STATE OF CATECHOLAMINE METABOLISM IN TETANUS

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Experiments on noninbred albino rats showed changes in the catecholamine metabolism in ascending tetanus. In the early stages of the action of the toxin (24 h) these changes consisted of increased liberation of catecholamines into the blood stream and their increased entry into the tissues. In the late stages (4th day) a marked disbalance was observed in the catecholamine metabolism, with gradual exhaustion of their reserves, a marked decrease in the content of catecholamines in the adrenals and heart, and a further increase in the adrenalin content in the hypothalamus.

Analysis of the pathogenic features of tetanus have led to the conclusion [3] that the autonomic nervous system is implicated in the pathological process in this disease, and that this may be a highly important factor in the general pathogenesis of the disease, with an important bearing on its outcome. A number of clinical observations [6-8] indicate the possibility of onset of hyperactivity of the sympathetic nervous system in tetanus.

For the reasons described above, it is extremely important to determine the state of catecholamine metabolism in tetanus. This problem has been studied using ascending tetanus as the model.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 250-280 g. Tetanus toxin was injected in a lethal dose, in a volume of 0.2 ml, into the left gastrocnemius muscle. Features of local tetanus were observed in the animals 24 h after its injection (when catecholamines were determined for the first time), and on the 4th day (the second determination of catecholamines) – the animals showed generalized ascending tetanus with the "universal forwarding station" phenomenon [3], spontaneous convulsions, general rigidity, etc. The animals died on the 5th day.

Estimations were made of the concentrations of adrenalin (A), noradrenalin (NA), DOPA, and normetanephrine (NMN) in the adrenals, blood, heart, and hypothalamus. The content of A, NA, and DOPA was determined by a fluorometric method with slight modifications [4, 5], and the content of NMN by the method described by Matlina et al. [4]. Each series consisted of 8 experiments, and in each experiment four rats (two experimental and two control) were used. Combined determinations were made on pieces of tissue of equal weight and in equal volumes of blood serum. Rats receiving injections of the toxin, inactivated by boiling, were used as the controls. The concentrations of the above substances were also determined in the organs of intact animals (normal). The animals were killed by decapitation.

EXPERIMENTAL RESULTS

The experimental results are given in Table 1.

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TABLE 1. Content of Adrenalin (A), Noradrenalin (NA), DOPA, and Normetanephrine (NMN) in Organs of Rats at Various Stages of Ascending Tetanus (M ± m)

Nature of experiment	Adrenals			Blood			Heart	
	A	NA	DOPA	A	NA	NMN	A	NA
Intact animals (10)	331±17	125±8	9,0±1,02	6,1±0,4	7,51±0,6	2,90±0,20	0,0489±0,0015	0,0722±0,0058
Injection of inactivated toxin (control) (8)	334±22	129±10	10,4±0,5	6,5±0,7	8,6±0,7	3,4±0,15	0,0508±0,0029	0,065±0,0029
Local tetanus after injection of toxin (8)	326±18	190±18 **	9,8±2,1	13,0±1,7 ***	9,3±2,0	3,2±0,32	0,0891±0,0057 **	0,120±0,009 ***
Injection of inactivated toxin, control (8)	314±19	146±10	8,9±0,5	6,45±0,48	7,8±0,5	2,5±0,10	0,0484±0,0029	0,086±0,012
Generalized tetanus after injection of toxin (8)	71±5 ***	54±8 ***	7,7±0,4	5,89±0,54	9,1±1,3	1,07±0,14 ***	0,0398±0,0030 *	0,050±0,007 **

Nature of experiment	Heart		Hypothalamus			
	DOPA	NMW	A	NA	DOPA	NMN
Intact animals (10)	0,0295±0,0014	0,0107±0,0004	0,222±0,017	0,732±0,044	0,189±0,015	0,0360±0,0014
Injection of inactivated toxin (control) (8)	0,0384±0,0062	0,0105±0,0007	0,190±0,015	0,97±0,10	0,201±0,021	0,0373±0,0036
Local tetanus after injection of toxin (8)	0,0206±0,0015 **	0,0147±0,0011 **	0,204±0,018	1,19±0,17	0,247±0,026	0,0378±0,0045
Injection of inactivated toxin, control (8)	0,0362±0,0021	0,0112±0,0003	0,218±0,020	0,882±0,141	0,198±0,020	0,0349±0,0017
Generalized tetanus after injection of toxin (8)	0,0223±0,0015 **	0,0061±0,0004 **	0,409±0,022 **	0,425±0,071 **	0,281±0,013 **	0,0361±0,0018

Note. Number of experiments in parentheses. Asterisks denote significance of differences between experimental results and corresponding control ($P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively).

They show that the concentrations of the tested substances were not significantly different in the control animals and in the normal series. Consequently, injection of inactivated toxin caused no significant changes in the state of the catecholamine metabolism. Nevertheless, remembering that the content of catecholamines may fluctuate as a result of many factors, their changes in tetanus must always be compared with changes in control animals receiving inactivated toxin at the same times, and kept under the same conditions as the experimental animals, and sacrificed simultaneously with them.

During the development of tetanus, marked changes were observed in catecholamine metabolism. An increased output of A into the blood was observed 24 h after injection of the tetanus toxin (the A level in the blood was increased by 100%), and the content of NA in the adrenals also was increased. On the 4th day of poisoning the content of A and NA was considerably reduced, by four and three times, respectively. The concentration of these substances in the blood was not significantly changed, evidently because the increased liberation was accompanied by increased utilization of these substances by the tissues.

The change in the content of catecholamines in the heart in tetanus indicates their increased metabolism in the myocardium. In the early stages of poisoning (24 h after injection of the toxin), a marked increase in the A content in the heart was observed, indicating increased arrival of catecholamines in the myocardium from the blood. At the same time, the decrease in DOPA content in the heart and the marked increase in the content of NA and NMN suggest changes in the synthesis and breakdown of catecholamines in the myocardium at this stage of the disease. In the late stage of poisoning, during generalized ascending tetanus, there was a marked decrease in the content of all test substances in the myocardium. This could have been due, on the one hand, to a decrease in the amount of catecholamines produced in the adrenals, or on the other hand to a disturbance of their synthesis in the myocardium itself.

In the hypothalamus 24 h after injection of the toxin no significant changes were found in the catecholamine content, but there was a marked tendency for the concentrations of A, NA, and DOPA to rise. On the 4th day the content of A was considerably (by almost 100%) increased, while the content of NA was equally considerably reduced, and the content of DOPA was raised. The increase in the content of A in the hypothalamus at this stage of the pathological process can be regarded as the result of an increase in permeability of the blood-brain barrier to A and an increase in the arrival of A in the hypothalamus from the blood stream. The decrease in content of the catecholamines recalled the response characteristic of different types of stress [1, 2].

Changes discovered in the content of A, NA, DOPA, and NMN suggest that in tetanus the sympathetic nervous system is intensively implicated in the pathological process. Changes in the catecholamine metabolism in various organs are found in the early stages of the disease, and at this period they are marked by increased functional activity of the sympathetic nervous system. In the late stages a definite imbalance is observed in catecholamine metabolism in the various organs, with gradual exhaustion of the adrenergic reserves. The decrease in the catecholamine and DOPA content was particularly marked in the myocardium, probably in connection with the clinically familiar disturbance of cardiac activity in the late stages or during a protracted course of tetanus [6, 7, 8]. Evidently changes in the catecholamine content in the hypothalamus are of considerable pathogenetic significance; they may be associated with the development of autonomic syndromes in tetanus [6-8].

The mechanisms of the changes discovered are apparently highly complex. An essential factor in their development must be the severe stress observed in the late stages of the disease, both on its own account and in combinations with the syndrome of convulsions and increasing hypoxia, periodic attacks of asphyxia, and so on. The results of investigations carried out simultaneously with this study showed that in another type of stress (a severe pain syndrome due to injection of tetanus toxin into the posterior horns of the spinal cord, in which convulsions are absent), considerable changes were observed in catecholamine metabolism, with exhaustion of the adrenals in the late stage and death of the animals with manifestations of pain shock and paralysis of the heart. However, the possible role of the tetanus toxin itself or of changes directly induced by it, in the disturbance of activity of the sympathetic nervous system and of catecholamine metabolism is not yet clear. This possibility cannot be ruled out, and indeed it seems likely [3, 6-8], although there is no direct evidence as yet to confirm this hypothesis.

Whatever the mechanisms of the changes discovered, they are highly important in the general pathology of this disease and they must be taken into consideration in the combined treatment of tetanus.

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