ADRENALIN-LIKE SUBSTANCES IN MYASTHENIA

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(Received January 4, 1957. Presented by Active Member of the AMN SSSR N. I. Grashchenkov)

The neuro-humoral theory of nerve excitation is largely responsible for the discovery of the pathogenesis of myasthenia. The elucidation of the role of acetylcholine in the process of excitation has led to a greater understanding of the intimate mechanisms of the motor disorders in myasthenia. On this basis considerable success has been achieved in the development of pathogenetically justified treatment, directed at regulation of the disturbed acetylcholine metabolism by means of the use of the so-called anticholinesterase preparations.

Numerous investigations on this problem have been devoted mainly to an exploration of the various possible causes of the acetylcholine deficiency: to its destruction, its inadequate synthesis, and to the blockade by curare-like substances, i. e. to factors leading eventually to a state of so-called "functional asynapsia" [3]. Investigations of this sort are characterized by some degree of one-sidedness. For a comprehensive investigation of the problem it is necessary to account for the role of another hormonal factor which is of essential importance in the normal processes of neuromuscular excitation, namely the role of adrenalin and of adrenalin-like substances. An explanation of the role of these factors in the mechanism of the disorders and of the restoration of function in myasthenia is all the more necessary since the activity of the cholinergic and adrenergic systems in the processes of neuromuscular activity in a number of cases is not antagonistic but synergistic.

In connection with these problems, the aim of our investigation was to study the changes in adrenalin and adrenalin-like substances in myasthenia in association with the use of drugs causing clinical improvement of myasthenic patients. Such factors include anticholinesterase preparations (proserin – prostigmin methylsulfate) and the adrenocorticotropic hormone (ACTH), and x-ray irradiation of the thymus gland.

EXPERIMENTAL METHOD

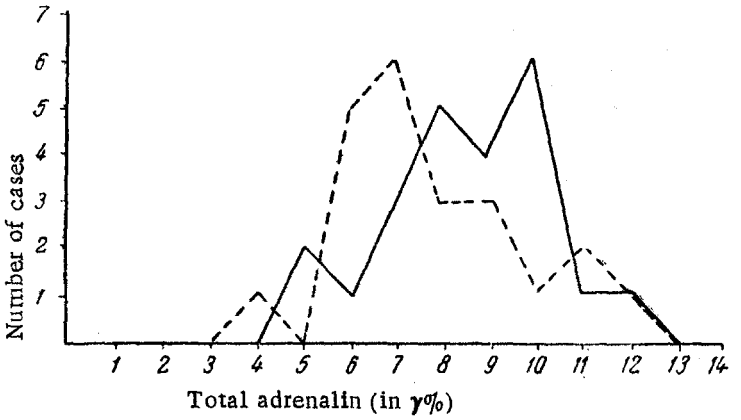
The adrenalin and adrenalin-like substances of the venous blood were determined by the method of Shaw [9] as modified by Utevskii and Butom [6]. The final staining was estimated colorimetrically on a type SF 4 spectrophotometer at a wavelength of 630 mμ. In this way the following fractions of adrenalin-like

TABLE 1

Adrenalin-Like Substances in the Blood of Normal Persons and of Patients with Myasthenia

Name of group	No. of cases	RAS		TA		CSP	
		M	m	M	m	M	m
Normal	24	7,8	0,40	8,0	0,39	0,9	0,06
Myasthenia	23	6,7	0,33	7,4	0,42	0,9	0,08

Symbols: M – arithmetic mean; m – mean square error of the arithmetic mean.



Total adrenalin content in the normal subject and in myasthenia;
——— normal; - - - - - myasthenia.

substances were determined: 1) in acid medium – the reduced adrenalin-like substances (RAS); 2) the content of dehydroadrenalin-like substances, by the difference between the content of RAS in the presence and absence of ascorbic acid; the total content of both fractions is referred to as "total adrenalin" (TA). The ratio between the values obtained by treatment with alkali and acid is an expression of the "coefficient of specificity" (CSP), which enables the relative content of adrenalin and of as yet unidentified adrenalin-like substances (chromogens) in the RAS fraction, a component of which is noradrenalin, to be judged. When the CSP > 2 it is considered that the RAS contains only adrenalin, and when the CSP < 1 adrenalin is absent. When 2 > CSP > 1 it is considered that the RAS is a mixture of adrenalin and of as yet unidentified adrenalin-like substances. In this paper the values of the RAS, TA and CSP are given in tables. Observations were made on 24 apparently healthy persons and on 23 patients with myasthenia before the commencement of treatment, in a state of myasthenic exhaustion.

EXPERIMENTAL RESULTS

The results of statistical analysis of the experimental findings are shown in Table 1.

Analysis of the figures in Table 1 shows that in myasthenia there is a tendency for the RAS content of the blood to fall. Under these circumstances the value of the CSP shows that both in the normal subject and in patients with myasthenia free adrenalin does not appear in the blood and only chromogens may be detected (CSP < 1). The tendency for the adrenalin-like substances to fall in myasthenia is also shown by the Gaussian distribution curves of the total adrenalin content in the normal subject and in myasthenia (see Figure). Some reduction in the content of adrenalin-like substances in the blood of patients with myasthenia we regard as the result of the acetylcholine deficiency in myasthenia.

The study of the movements of the content of adrenalin-like substances in the blood of 21 patients (35 observations) before and 45 minutes after the subcutaneous injection of 2 ml of a 0.05% solution of proserin (when a sudden improvement in the clinical condition of the patients took place) showed that in the majority of cases (29 out of 35) there was an increase in the total content of adrenalin-like substances, mainly due to the unoxidized fractions. Under these conditions the CSP of these simple changes was not ascertained. In different patients the increase in the adrenalin-like substances differed (from 0.3 to 4 γ%) and varied in the same patient during repeated examinations, but as a rule there was a clear tendency towards an increase in the adrenalin-like substances.

In Table 2 are shown the results of a study of the effect of proserin on the content of adrenalin-like substances in the blood – the arithmetic mean values of the RAS, TA and CSP, their mean square errors and coefficients of significance.

It can be seen from Table 2 that after the injection of proserin into the patient there is observed an increase in the RAS and TA, and the differences observed are statistically significant, $t \geq 3$.

We also observed similar changes in the content of adrenalin-like substances in the CSF in three patients under observation 10 minutes after the subcutaneous injection of proserin (Table 3).

TABLE 2

Effect of the Injection of Proserin on the Content of Adrenalin-Like Substances in the Blood of Patients with Myasthenia*

Fractions tested	No. of observations	Conditions	M	m	t
Reduced adrenalin-like substances	35	Before injection of proserin	6.3	0.36	
	33	After injection	8.6	0.51	3.7
Total adrenalin	35	Before injection of proserin	8.1	0.59	
		After injection	10.2	0.43	3.0
Coefficient of specificity		Before injection of proserin	1.1	0.10	
		After injection	1.0	0.04	0.9

Note: M – arithmetic mean; m – mean square error of the arithmetic mean; t – coefficient of significance calculated from the formula:

$$t = \frac{M_1 - M_2}{\sqrt{m_1^2 + m_2^2}}.$$

when $t \geq 3$ the material is considered to be significant.

* The study of the effects of proserin was carried out in patients, both undergoing treatment and not.

TABLE 3

Adrenalin-Like Substances in the Blood and Cerebrospinal Fluid of Patients with Myasthenia Under Treatment with Proserin, ACTH and X-rays

Surname	Material examined	Treatment	RAS, γ %		TA, γ %		CSP	
			before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
P - in	Cerebrospinal fluid	Injection of proserin	4,3	6,3	—	—	—	—
K - ov	The same	The same	3,5	4,0	—	—	—	—
N - ov	" "	" "	6,7	7,4	—	—	—	—
N - ov	Blood	X-ray therapy	7,0	13,4	7,0	17,0	1,1	0,9
Sh-va	"	The same	2,5	7,1	2,5	7,8	1,2	0,8
M-in	"	Treatment with ACTH	6,8	16,1	6,8	18,2	1,0	1,1
M-in	"	The same	10,6	3,8	10,6	5,6	1,4	1,7
K - na	"	" "	10,0	14,0	11,7	14,0	0,8	0,9
B - va	"	" "	4,8	8,5	5,7	9,9	0,7	0,8
M-in	"	One injection of ACTH	10,6	9,4	10,6	12,7	1,4	1,1
Sh-ev	"	The same	12,2	13,0	12,2	13,0	0,4	0,7

The injection of ACTH (both as a single injection of 20 units and after a course of 6 daily injections of 40-60 units) led to an obvious increase in the content of adrenalin-like substances in the blood (see Table 3).

A course of irradiation of the thymus gland with x-rays leads to clinical improvement and is accompanied in these patients by an increase in the content of adrenalin-like substances in the blood too.

The results given are not equivalent in a quantitative respect for the different forms of treatment.

Nevertheless the identity of the humoral changes, leading in the same direction after different forms of treatment, and the similarity of the clinical effects suggest that the increase in the content of adrenalin-like substances is an important functional factor in the improvement of the condition of patients suffering from myasthenia.

It must be pointed out that the factors under study – proserin, ACTH and x-ray therapy – affect in different ways the increase in the reserves of acetylcholine (proserin suppresses cholinesterase activity, ACTH increases acetylcholine synthesis [10], x-ray therapy suppresses the formation in the thymus of a factor inhibiting acetylcholine activity [11]).

An increase in the acetylcholine in the preganglionic formations of the sympathetic nervous system and the parasympathetic endings innervating the medullary layer of the adrenals, leads to an increase in the reduced forms of adrenalin-like substances. Accumulation of adrenalin-like substances may have a stimulating action on the oxidative and glycolytic processes in muscle and on its working capacity [1, 2, 5, 8].

The results obtained give grounds for postulating that the action of proserin, ACTH and x-ray therapy, while improving the condition of a myasthenic patient, may also produce an increase in the content of adrenalin-like substances, leading to improvements in muscle metabolism.

It has to be pointed out that the investigations of L. B. Perel'man, N. V. Raeva and R. A. Stavitskaia [4] on a biological test object demonstrated the regulatory role of anticholinergic drugs on sympathetic as well as acetylcholine effects.

Our investigation has confirmed this and has also enabled us to understand the positive action of ephedrine in combination with proserin in overcoming myasthenic disorders. Ephedrine is known to inhibit the destruction of adrenalin by aminooxidase, thereby bringing about its accumulation [7].

Our findings stress the importance of combined investigation of both mediators in the study of the pathogenesis and the mechanism of restoration of function in myasthenia.

SUMMARY

The majority of the studies on the significance of neurohumoral factors in the pathogenesis of myasthenia were limited to the ascertaining of the role played by acetylcholine. This work was devoted to the other mediator factor – adrenalin and adrenalin-like substances. An association was demonstrated between the shifts of the adrenalin-like substances and the changes in the clinical conditions of the myasthenic patients. An increase in the concentration of adrenalin-like substances was noted in the blood after treatment by proserin, ACTH and X-ray therapy.

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