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STATE OF NEUROMUSCULAR TRANSMISSION IN RATS WITH EXPERIMENTAL HYPOPARATHYROIDISM

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UDC 616.447-008.64-092.9-07:612.816.3

A disturbance of neuromuscular transmission, characterized by a decrease in the threshold strength of indirect stimulation, a decrease in the amplitude of the combined action potential of the muscle, a shortening of the latent period and of the absolute and relative refractory phases, and changes in the character of the response of the muscle to indirect repetitive stimulation was found in experiments on albino rats with experimental hypoparathyroidism. After intravenous injection of neostigmine into the experimental animals the various indices showed a tendency to return to their values in the control experiments. It is concluded that the disturbance of neuromuscular transmission is connected with a presynaptic defect and that it may be of definite importance in the development of the motor disturbances observable in hypoparathyroidism.

KEY WORDS: hypoparathyroidism; neuromuscular synapse; calcium; acetylcholine.

A leading place in the clinical picture of hypoparathyroidism is occupied by the syndrome of tetany, the pathogenesis of which can, it is reasonable to suppose, be elucidated by investigation of the functional state of the neuromuscular synapse, to which purpose the investigation described below was devoted.

EXPERIMENTAL METHOD

Experimental hypoparathyroidism was produced in albino rats by electrical coagulation of the parathyroid glands. The animals were used in the experiments on the fifth to eighth day after the operation. The development of hypoparathyroidism was judged from the serum calcium concentration, determined photometrically. At the time mentioned above it had fallen from 8.7 ± 0.28 to 4.7 ± 0.52 mg %.

Under pentobarbital anesthesia the tibial nerve was dissected and divided, and the peripheral end was stimulated by single, paired, and repetitive square pulses of supramaximal strength and 0.1 sec in duration. For repetitive stimulation a volley of 15-20 pulses with a frequency of 5 to 400 Hz was used. Electrical responses of the gastrocnemius muscle were recorded by silver electrodes, the active electrode being placed at

Central Research Laboratory, Erevan Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 83, No. 6, pp. 654-656, June, 1977. Original article submitted August 11, 1976.

TABLE 1. Changes in Indices of Neuromuscular Transmission in Hypoparathyroidism

Series of experiments	Threshold, V			Latent period, msec			Amplitude of action potentials, mV			Refractory period, msec					
										absolute			relative		
	$M \pm m$	n	P	$M \pm m$	n	P	$M \pm m$	n	P	$M \pm m$	n	P	$M \pm m$	n	P
Control	0,54±0,019	15	<0,01	1,3±0,04	15	<0,01	38,7±2,35	15	<0,01	3,46±0,16	15	<0,01	13,27±0,59	15	<0,01
Hypoparathyroidism	0,34±0,031	10		1,03±0,04	10		27±2,53	10		2,5±0,31	10		9,5±0,97	10	
Hypoparathyroidism + neostigmine	0,35±0,018	6		1,1±0,06	6		33,7±3,92	6		4,45±0,67	6		31,0±2,47	6	

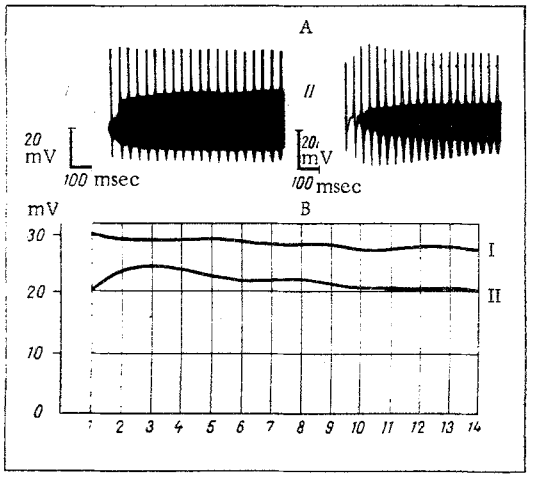

Fig. 1. Responses of gastrocnemius muscle of control (I) and hypoparathyroid (II) rats to stimulation of peripheral end of divided tibial nerve by square pulses of supramaximal strength and with a frequency of 30 Hz. A) Electrical responses; B) amplitude of action potentials (mean results of six experiments). Abscissa, serial numbers of stimuli; ordinate, amplitudes of action potentials (in mV).

the point of entry of the nerve into the muscle and the reference electrode inserted into the tendon. A "bath" was formed by the skin flaps formed around the wound and the exposed muscles were covered with mineral oil warmed to 36.9°C.

To assess the functional state of the neuromuscular synapse the threshold strength of stimulation, the latent period of the electrical response of the muscle and its amplitude, and the duration of the absolute and relative refractory phases were determined, and the character of the responses to repetitive and continuous stimulation under normal conditions, during hypoparathyroidism, and during additional intravenous injection of neostigmine (0.2 mg/kg) also was taken into account.

EXPERIMENTAL RESULTS

Experimental hypoparathyroidism led (Table 1) to a marked decrease in the threshold of the electrical response, a decrease in amplitude of the combined muscle action potential, and shortening of the latent period of response and the duration of the absolute and relative refractory phases. During indirect repetitive stimulation of the muscle, its ability to respond by action potentials of increasing magnitude to the first stimuli,

followed by a decrease in the response was observed (Fig. 1). In the control experiments depression of the responses was recorded only to stimulation of the nerve with a frequency of 40-80 Hz, but in the hypoparathyroid animals the depression of the responses following their increase could be detected in response to stimulation at frequencies as low as from 20 to 40 Hz. Furthermore, whereas the block to neuromuscular transmission develops in the animals of the control group during stimulation at a frequency of between 130 and 200 Hz, in some of the rats of the experimental series the block was observed only at frequencies of 250 Hz and higher.

The facts described above indicate disturbance of neuromuscular transmission in experimental hypoparathyroidism. Comparison of these results with data in the literature [1, 3-6] suggests that changes observed in hypoparathyroidism may be due to hypocalcemia and disturbance of the liberation of mediator in the myoneural synapse. This is shown, in particular, by a decrease in the amplitude of the combined action potentials of the muscle and the character of the dynamics of amplitudes of the responses to repetitive stimulation. The gradual increase in amplitude of the primary responses during repetitive stimulation and the relative variability of responses of the muscle in some hypoparathyroid animals to high-frequency stimulation are evidence not of an increase in the functional capacity of the neuromuscular synapse, but rather of functional dispersion of the muscle fibers, manifested as their asynchronous (by contrast with the normal response) involvement in the overall response. From this point of view our results agree with those of investigations obtained in experiments using tetanus toxin and in experimental thyrotoxicosis, in which similar changes in the functional state of the neuromuscular apparatus were found [1, 3-6].

In the light of the facts described above it is interesting to consider the results of the experiments in which the anticholinesterase drug neostigmine, which was used in the investigations cited above, was given. Neostigmine was given because, if the effects described above were due to acetylcholine deficiency, neostigmine would have restored the disturbed indices to normal to some extent and brought them close to the control values, whereas if they were due to an excess of mediator, neostigmine would have aggravated the disturbances or, at best, left them unchanged. After administration of neostigmine a tendency was observed for the indices of neuromuscular conduction to be restored, although not equally. The results of these experiments, although confirming the conclusion regarding a deficiency of mediator, nevertheless do not rule out a possible role of other factors in the disturbances of neuromuscular conduction. For instance, whereas the decrease in amplitude of the combined action potential and the increase in amplitude of the first action potentials in the series of repetitive stimulation are in harmony with the assumption that the liberation of mediator is disturbed, shortening of the latent period and of the duration of the refractory phases and the decrease in the threshold strength of stimulation are difficult to explain by a deficiency of mediator alone, although after administration of neostigmine a tendency was observed for these indices to recover. These facts can all be explained by recalling that in hypoparathyroidism, which is characterized by hypocalcemia, the electrical and mechanical excitability of the tissues is increased [9] and the critical depolarization level is lowered [7]. The functional dispersion of the motor units observed in hypoparathyroidism and, consequently, their asynchronous involvement in the excitation process, may in turn lead to the changes described.

It can thus be concluded that in hypoparathyroidism the disturbance of neuromuscular conductivity is based, first, on functional changes in the electrogenic structures of the synaptic apparatus, and, second, on damage to the mechanisms of liberation of mediator: the depression of its discharge and synthesis, or even a reduction of its effectiveness under conditions of a reduced tissue calcium concentration [8, 10, 11]. Admittedly, in that case, it is mainly the liberation of the mediator that is impaired and not its storage, to judge from the ability of the synapses to undergo activation and their relative resistance to the blocking action of high-frequency stimulation.

The disturbance of the functional state of the neuromuscular synapse revealed by this investigation may be of definite importance in the development of the motor disorders observed in hypoparathyroidism.

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RESERVE RENIN PRODUCTION BY GLOMERULAR MESANGIAL CELLS AFTER EXPERIMENTAL REDUCTION OF THE RENAL CIRCULATION

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UDC 616.61-005.4-092.9-07:616.61-008.931:577.152.344

The abdominal aorta of rats was constricted between the orifices of the renal arteries. Renin activity was studied separately in the capillary part of the isolated glomeruli and in their arterioles. Renin activity was found in the capillary part of the glomeruli 3-4 weeks after the operation, and evidence of activation of the granular and agranular endoplasmic reticulum and Golgi complex was found in the mesangial cells. The results are interpreted as confirmation of the postulated reserve production of renin by the mesangial cells during a prolonged reduction in the renal circulation.
KEY WORDS: renin; mesangial cells; juxtaglomerular apparatus; renal hypertension; body reserves.

Many morphological investigations have shown a common origin of the juxtaglomerular (JGC) and mesangial (MC) cells and the appearance of similar changes in them in various situations. However, the physiology of MC has not yet been studied. Theoretical views of reserve powers in physiological systems [3], based on biogenetic principles and data in the literature on the morphology of MC during stimulation of the juxtaglomerular apparatus (JGA), have suggested that MC are reserve sources of renin [4].

The investigation described below was carried out to test this hypothesis.

EXPERIMENTAL METHOD

A nichrome wire loop was tied around the abdominal aorta of Wistar rats weighing 160-250 g, between the orifices of the renal arteries. The diameter of the loop was chosen so as to reduce the blood flow in the left kidney by about 75% [2]. The animals were killed at weekly intervals during the first 1.5 months of the experiment, and then 2 and 3 months after the operation. Intact rats served as the control. The blood pressure in the carotid artery of all the animals was measured before sacrifice by means of a strain gauge. Individual glomeruli and their JGA were isolated from the left kidney by the method of Dahlheim et al. [7] and the fragment containing arterioles was separated from the capillary glomerulus proper (the capillary fragment) by microdissection. Renin activity (RA) was determined in each fragment by the writers' modification of the

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