RESPONSE OF THE HYPOTHALAMIC-NEUROSECRETORY SYSTEM TO EXPERIMENTAL TETANUS

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The response of the hypothalamic-pituitary neurosecretory system (HPNS) to tetanus toxin was investigated histochemically and morphometrically in rats. The response of the HPNS was found to occur soon after injection of the toxin, before the appearance of clinical manifestations of the disease. Synthetic processes in the hypothalamic neurons were activated, evidently in response to the stressor, for a similar effect was produced by the injection of inactivated toxin. In the late stages, during generalized ascending tetanus, activity of the HPNS was inhibited. The results confirm the hypothesis put forward previously by the authors to the effect that tetanus is a polysystemic disease.

Neuro-endocrine changes are an important component of the pathogenetic mechanisms of tetanus [4]. Changes in mineralocorticoid metabolism, sodium excretion, and the concentrating power of the kidney, increased reabsorption and the development of anuria [4, 8, 9], and changes in glucocorticoid [3] and catecholamine [7, 10, 11] metabolism are all evidence of serious disturbances in the neuro-endocrine system in tetanus. Meanwhile no special analysis has yet been made of the state of the hypothalamic-pituitary neurosecretory system (HPNS), the most important component of the neuro-endocrine system, in tetanus.

This paper describes some results of a study of the state of the HPNS in experimental tetanus.

EXPERIMENTAL METHOD

In experiments on 22 male albino rats weighing 250-280g, a lethal dose of tetanus toxin in 0.25 ml 0.85% NaCl solution was injected intramuscularly into the left leg. Signs of local tetanus appeared after 24 h in the animals, with generalized ascending tetanus accompanied by spontaneous spasms and general rigidity after 72 h. Another group of animals received an injection of the same volume of inactivated toxin (heated for 2 h at 56° C). Intact animals served as the second control. The rats were decapitated 5 h and 1 and 3 days after injection of the toxin. The brain (hypothalamus and pituitary) was fixed in Bouin's fluid. Neurosecretion was demonstrated in serial paraffin sections in neurons of the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus [7]. The content of neurosecretory material was estimated visually, micrometrically using the MOV-1-15 ocular micrometer and measuring the longest diameter of the perikaryons and nuclei by the blind control method, and also by counting and calculating the relative percentages of the various types of neurosecretory neurons [2].

EXPERIMENTAL RESULTS

Signs of increased functional activity with a decrease in the longest diameters of the cells and nuclei were clearly recorded in the neurons of the hypothalamic SON and PVN 5 h after the injection of tetanus

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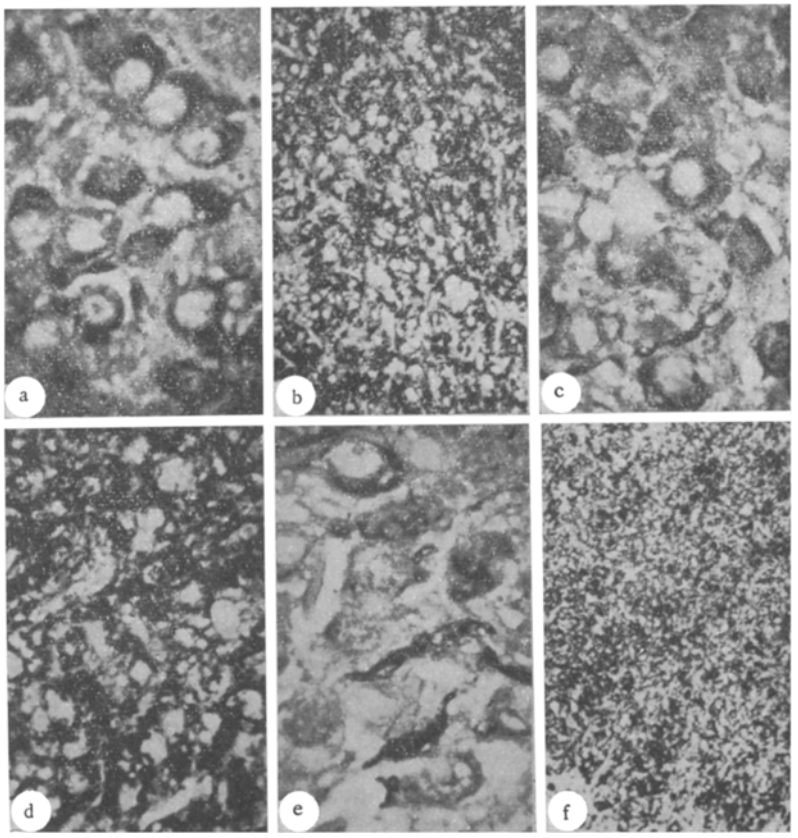

Fig. 1. Reaction of hypothalamic-pituitary neurosecretory system to the development of experimental tetanus in rats: a) paraventricular nucleus: mobilization of neurosecretion from perikaryons (600×, immersion); b) neurohypophysis: disappearance of neurosecretion (100×); c) paraventricular nucleus: displacement of neurosecretion into axons (600×, immersion); d) neurohypophysis: vasodilatation and reduced content of neurosecretion (100×); e) disturbance of synthesis of neurosecretion (ocular 10, objective 6P, immersion); f) neurohypophysis: uneven deposition of neurosecretion (100×). a,b) 5 h; c,d) 24 h; e,f) 3 days. Gomori's stain in Maiorova's modification.

toxin (Table 1). The neurosecretory granules and perikaryons were reduced in size and the latter became translucent (Fig. 1a), and the secretory product was eliminated into the processes of the neurons and the posterior lobe of the pituitary. The content of neurosecretory material in the latter was moderately reduced and this was accompanied by vasodilatation of the capillaries (Fig. 1b).

A decrease in the aldehyde-fuchsinophilic granulation was observed in the perinuclear zones of the perikaryons of the SON and PVN neurons 24 h after the injection of toxin, the cytoplasm of the neurosecretory cells was clearer still, neurosecretory material had shifted into the processes of the neurons (Fig. 1c), and its evacuation from the posterior pituitary into the general circulation was intensified (Fig. 1d). Besides the maintenance of the increased outflow of neurosecretory material into the processes of the neurons and into the fibers of the supraoptico-pituitary tract in the region of the median eminence, there was a well-marked reduction in the amount of tigroid material in the cytoplasm of neurons of the neurosecretory nuclei (Fig. 1e) 3 days after the injection, and the principal posterior part of the neurohypophysis showed a mosaic staining pattern on account of the uneven retention of aldehyde-fuchsinophilic material (Fig. 1f). By the same time the number of pycnomorphic cells among neurons of SON and PVN had risen to a maximum (Fig. 2) and the mean diameters of the neurons and their nuclei were reduced.

The development of experimental ascending tetanus was thus accompanied by changes in the function of the HPNS in various directions. In the early stages after injection of the toxin (5 h) phenomena developed which could be interpreted as an increase in HPNS function. After 24 h the functional stress on all components of the HPNS reached a maximum and this was accompanied by definite mobilization of neurohormones. On the 3rd day there was marked inhibition of the synthesis of neurosecretory material in the

TABLE 1. Diameter of Neurons and Their Nuclei (in μ) in Hypothalamic SON and PVN in Rats Receiving Tetanus Toxin (M ± m for 20 cells)

Treatment	SON		PVN	
	Neuron	Nucleus	Neuron	Nucleus
Intact animals (control)	43,0±0,7	23,0±0,5	41,0±0,5	21,4±0,5
2. Inactivated toxin, 5 h	37,7±0,7	20,4±0,3	39,8±0,4	23,3±0,5
P_{2-1}	<0,001	<0,001	0,05	0,007
3. Toxin, 5 h	33,3±0,2	18,4±0,5	36,3±0,7	21,0±0,4
P_{3-2}	<0,001	<0,001	<0,001	0,05
4. Inactivated toxin, 1 day	33,5±0,5	17,4±0,4	32,7±0,6	20,0±0,5
P_{4-1}	0,01	<0,001	<0,001	0,05
5. Toxin, 1 day	32,8±0,2	14,9±1,5	32,7±0,5	19,1±0,4
P_{5-4}	0,08	<0,001	<0,001	0,007
6. Inactivated toxin, 3 days	34,8±0,6	20,0±0,4	33,0±0,6	20,2±0,4
P_{6-1}	<0,001	<0,001	<0,001	0,05
7. Toxin, 3 days	31,3±0,7	18,6±0,6	31,0±0,4	18,9±0,4
P_{7-6}	<0,001	<0,001	<0,001	<0,001

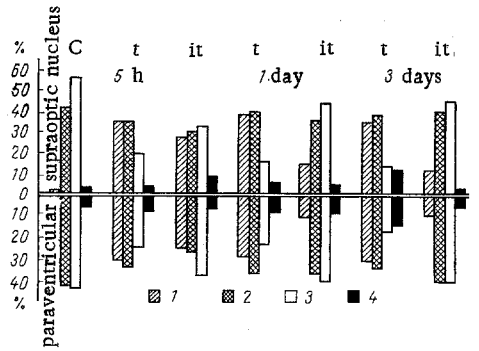

Fig. 2. Relative percentages of different types of neurosecretory neurons after injection of tetanus toxin: 1) neurons with a high content of neurosecretion; 2) with a moderate content; 3) with a low content; 4) pycnomorphic neurons. C) Control, t) toxin, it) inactivated toxin.

neurons and the outflow of neurohormones was blocked. It can be concluded from these observations that the development of generalized ascending tetanus is accompanied by inhibition of the response of the neuro-endocrine complex of the brain.

Injection of inactivated toxin at these times led to a moderate increase in HPNS function with changes in the secretory cycle, reflected in an increase in the number of cells loaded with neurosecretion (in the first 5 h), followed on the 3rd day by an increase in the translucency of the cells (Fig. 2). Synthetic processes in the perikaryons of the neurosecretory cells were undisturbed at this stage and the changes in the relative percentages of neurosecretory cells were not phasic in character.

At various times (until 1 day) after the injection of the active and inactivated tetanus toxin, no differences in principle were seen between the changes in the HPNS. Later the changes in the state of the HPNS proceeded in different directions in animals with generalized ascending tetanus and in animals receiving the inactivated toxin. In the animals with tetanus there was a marked decrease in HPNS activity and in the intensity of synthesis in the neurosecretory neurons, whereas in the animals without tetanus (receiving the inactivated toxin) there were no profound disturbances of synthesis and some activation of the HPNS was present. This activation could be connected with the effect of the heterogeneic protein [1]. Changes in the HPNS in the early periods of the experiment were evidently attributable to the initial stress which was common to both groups of animals (injection of the foreign protein, the actual manipulation of the injection, etc.). The most important changes in the animals affected by tetanus, however, were connected with the development of the disease and evidently formed part of its pathogenetic structure. The direct mechanisms of these changes are not yet clear. The facts described above support the writer's previous view that tetanus is a polysystemic disease [5, 6].

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