Trials of the apparatus in practice have shown its reliability in operation and the good reproducibility of the results.

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QUANTITATIVE ANALYSIS OF STIMULATION FREQUENCY TRANSFORMATION IN THE NEUROMUSCULAR APPARATUS

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UDC 612.816

The dependence of the parameters of neuromuscular transmission on the frequency of stimulation was determined. This dependence was analyzed in relation to "fatigue" of the synapse arising during prolonged repetitive stimulation of muscle. The proposed mathematical model and the method of statistical analysis of the records of evoked responses of the muscle derived from it permit approximate estimates to be made from the experimental data of parameters quantitatively reflecting frequency (transmission) properties of the neuromuscular apparatus.

KEY WORDS: *Electrical activity of muscle; models of neuromuscular transmission; electromyogram.*

Investigation of the dependence of parameters of neuromuscular transmission on the frequency of stimulation is of great importance both to the analysis of the experimental data and to the diagnosis of diseases associated with the disturbance of this transmission. This dependence is studied in the investigation described below as it applies to the development of "fatigue" processes in the synapse during prolonged repetitive indirect stimulation of a muscle, although the approach to be considered can also be used to analyze other work regimes of the neuromuscular apparatus (NMA).

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(Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 82, No. 8, pp. 1016-1018, August, 1976. Original article submitted November 3, 1975.

The process of fatigue in the peripheral NMA is characterized in particular by the tailing off through a stationary level of work, when for a certain period of time a relatively stable mean value of the evoked muscle potential is recorded [1].

Under these conditions the mean frequency of the flow of responses (action potentials, AP) of single muscle fibers arises with an increase in the frequency of stimulation (f_{st}) and then, starting with a definite frequency, it falls until transmission is inhibited. At the beginning of the first phase of a change in f_{st} an interval of rhythm reproduction is usually observed.

The dependence of integral electrical activity of a muscle, as defined by the product of the mean amplitude of the evoked potentials and f_{st}, on the value of f_{st} itself is similar in character to the patterns of frequency characteristics recorded in single muscle fibers [2].

Changes in the frequency characteristics of the AP flow in the muscle fiber and in the amplitude of integral evoked activity of the muscle are connected with variations in the intimate mechanisms of transmission of excitation from nerve to muscle and the parameters of various structures of the neuromuscular synapse (NMS).

The model suggested in this paper and the method of statistical analysis of records of evoked muscle responses (the electromyogram, EMG) can be used to determine approximate values of certain characteristics which reflect quantitatively the frequency (transmission) properties of the NMA.

To design the model consideration must be paid to some features distinguishing processes taking place in a single synapse during prolonged stimulation of the muscle by pulses of different frequency, when the reliability factor is lowered and the amplitude of the end-plate potentials (EPP) comes close to the threshold for the muscle fiber. Under these circumstances the mean frequency of responses of a single muscle fiber to stimulation by pulses above the threshold for the nerve fiber, and with an arbitrary fixed frequency and the mean amplitudes (m) of the EPPs recorded in this case show changes in the same direction: with an increase in the value of m the frequency of the AP flow (f_{resp}) rises. The reason why these dependences are similar in character will be clear from an examination of the process of formation of the AP flow of the fiber when the EPP exceeds the threshold (h) of the muscle membrane, assuming constancy of the value of h [3].

It may also be considered, as is usually done during the analysis of neuromuscular transmission [6, 7], that the quantum composition of the EPP and, correspondingly, its amplitude depend in an established regime on the quantity of mediator (A) contained in the operative (ready for liberation) fraction of its stock. It follows from these premises that the change in f_{resp} of AP will be of the same character as the change in the value of the operative mediator, i.e., the value of A as a function of f_{st} rises steadily in the phase of potentiation and falls in the phase of depression. The value of A, as it changes continuously with time, is thus also a function of the frequency of the flow of impulses reaching the terminal of the nerve fiber, i.e., $A=A(t, f_{st})$.

The rate of change of A in time $\partial A/\partial t$ or as a function of the stimulation frequency $\partial A/\partial f_{st}$ depends on the parameters of processes taking place in the various components of the mediator transport system. Basically these rates are dependent on the processes of liberation of mediator from the operative fraction of the stock and on restoration of the discharged mediator as a result of its resynthesis.

It can be taken that the rate of change of A as a function of t and f_{st} is influenced by two groups of antagonistic factors, one group of which is connected with an increase in the value of A (processes of replenishing of the operative fraction), whereas the other group (processes of liberation of mediator from this fraction) are associated with its decrease. These antagonistic factors, which are mentioned in experimental papers [4, 5], can be precisely defined in terms of a mathematical model of mediator transport [8].

It can be concluded from the above description that the empirical dependence of the mean frequency of AP flow in the muscle fiber on the frequency of stimulation $f_{resp}=f_{resp}(f_{st})$ during a fixed time t reflects, although very indirectly, the influence of the two abovementioned antagonistic factors on the rate of change of the operative reserve A.

It can be taken as a first approximation that these factors are linear functions of f_{st}, i.e., that the following equations are satisfied:

$$\begin{cases} V^p = V_0^p - \alpha^p f_{st} \\ V^d = V_0^d + \alpha^d f_{st} \end{cases}, \qquad (1)$$

where V^p and V^d are components of the rate of change of the mean frequency of the responses $\bar{f}_{resp}$ of the muscle fiber at different frequencies of stimulation f_{st}, connected with factors replenishing the mediator or liberating it from the operative fraction A. V_0^p and V_0^d are the initial values of these components at a very low frequency of stimulation (under 1 pulse/sec), and α^p and α^d are the rates of change of the values of V^p and V^d during a change in the frequency of stimulation, i.e., the corresponding components of the second derivative $d^2 f_{resp}/df_{st}^2$.

Equations (1) are examined at values of f_{st} lower than the frequency at which a complete block of transmission takes place.

The values of V^p and V^d are, generally speaking, also functions of time. However, the quantitative description of the frequency properties of the NMS given above is satisfied without regard to the dependence of V^p and V^d on time. The quantitative description of the temporal course of potentiation and depression can be given on the basis of the use of a model of the dynamics of mediator circulation [8].

Only the static characteristics $V^p = V^p(f_{st})$ and $V^d = V^d(f_{st})$ are thus examined. This is equivalent to stating that these values are considered to be means for a certain sufficiently short time interval τ:

$$V^p = \frac{1}{\tau}\int_0^\tau V^p(t, f_{st})\,\partial t; \quad V^d = \frac{1}{\tau}\int_0^\tau V^d(t, f_{st})\,\partial t.$$

The rate of change f_{resp} observable experimentally in the function f_{st} can be determined as the difference between the values of V^p and V^d:

$$V = V^p - V^d = \frac{\partial F_{resp}}{\partial f_{st}}. \qquad (2)$$

The following differential equation can be deduced from Eqs. (1) and (2):

$$\frac{\partial F_{resp}}{\partial f_{st}} = (V_0^p - V_0^d) - (\alpha^p + \alpha^d) f_{st} \qquad (3)$$

with zero initial conditions:

$\bar{f}_{resp} = 0$ when $f_{st} = 0$.

Equation (3) has the solution:

$$f_{resp} = V_0 f_{st} - \frac{1}{2}(\alpha^p + \alpha^d) f_{st}^2, \qquad (4)$$

where $V_0 = V_0^p - V_0^d$.

With these assumptions, it is thus found that f_{resp} is a parabolic function of f_{st}.

Other approximate equations for the relationship $f_{resp} = f_{resp}(f_{st})$ can also be determined similarly by making more sweeping assumptions.

Statistical analysis of the electrical responses of single muscle fibers of the isolated NMA to stimulation by series of pulses of above-threshold strength and of varied frequency f_{st} has established differences between NMS based on frequency properties [1]. In the present investigation a method of calculating the parameters of distribution of muscle fibers by frequency of rhythm binding f° and coefficients of potentiation and depression K^p and K^d was described. Determination of the law of distribution of NMS by the parameters V_0^p, V_0^d, α^p, and α^d is also of great importance for analysis of the properties of synaptic transmission.

A method of calculating the distributions of NMS by these parameters can be suggested. Let us use it as an illustration in the case when the value V^d depends only on one unknown parameter, i.e., it can be written in the form: $V^d = \alpha^d f_{st}$. In that case the equations (1) assume the form:

$$\begin{cases} V^p = V_0^p - \alpha^p f_{st}, \\ V^d = \alpha^d f_{st}. \end{cases} \qquad (5)$$

To calculate the desired distribution of NMS by frequency parameters, let us examine NMA as a system of independent elements identical in function. It follows from Eqs. (4) and (5) that a single element transforms a sequence of impulses arising in the nerve fiber during frequency stimulation into an AP flow of the muscle fiber in accordance with the rule:

$$f_{resp} = V_0^p f_{st} - \frac{1}{2}(\alpha^p + \alpha^d) f_{st}^2. \qquad (6)$$

By using Campbell's theorem of the moments of a pulsed random process and the rule (6) let us find the mathematical expectation of integral activity at the output of a system of elements as a function of stimulation frequency:

$$M(f_{st}) = S\left[\sum_{i=1}^{k} n_i\left(V_0^p f_{st} - \frac{1}{2}\left(\alpha_i^p + \alpha_i^d\right) f_{st}^2\right)\right], \qquad (7)$$

where k is the number of groups of elements each numbering n_i, with equal frequency parameters; S the area of a single AP of a muscle fiber.

The equation (7) at different frequencies f_{st} is a system of linear algebraic equations the solution of which gives the desired distributions of NMS relative to the parameters V_0^p, α^p, and α^d.

The use of the model examined in this paper for the analysis of clinical and experimental data will be described in a separate communication.

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