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STATE OF MUSCLE CONTRACTILITY IN CHRONIC DISTURBANCES OF NEUROMUSCULAR TRANSMISSION

B. M. Gekht, A. G. Sanadze, and I. A. Strokov

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Ever-increasing attention is being paid in the study of muscle function, of fatigue, and of mechanisms of disturbance of the contractile act in various pathological states, to the objective testing of muscle contractility, based on the study of the evoked mechanical response of the muscle to indirect stimulation [2, 4-7]. Investigators have noted the informativeness of determination of the ability of the muscle to undergo staircase potentiation and post-tetanic potentiation (PTP) and twitch time. These parameters vary in the course of fatigue due to physical exercise [5, 7] and also in endocrine myopathies [11]. Analysis of the force of a muscle during a single contraction may be difficult because of the high variability of this parameter in normal subjects [4, 6]. The study of the time course of force of a single twitch (FST) of a muscle has shown that it may not only be reduced, but also increased under certain conditions. The paradoxical phenomenon of an increase in amplitude of a single evoked mechanical response of a muscle during denervation and its decrease during reinnervation has been associated with a relative increase in the quantity of sarcoplasmic reticulum in atrophied muscle fibers [9].

The aim of this investigation was to analyze changes in amplitude of the evoked mechanical response of the muscle during chronic reversible disturbances of neuromuscular transmission.

EXPERIMENTAL METHOD

Altogether 84 patients were studied in whom chronic disturbance of neuromuscular transmission was due to myasthenia, an autoimmune disease which, in the modern view, leads to a decrease in the number of acetylcholine receptors on the postsynaptic membrane [10]. The patients' ages varied from 16 to 67 years and the duration of the disease from 1 month to 15 years. In 64 patients treated with anticholinesterase drugs, these were withheld for at least 12 h before the investigation; 20 patients were not previously treated with anticholinesterase drugs. Repeated tests were carried out on 23 patients before and during glucocorticoid treatment, at intervals of 3-6 months for 1.5-2 years.

Control group consisted of 24 healthy subjects aged from 20 to 55 years and 4 patients with hypothyroidism aged from 24 to 50 years; the latter were tested before and during replacement therapy.

The tests were carried out on an ÉMG 4-03 electromyograph with dc amplification channel for recording muscular contractions. The work done by the opponens pollicis muscle when contracting under isometric conditions (initial stretching of the muscle 500 g) was recorded. Stimulation of the ulnar nerve in the region of the wrist with square pulses of current from 0.2 to 0.5 msec in duration and of supramaximal strength was applied. To record the mechani-

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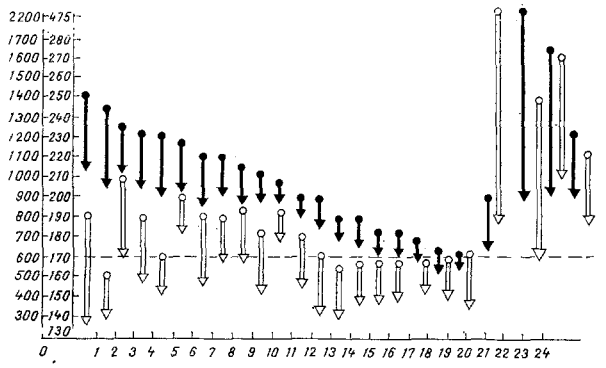

Fig. 1

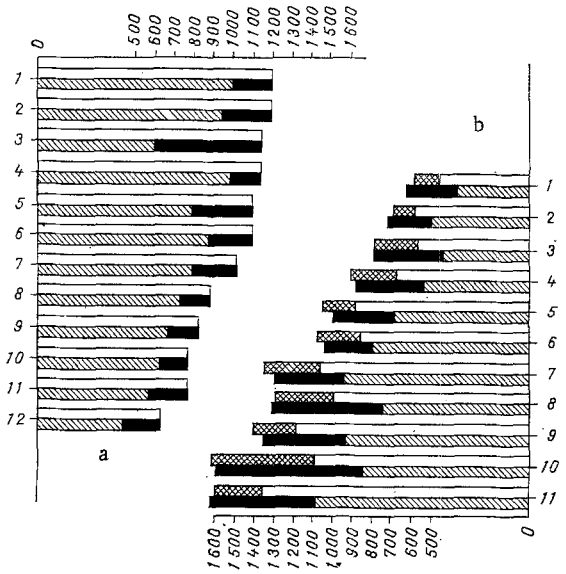

Fig. 2

Fig. 1. Changes in FST (black arrows) and twitch time (white arrows) before (empty circles) and after (empty triangles) course of hormone therapy in patients with myasthenia (Nos. 1-20) and replacement therapy in patients with hypothyroidism (Nos. 21-24). Abscissa, serial number; ordinate: I) FST (in g), II) twitch time (in msec). Broken line indicates limit of maximal values of twitch time under normal conditions.

Fig. 2. Changes in FST and PTP in patients with disturbances of neuromuscular transmission before and during treatment with glucocorticoid preparations. Abscissa, FST (in g); ordinate, serial number. a) Subjects with absence of PTP; b) subjects with presence of PTP before beginning of treatment. Unshaded columns — FST before treatment, obliquely shaded — FST after treatment, cross-hatching — PTP before treatment, black columns — PTP after treatment.

cal effort developed by the muscle, a strain-gauge mechanograph with linear parameters of sensitivity from 10 g to 2 kg and from 1 to 20 kg was used. Electrical and mechanical responses of the muscle were recorded on photographic paper and by means of an ink writer. The state of neuromuscular transmission was assessed by the ratio of amplitude of the negative phase of the action potential (AP) of the fifth response to the first in percent, during stimulation with a frequency of 3 Hz. Parameters of the mechanical response underwent parallel analysis: FST, twitch time — the sum of the duration of contraction and semirelaxation of the muscle, the ability of the muscle to potentiate FST during low-frequency stimulation — the staircase phenomenon (SP), determined as the ratio of the 240th response to the first response in the series during stimulation with a frequency of 2 Hz for 2 min, and also the ability of the muscle to potentiate FST after tetanus (PTP), determined as the ratio of the first response 10 sec after tetanus to the mechanical effort of control contraction. The results are given as mean values (M ± m) and limits of individual variations.

EXPERIMENTAL RESULTS

FST of single evoked responses of the muscle in normal subjects (865.0 ± 84.6 g; 550-1400 g) and in patients with disturbances of neuromuscular transmission before treatment (864.2 ± 25.4 g; 400-1400 g) varied within very wide limits and did not differ from one another. Meanwhile in all 23 patients FST, determined after treatment, was significantly lower than before treatment (Fig. 1). The higher the initial FST, the greater the degree of its decrease. The fact will be noted that parallel with the decrease in FST, the twitch time also decreased. In all patients during treatment the twitch time returned to normal, and only in 2 patients did it exceed the normal slightly. Definite correlation was found between values of the change in FST and the twitch time. The mean value of the initial FST in subjects with normal initial values of twitch time (up to 170 msec) was 730.4 ± 28.3 g (500-800 g), and the degree of its decrease after treatment was 75.3 ± 15.3 g. In subjects with a twitch time of over 170 msec, FST was 875.6 ± 58.7 g (700-1100 g), and after treatment FST fell by 125.3 ± 26.9 g ($P > 0.05$).

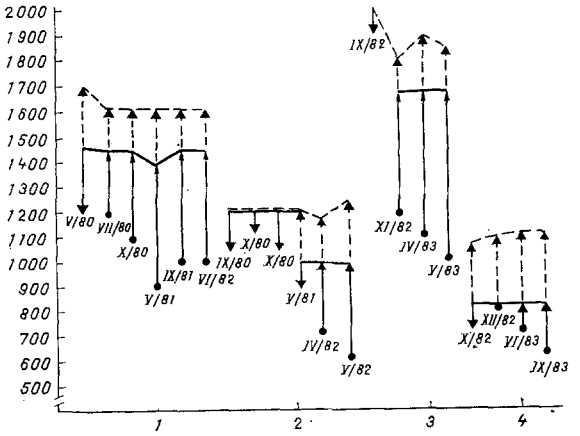

Fig. 3. Changes in staircase potentiation and PTP in patients with myasthenia and hypothyroidism at different times after beginning of pathogenetic treatment. Abscissa: 1 and 2) patients with myasthenia, 3 and 4) patients with hypothyroidism; ordinate, FST (in g). Circles — initial force of muscle; triangles — direction and final FST during determination of SP (continuous line) and PTP (broken line). Numbers on figure indicate month and year of testing.

On account of the fact that the reliability of neuromuscular transmission was reduced in most of the patients studied, the magnitude of the evoked mechanical response of the muscle was compared with the degree of blocking of neuromuscular transmission. In the case of blocking by under 10% the mean value of FST was 850.3 ± 50.4 g, and the twitch time was 143.1 ± 2.0 msec; if the block was under 20%, the corresponding figures were 876 ± 64.9 g and 150.3 ± 2.4 msec, whereas with a block of up to 30%, FST was 1100.0 ± 53.3 g and the twitch time was 178.1 ± 5.3 msec. Definite correlation was thus found between the degree of blocking of neuromuscular transmission and the degree of increase in FST and twitch time.

An increase in FST and twitch time was observed after experimental denervation of muscles [9]. The question arises whether the changes observed are the result of marked changes in structure of the muscle in the patients studied. Morphological changes are known to be ill-defined in patients with myasthenia [1, 3, 8]. The study of the histochemical structure of muscles with quantitative analysis of the number of muscle fibers of types I and II in the same patients revealed no marked changes in the types of muscle fibers which could account for the considerable increase in FST and twitch time. No significant changes in the duration of AP of the motor unit or spontaneous activity of muscle fibers, which would allow severe denervation disorders to be regarded as the cause of the changes in muscular force, likewise were found in the muscles tested.

The ability of the muscle to exhibit staircase potentiation and PTP (Figs. 2 and 3) appeared for the first time or was enhanced in the course of treatment, i.e., in the course of a decrease in FST. An extremely curious fact was discovered: The greatest possible force of the evoked mechanical response, determined as PTP, was constant in most cases, i.e., the increase in FST reflected the difference between FST at the given moment and FST at its maximal value.

The fact will be noted that the ability of the muscle to develop maximal force in response to a single stimulation is a stable value (Figs. 2 and 3). Its maximal value is determined in relation to PTP. In patients found to have maximal values of FST, PTP was absent, i.e., FST corresponded to the greatest ability of the muscle to develop mechanical force in response to indirect supramaximal stimulation. As FST increased, the value of PTP equalled the difference between the initial FST and its peak value, obtained before treatment; these principles, moreover, were found in all patients (Fig. 2). Repeated tests on individual subjects at intervals of 2-3 months for 1.5-2 years of observation revealed the high stability of the maximal force contraction, i.e., of the sum of FST after treatment and the value of PTP (Fig. 3). Everything stated above applies equally to SP also, the only difference being that the peak value of FST which can be achieved by stimulation with a frequency of 2 Hz for 2 min was lower than the value of PTP. The presence or absence of SP evidently reveals only the

level of activation of the system of the sarcoplasmic reticulum which corresponds to the standard value for the given muscle. On account of the wide variability of FST, its value itself cannot serve as indicator of the state of the electromechanical system of the muscle. However, it was noted that with twitch times exceeding 170 msec, a positive SP could not be observed in any of the 84 cases. Moreover, maximal values of FST and twitch time were noted in patients with the greatest degree of blocking of neuromuscular transmission, but they could be the same in the absence of a block or the presence of minimal degrees of block.

These phenomena were observed not only in the presence of disturbances of neuromuscular transmission, but also in a number of reversible endocrine–metabolic myopathies. The results of tests on 4 such patients are given in Figs. 1 and 3. As these results showed, in hypothyroidism, during normalization of muscle function, depression of FST and the corresponding increase in the rise in FST during SP and PTP also was observed.

These results suggest that the increase in FST and twitch time is a reflection of activation of an adaptive mechanism, controlling activity of the system of the sarcoplasmic reticulum. This suggests the presence of a regulating system and mechanism responsible for changes in FST and twitch time. Since hormone therapy in patients of this group leads to an improvement in neuromuscular transmission, it can be postulated that the cause of the disturbances discovered was absence of any functional influences of the nerve on the muscle, such as disturbance of mediator release, as well as other, possibly trophic, influences.

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