Another, simplified variant of the method has been developed in which the incision in the uterus is not longer than 1-1.2 cm. In this variant the amniotic sac bulges into the incision but it is not completely withdrawn from the uterus. The fetus in utero is rotated through 180° and manipulated toward the incision in the uterus so that its chest wall at the site destined to be punctured is immediately beneath the incision and is clearly visible to the eye. In this position the fetus is fixed with the fingers and the subsequent course of the operation is as before.

A second variant of the method has been used in 52 operations. A positive result was obtained in 36 cases (about 69.2%) and 16 operations terminated in abortion (30.8%).

The fetal heart is punctured with a steel needle 5 cm long and 1.5 mm in diameter, tapering below to a point. At a distance of 0.8 cm from the lower end of the needle there is a guard which prevents the needle from penetrating too deeply into the fetus.

The method of injuring the myocardium described in this paper presents no risk to the mother's health. No deaths following the operation were observed. The mothers get up on the average 3-5 h after the operation. If the operation is successful they give birth to viable animals at term, which grow and develop normally. Some time (usually 1-2 months) after the operation some of the females have become pregnant again and given birth to normal young. The suggested method thus has no significant effect on the reproductive function of the female. As a rule, the operations on these females can be repeated.

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ANALYSIS OF ELECTRICAL ACTIVITY OF A MUSCLE DURING INDIRECT REPETITIVE STIMULATION

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A mathematical model of the transformation of electrical signals in the peripheral neuromuscular apparatus and a method of analysis of the experimental data obtained during indirect repetitive stimulation of a muscle and the muscle fibers of the rat diaphragm are described. By analysis of the record of electrical activity parameters characterizing the muscle with respect to the properties of frequency potentiation and depression were determined.

KEY WORDS: simulation of neuromuscular transmission; neuromuscular apparatus; action potential of muscle fiber.

This paper is devoted to the use of a mathematical model of transmission and transformation of signals in the neuromuscular apparatus (NMA) and of methods of analysis of the data obtained in experiments in which the transmission of electrical activity in a muscle fiber and muscle in response to its indirect repetitive stimulation were studied. The results are used to examine the distinguishing features and to determine the quantitative parameters of the processes studied under normal conditions and in some types of neuromuscular pathology.

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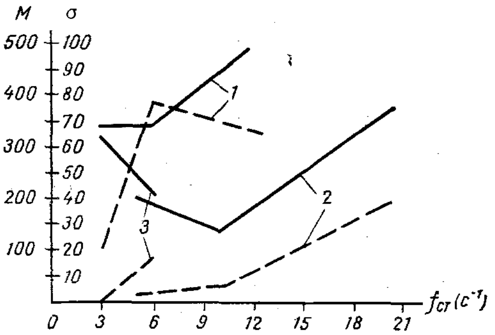

Fig. 1

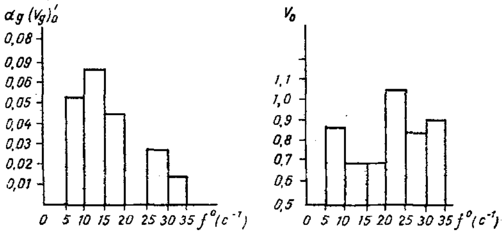

Fig. 2

Fig. 1. Changes in paramters of distributions of interspike intervals in activity of different groups of fibers: 1,2,3) No. of fibers. Continuous lines represent M, broken lines σ.

Fig. 2. Distribution of frequency parameters of various groups of muscle fibers.

The functioning of the NMA as a whole is largely determined by the characteristics of transmission and transformation of signals in a single neuromuscular junction. Statistical analysis of electrical responses of muscle fibers (MF) to stimulation of varied frequency (f_{st}) in experiments with indirect stimulation of the motor nerve of an isolated nerve-muscle preparation under conditions of fatigue by pulses of current of above-threshold strength has revealted the following distinguishing features of stimulus transmission through the NMA [1,2].

The range of mean frequencies of responses of MF ($\bar{f}_{res}$) to a sequence of stimuli with frequency f_{st} can be split into three characteristic parts. The first part is the part of rhythm binding, in which $\bar{f}_{res}$ is equal to the frequency of stimulation. The length of this part is determined by the limiting frequency of binding the rhythm of stimulation (f^0), which will subsequently be termed the "intrinsic" frequency.

The second part is characterized by a further increase in $\bar{f}_{res}$ and is bounded by the restriction $\bar{f}_{res}^{max}$ when $f_{st} = f_{opt}$, when $\bar{f}^0 < \bar{f}_{res} < f_{st}$.

In the third part a decrease in $\bar{f}_{res}$ is observed until the responses of MF disappear completely (transmission block) at a value of f_{st} known as f_{bl}.

The derived function of $\bar{f}_{res} = F(f_{st})$ in the first of these parts in $d\bar{f}_{res}/df_{st} = 1$; in the second part it is given by $0 < df_{res}/df_{st} < 1$; and in the third part $d\bar{f}_{res}/df_{st} < 0$.

The character of the change in $\bar{f}_{res}$ in the second and third parts can be explained on the ground that during transmission of the stimulus from nerve to muscle mechanisms of facilitation and inhibition of liberation and replenishing of the operative stock of mediator are manifested, with facilitation acting predominantly in the second part and inhibition in the third part. The rate of change of $\bar{f}_{res}$ in these parts, as a linear approximation, will be equal to the angular coefficients K^p and K^d, which indirectly characterize the processes of frequency potentiation and depression. It must be noted that there are fibers for which the second part, with predominance of potentiation, is absent.

During stimulation of the motor nerve with a series of pulses of the same frequency, trains of action potentials of MF, differing in their parameters, are recorded in different groups of MF. Graphs of the parameters of distributions of interspike intervals of these trains are shown in Fig. 1 as functions of the frequency of stimulation for several MF; they are plotted from the results of experiments performed on a single MF of an isolated strip of rat diaphragm [1,2].

The heterogeneity of MF with respect to frequency properties (values of f^0, f_{bl}, $\bar{f}_{res}^{max}$) was taken into account during the construction of a phenomenological model of the transimission of excitation from nerve to Mf [2,3]. Transformation of the frequency of stimulation at the input of the neuromuscular synapse (NMS) into the mean frequency of responses of MF was examined in the model. The NMS was replaced in the model by a formalized element with frequency parameters of: f^0, $\bar{f}_{res}^{max}$, and f_{bl} and with parameters of K^p and K^d characterizing the mean rate of change in $\bar{f}_{res}$ within the corresponding ranges of f_{st}.

The operator of the connection between the mean frequency of the train of action potentials of MF ($\bar{f}_{res}$), the frequency of stimulation f_{st}, and the basic parameters of the element can be written in the form:

$$\bar{f}_{res} = \psi(f_{st}, f^0, K^p, K^d, t). \quad (1)$$

This operator, generally speaking, is nonlinear and nonstationary. Because of the assumptions made relative to the properties of NMS it can be regarded as dependent on time t as its parameter and as bilinear with respect to the other parameters, and it can be written in the form:

$$\bar{f}_{res} = \begin{cases} f_{st} & \text{when } 0 < f_{st} < f^0 \\ f^0 [1 + K^p (f_{st} \cdot f^{0-1} - 1)] & \text{when } f^0 < f_{st} < f_{opt} \\ f^0 \{[1 + K^p (f_{st} \cdot f^{0-1} - 1)] - K^d (f_{st} \cdot f^{0-1} - \\ - m_1)\} & \text{when } f_{opt} < f_{st} < f_{bl}, \end{cases}$$

$$K^p = \frac{\bar{f}_{res} - f^0}{f_{st} - f^0}, \quad K^d = \frac{\bar{f}_{res}^{max}}{K^p (f_{st} - f^0) - \bar{f}_{res}^{max} + f^0},$$

$$m_1 = \frac{f_{opt} - f^0}{f^0}. \quad (2)$$

NMA as a whole was regarded as a system of a large number of functionally uniform and independent elements.

By Campbell's theorem of the moments of a stationary random process, the magnitude of the mathematical expectation of a pulsed process at the output of such a system (a train of evoked muscle responses to indirect respective stimulation) is determined by the equation:

$$M(f_{st_j}) = S\left\{\sum_{i=1} n_i f_i^0 \left[1 + K_i^p \left(\frac{f_{st_j}}{f_i^0} - 1\right)\right] - \sum_{i=1} n_i f_i^0 \cdot K_i^d \times \left(\frac{f_{st_j}}{f_i^0} - m_1\right) + \sum_{i=j}^{r} i n_i f_i^0\right\} \quad (3)$$

$$i = 1, 2, \ldots, n, \; j = 1, 2, \ldots, l,$$

where i is the number of the group of elements with equal values of the parameters f^0, K^p, K^d, r is the number of groups, and f_i^0 the "intrinsic frequency" of the NMS of the i-th group, S the area of a single action potential of MF, and $f_{st_j} = j \cdot f_{st_0}$.

Analysis of the experimental data in order to calculate the estimates of the laws of distribution of the frequency parameters of NMA was carried out with the aid of equations (3) using values of $f_{min}^0 = 5$ Hz and $r = 7$ and breaking up the range of change of frequency into steps of $\Delta f_{st} = f_{min}^0 = 5$ Hz. The empirical laws of distribution of f_i^0, K^p, and K^d calculated from the results of experiments on an isolated strip of rat diaphragm [1,2] indicate that the fibers are heterogeneous as regards their frequency properties. The character of transformation of these distributions during a change in f_{st} is evidence of the inequality of the contribution of the different groups of NMS.

Values of K^p higher than 1, discovered for some groups of fibers, indicate recruiting of other fibers into the response of the muscle which were not involved in the response to a lower frequency of stimulation, i.e., their recruiting, given a sufficiently high value of f_{st}, from the subthreshold border.

The dependence of the mean frequency of the train of action potentials of MF on the frequency of stimulation reflects the influence of two antagonistic factors, one connected with an increase in value of the operative raction of the stock of mediator (processes of replenishing the operative fraction), the other with its decrease (processes of liberation of mediator from this fraction). Let these factors be represented by the symbols V^p and V^d.

Let us assume that the values of V^p and V^d are linear functions of f_{st}, i.e., that

$$\begin{cases} V^p = V_0^p - \alpha^p \cdot f_{st} \\ V^d = V_0^d - \alpha^d \cdot f_{st}, \end{cases} \quad (4)$$

so that: $V = (V_0^p - V_0^d) - (\alpha^p + \alpha^d) \cdot f_{st}$

whence:

$$\bar{f} = V_0 f_{st} - \frac{\alpha^p + \alpha^d}{2} f_{st}^2, \tag{5}$$

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

Using this relationship it is possible to transfer from the laws of distribution of the parameters f^0, K^p, and K^d to distributions of the parameters V^0, α^p, and α^d. For this purpose, let us substitute in equation (5) the values of the frequency of stimulation, namely:

$$f_{st_1} = f^0,\ f_{st_2} = f^0(1+m_1),$$
$$f_{st_3} = f^0\left(1 + m_1 + \frac{1+m_1 K^p}{K_d}\right).$$

As a result we obtain the following system of linear algebraic equations with which to determine the parameters V_0, α^p, and α^d:

$$\begin{cases} f^0 = V_0 f^0 - \dfrac{\alpha^p + \alpha^d}{2} f^{0^2} \\ f^0 \cdot (1 + m_1 K^p) = V_0 (1+m_1) f^0 - \dfrac{\alpha^p + \alpha^d}{2} \times \\ \qquad \times (1+m_1)^2 f^{0^2} \\ 0 = V_0 \cdot f^0 \left(1 + m_1 + \dfrac{1+m_1 K^p}{K^d}\right) - \dfrac{\alpha^p + \alpha^d}{2} \times \\ \qquad \times \left(1 + m_1 + \dfrac{1+m_1 K^p}{K^d}\right)^2 f^{0^2}. \end{cases} \tag{6}$$

The values of the coefficients of potentiation and depression K^p and K^d obtained in [4] were used for determining the parameters V_0 and α^d. By solution of the system (6) the distributions of these parameters were obtained. From the statistical characteristics of the distributions it is possible to estimate the frequency properties of a large group of NMS of the test muscle under conditions of fatigue.

Histograms of distributions of V_0 and α^d are given in Fig. 2. It follows from analysis of these histograms that the most active group of NMS, the one with the greatest ability to activate the liberation of mediator in response to repetitive stimulation, is the frequency group with f^0 = 20 Hz; the processes of inhibition of liberation of the mediator are most marked in the low-frequency groups (5-15 Hz) of the same muscle.

The method described above is most effective in comparative analysis of two muscles or of one muscle in two different states. It can be used: 1) to differentiate between the two basic frequency properties of the process of stimulus transmission through NMS: activation and inhibition of liberation of the mediator; 2) to obtain statistical characteristics of the electromyogram of a muscle that can be used in the diagonsis of neuromuscular diseases.

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