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ANALYSIS OF DISTURBANCE OF MUSCLE CONTRACTILITY BASED ON ESTIMATION OF THE DEGREE OF POTENTIATION OF ITS EVOKED MECHANICAL RESPONSE

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UDC 615.22:547.944].015.44:612.178

KEY WORDS: post-tetanic potentiation; duration of contractile act; paired stimulus.

In a previous study of muscle contractility in patients with disturbance of neuromuscular transmission the writers showed that, during chronic denervation of the muscle an increase in amplitude of the evoked mechanical response (EMR) of the muscle, an increase in the temporal parameters of the contractile act, and a decrease in the ability of the muscle to exhibit staircase and post-tetanic potentiation (PTP) are observed [1]. It was also shown that the maximal amplitude of EMR observed during PTP is a stable value for each muscle, and that the increase in PTP depends on the difference between the maximal amplitude of EMR and that detectable at the given moment.

The aim of the present investigation was to analyze the ability of a muscle to undergo PTP, depending on the initial amplitude of EMR of the muscle and its ability to increase the amplitude of EMR in response to paired stimulation.

EXPERIMENTAL METHOD

Observations were made on 24 healthy subjects, 10 patients with a lesion affecting mainly the spinal motoneurons and axons of peripheral motor nerves, 30 patients with chronic disturbance of neuromuscular transmission associated with myasthenia and 8 patients with a metabolic disturbance due to hypothyroidism. The tests were carried out on an MG-400 electromyograph (Medicor, Hungary), with dc amplification channel. Supramaximal stimulation of the ulnar nerve was carried out in the region of the wrist by square pulses of current from 0.05 to 0.1 msec in duration. Single, paired, and tetanic (50 pulses/sec for 5 sec) stimulation was used. The force of isometric contraction of the adductor pollicis muscle was recorded using a strain gauge mechanograph with linear parameters of sensitivity from 10 g to 2 kg and from 1 to 20 kg. Electrical and mechanical responses were photographed from the oscilloscope screen. The following parameters of EMR of the muscle were studied: the amplitude of EMR in response to a single stimulus, defined in the literature as P_t; the duration of the contractile act (DCA) – the total time of contraction and semirelaxation of the muscle; the amplitude of EMR and DCA in response to the second stimulus, when using paired stimuli (P_2 and DCA_2); the maximal amplitude of tetanic contraction (P_0); the value of PTP – the ratio of the amplitude of EMR, measured in the muscle 10 sec after tetanus, and the initial amplitude of EMR; the ratios P_t/P_0, P_2/P_t, and DCA_2/DCA also were studied.

EXPERIMENTAL RESULTS

When healthy subjects were tested a considerable fluctuation of amplitude of EMR (from 4.9 to 14.7 N) and of the ability of the muscle to undergo PTP (from 120 to 200%) were observed. The value of PTP was

Laboratory of Clinical Pathophysiology, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 99, No. 5, pp. 552-554, May, 1985. Original article submitted July 11, 1984.

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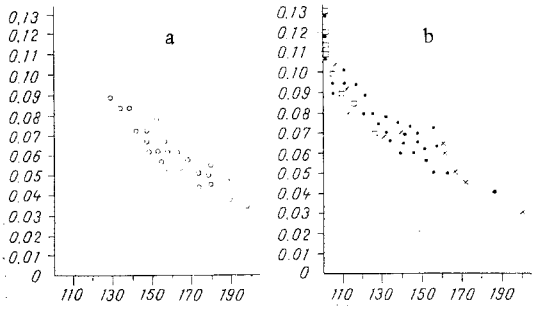

Fig. 1. Dependence of ratios of force of a single contraction (P_t) to strength of tetanus (P_0) and ability of muscle to undergo PTP in normal subjects (a) and patients (b). Abscissa, PTP (in percent); ordinate, P_t/P_0. Empty circles – normal subjects, crosses – patients with lesion of motoneurons and their axons; filled circles – patients with disturbance of neuromuscular transmission (myasthenia); squares – patients with hypothyroidism.

therefore compared with the ratio P_t/P_0 (Fig. 1), as the most stable parameter reflecting the functional state of the muscle [4, 5]. Similar relations were discovered between the value of PTP and the ratio P_t/P_0 in patients with chronic denervation superposed on a lesion of the motoneurons and axons of peripheral motor nerves, and with disturbance of neuromuscular transmission, and also in patients with hypothyroidism (Fig. 1b). Comparison of the data shown in Fig. 1a and b, shows no fundamental difference between the ratio of P_t/P_0 to PTP in the patients and normal subjects. The increase or decrease in the value of PTP depends on the initial amplitude of EMR. This confirms our previous conclusion regarding high plasticity of the contractile system of the muscle and the existence of an adaptive mechanism permitting fluctuations in strength of the muscle and its ability to undergo PTP under normal and pathological conditions [1].

To analyze the mechanisms of fluctuations in force of the muscle and its ability to undergo PTP, an experimental technique devised by the writers previously was used: estimation of the ability of the muscle to increase the amplitude of EMR in response to paired stimuli with short intervals between them [10]. A considerable gain was observed in 10 normal subjects in response to the second stimulus P_2, and it reached a maximum when intervals between stimuli were from 1.7 to 3.0 msec, and remained at that level up to an interval of 20.0 msec or more between stimuli. In patients whose DCA exceeded that of healthy subjects, the maximal value of P_2/P_t was observed in the period from 1.7-2.0 msec up to intervals measuring 70.0-80.0 msec. To standardize the investigation, the second stimulus was therefore applied at a point corresponding to a vertical line dropped from the contraction curve, and corresponding horizontally to the point of semirelaxation of the muscle.

In 10 patients with a chronic denervation syndrome associated with a lesion of the motoneurons and axons of the motor nerves, and also in 10 patients with chronic forms of disturbance of neuromuscular transmission and in 8 patients with hypothyroidism, the increase in amplitude of EMR to the second stimulus varied from 200 to 280% of its initial value (Fig. 2a). The change in character of the relationship between the P_2/P_t and P_t/P_0 will be noted: the greater the contribution of P_t to the strength of tetanus, the smaller the increase in response to the second stimulus. Direct correlation also was discovered between the value of the ratios P_2/P_0 and the ability of the muscle to undergo PTP (Fig. 2b).

Comparison of the ratio P_t/P_0 and PTP, depending on the increase in DCA during paired stimulation of the muscle revealed reciprocal relationships (Fig. 3a, b), evidence that the ability of the muscle to undergo PTP is higher in cases when the initial value of DCA is smaller, but when paired stimuli are used, its parameters may increase. The data in Fig. 3 show that this situation applies in cases when ratios P_t/P_0 are less and, consequently, ability to undergo PTP is greater, as can be clearly seen in the previous graph (Fig. 2a, b).

There are indications that the increase in force in response to a paired stimulus is connected with the type of muscle studied in the experimental animals, and the contribution of P_t to the strength of tetanus [3, 5, 6, 8]. A "slow" muscle has also been shown to have less ability to undergo PTP and an increase in the amplitude of EMR during paired stimulation [2, 5, 11, 12].

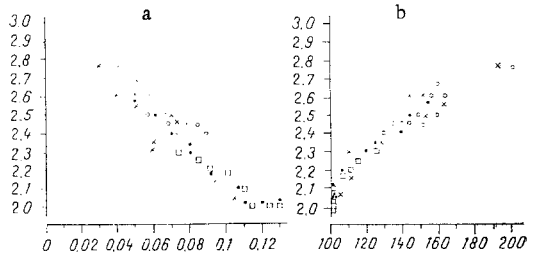

Fig. 2

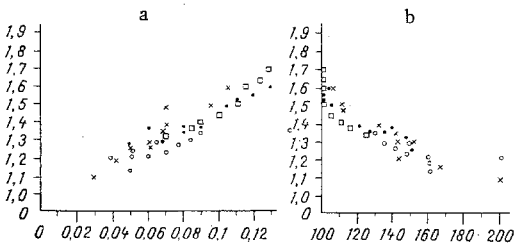

Fig. 3

Fig. 2. Increase in force of contraction in response to paired stimulus P_2/P_0 depending on ratio of force of single contraction to force of tetanus (P_t/P_0) (a) and value of PTP (b). Legend as to Fig. 1.

Fig. 3. Increase in duration of contractile act in response to paired stimulus DCA_2/DCA depending on ratio between force of a single contraction and force of tetanus P_t/P_0 (a) and on value of PTP (b). Legend as to Fig. 1.

The results indicate that the cause of the change in the ability of the muscle to undergo PTP is fluctuations in the intensity of the active state, both under conditions created in the muscle by the use of paired stimuli and on a change in the functional state of the muscle as a result of tetanization. However, from our point of view, the most interesting fact is that a change in intensity of the active state and, correspondingly, in the ability of the muscle to give EMR of greater amplitude, may arise under pathological conditions. It will be noted that similar changes in ratios of P_2/P_t to P_t/P_0 and to PTP, as well as ratios of DCA_2/DCA to P_t/P_0 and to PTP are created in very widely different pathological states (chronic denervation syndrome and metabolic disturbances). These changes cannot be connected with fatigue, for it has been shown that different forms of fatigue (during maximal voluntary effort and low-frequency stimulation under conditions of ischemia) lead to a decrease, and not an increase, in the amplitude of EMR [3]. Moreover, a decrease in force is observed for a long time after the end of loading, whereas the half-relaxation time of the muscle and the EMG return to normal [9].

If the view expressed in the literature on limiting values of the active state for each concrete case, and for a given degree of stretching of the muscle and temperature, is valid [5], the increase in amplitude of EMR at rest under pathological conditions in chronic denervation syndromes is connected with an increase in the intensity of the active state and an increase in its duration.

The problem of the mechanisms of intensification of the active state when paired stimuli are used has frequently been discussed in the literature, and it is linked with the efficiency of the initiator of muscular contraction, probably, of the system of coupling, i.e., that of release and binding of calcium [7, 13, 14].

The basically common nature of fluctuations in amplitude of EMR of a muscle and its ability to undergo potentiation under various conditions, which were revealed in this investigation of normal subjects and the muscles of patients at different stages of the denervation–reinnervation process, will be noted. This state of affairs, and also the possibility of formation of similar phenomena in hypothyroidism, suggest that the mechanism we have discovered is a universal method of regulation of the functional state of contractile elements of a muscle in health and disease.

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MICROVASCULAR PERMEABILITY IN RATS PREDISPOSED AND NOT PREDISPOSED TO DEVELOP EXPERIMENTAL ALCOHOLISM

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UDC 616.89-008.441.13-092.
9-07:616.16-008.6

KEY WORDS: microcirculation; ethanol; microvascular permeability; automatic image analysis.

Previous investigations [2] showed that ethanol, if injected intraperitoneally into rats predisposed to develop experimental alcoholism, enters the blood stream more slowly but is excreted from it more rapidly than in rats rejecting alcohol. It was suggested that these differences in the pharmacokinetics of ethanol in animals of these groups were connected with differences in the functioning of their microcirculation and, in particular, differences in permeability of the walls of the microvessels.

It was therefore decided to compare the state of permeability of the microvascular walls in rats predisposed and not predisposed to develop experimental alcoholism (PR and NPR) respectively.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 200-250 g. The rats were tested for predisposition to form experimental alcoholism by determining the duration of ethanol anesthesia, judged by the time spent by the animal in the side position after intraperitoneal injection of a 25% solution of ethanol in a dose of 4.5 g/kg [1]. Rats remaining only a short time in the side position (under 60 min), which are predisposed to voluntary consumption of ethanol, formed group 1. Group 2 included animals staying for a long time (over 120 min) in the side position. Each group consisted of 9 rats. Under pentobarbital anesthesia (mean dose 50 mg/kg, intramuscularly) a cannula was introduced into the left carotid artery of the rat in the proximal direction, fixed with a ligature, and the distal end of the artery was ligated. The anterior abdominal wall was opened and a loop of small intestine brought out through the incision, and wrapped around a light guide on a constant-temperature stage. Biomicroscopy of the mesenteric vessels was carried out in the usual way [3] under an optical magnification of 31.

Permeability of the walls of the mesenteric microvessels was studied by a luminescence method. The contents of 2 ampules, each containing 0.5 ml of dried serum (rabbit luminescent serum, produced by the N. F. Gamaleya Institute of Epidemiology and Microbiology, Academy of Sciences of the USSR), labeled with fluorescein isothiocyanate (FITC), were dissolved in 0.8 ml of physiological saline. Through a cannula 0.5 ml of serum was injected into the aorta, and its outflow from the microvessels was observed during illumination with UV rays through an opaque illuminator (exciting filter of BP type (390-480 nm), cutoff filter of LP type (515 nm)). The process of outflow of the indicator was recorded on RF-3 photographic film 1, 5, 10, 15, 20, and 30 min after its injection. Images obtained on negatives were estimated quantitatively by means of a TAC television analyzing system (Ernst Leitz, West Germany) [4]. In this way values of the area of spread of the indicator from a test microvessel were obtained during different periods after injection: S_n, S_{n+1}, S_{n+2}. The

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