in n. paraventricularis of hypothalamus. The same notation as in Fig. 1

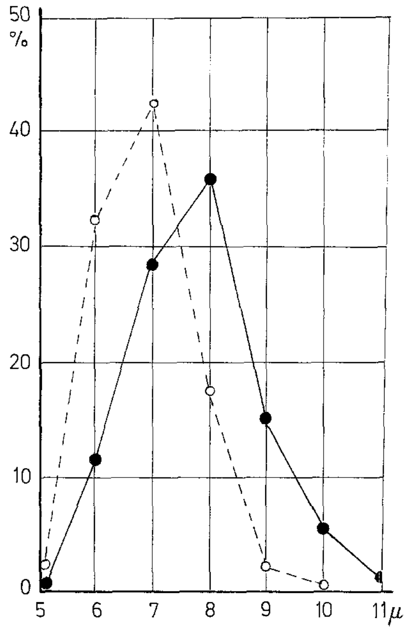

Fig. 4. Spectrum of sizes of neuronal nuclei in n. habenularis of epithalamus. The same notation

The functional hypertrophy of the neurons in the supraoptic and paraventricular nuclei indicates, with high probability, that the level of secretion of the antidiuretic hormone (ADH) and oxytocin was elevated in the patients with ssential hypertension. If we take into consideration that one of the principal hysiological functions of the mentioned hormones consists in ensuring water esorption in the distal part of the nephron and in the collecting tubules of the enal medulla (according to Chan and Sawyer (1962), oxytocin supports the ntidiuretic hormone in this action), the elevation of the functional activity of he neurosecretory nuclei in the anterior hypothalamus may be attributed to at east two factors.

The first may be a decrease of sensitivity of the target (in this case—the pithelium of the collecting tubules and, probably, of the distal part of the ephrons) with reference to the action of these hormones. The other possible actor is that a much higher volume of the filtrate, exceeding the normal one, s supplied to the distal part of the nephron and to the collecting tubules, so that, n the process of maintenaning homeostasis, these structures become functionally verloaded, and water resorption increases.

The latter factor seems to be more probable since the morphological study f the HHNS and kidneys on some models of experimental hypertension demon- trated that an activation of the function of the hypothalamic neurosecretory uclei correlates with the development of the functional hypertrophy of the renal nedulla, especially of the inner medulla (Postnov, 1971, 1972). This fact, as well s the data on the depression of proximal reabsorption in hypertension (Koch t *al.*, 1968) gave grounds to suggest that the working regime of the kidneys in ypertension is characterized by a functional overloading of the renal medulla nd the increasing water resorption in the inner medulla reflects the existence of relative (or absolute) insufficiency of the function of the counter-current oncentrating multiplier. The interrelations observed in the experiment may also xist in essential hypertension, and the increased functional activity of the HHNS s apparently of a compensatory nature in such cases, being related to the haracteristics of the working regime of the kidneys, particularly to the functional verloading of the medulla and especially—of the inner part of medulla. This unctional regime accounts to a great extent for the "exaggerated natriuresis", vhich is characteristic for hypertonic patients after an acutely excessive administra- ion of sodiumchloride (Farnswarth and Barker, 1943; Thompson *et al.*, 1954; Buckalew *et al.*, 1969).

A support of the actual existence of a functional overloading of the medulla n essential hypertension seems to follow from the study of Haggit *et al.* (1971) vhich shows a distinct relationship between the development of hyalinosis of the nterstititum of renal medulla and arterial hypertension. Interstitial hyalinosis s a form of dystrophy may, naturally, be due to the sum total of various ffects, but its development manifests, mainly, a prior prolonged increased resorp- ion process in the renal medulla.

It would be difficult to give a sufficiently substantiated explanation of the ncreased function of the n.habenularis in essential hypertension, since the data n the concrete role played by this nucleus in the regulation of salt homeostasis re limited. It may be only assumed that the hyperfunction of the n. habenularis, vhich seems to stimulate the aldosterone biosynthesis in the adrenals, may ssociate with a feed-back mechansim preventing the loss of sodium due to the bove "readiness" of the kidneys to excrete the administred sodium. Some proof of this assumption may be also found in the presence of signs of an increasing function of the adrenal cortex (increased weight).

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