Simulation of Resting Membrane Potential Change in Denervated Muscle Fiber

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Abstract - *A computer model for change of resting membrane potential of the denervated skeletal muscle fiber has been developed.*

It has been shown that after denervation the number of extrajunctional acetylcholine-gated ion channels (AChR) increases, whereas the number of chloride ion channels and the intracellular concentration of chloride decrease. These processes lead to a long term change of resting membrane potential (V_{rest}). Chronic functional electric stimulation (FES) avoids these changes and even reverses the membrane conditions almost back to normal.

In this work the above mentioned changes of membrane properties are described by the "membrane condition parameter (P_{mc})". The increase in the rate of AChR synthesis leads to an increase of sodium conductivity up to an estimated maximum of 150%. The changes referred to chloride result in a decrease of leakage conductivity down to 50% as well as a shift of leakage equilibrium potential towards depolarization up to 15mV.

The sum of all membrane currents over a range of membrane potential is plotted for a set of P_{mc}. The resting membrane condition is fulfilled if the sum of all membrane currents is zero. In this way each resting potential corresponding to its P_{mc} is determined. V_{rest} changes from –90mV up to -72mV corresponding to a P_{mc} from 0 to 1.

Keywords: *FES, Denervation, Resting potential, Ionic channels, Hodgkin-Huxley model type.*

1. Introduction

A cell membrane is a double lipid layer, which contains a lot of proteins, called ionic channels. The membrane represents the border between two different electrolytic fluids, which are communicating through these ionic channels. There are different kinds of ionic channels corresponding to the specific types of ions.

The most important ionic currents for the changes of membrane potential are evoked by sodium (Na), potassium (K) and chloride (Cl). If there are only neglectable currents flowing over the membrane, the membrane potential is constant and the potential at this state is called resting membrane potential V_{rest}. In this case the fiber remains in the resting state.

When the amount of Na-channels is increasing - e.g. by a pathologic reason - the entire Na-conductivity is also increasing and at the same time the portion of Na-current is rising as well. The membrane will be out of electric balance until the membrane potential has been adapted to the new condition. The result is a new resting membrane potential V_{rest}.

Persisting denervation leads to many cellular and molecular changes in skeletal muscle. The muscle membrane will be sensitive for acetylcholin (ACh) on its entire length [1][2], caused by an increased rate of extrajunctional acetylcholine-gated ion channel (AChR) synthesis [3]. Additional, the Cl-conductivity of denervated muscle fibers is low in comparison to healthy innervated fibers [4][5][6][7]. Experiments of Heathcote [8] showed, that AChR and Cl-channels are responsible for the resting conductivity of the muscle cell and they are expressed in an anticoordinate fashion to each other.

2. Method

A single muscle fiber is physiologically located in a bundle of fibers where a certain extracellular ionic concentration is predominant. Caused by the intracellular ionic concentration, which is approximately equal in each fiber, a potential difference between intra- and extracellular space

$$V_{\mathrm{Re}\,st} = V_i - V_e \qquad (1)$$

is present for a fiber in the resting state and is called the resting membrane potential.

If there is no electric field applied to the muscle fiber or no action potential is propagating, the whole cell is in a stationary state. In case of the membrane model type of Hodgkin and Huxley [9]

$$c \cdot \frac{dV}{dt} = i_{St} - i_{ion}, \qquad (2)$$

where c represents the capacity of the membrane by membrane unit area, the membrane potential is constant in time ($dV/dt = 0$) and the density of the stimulation current is zero ($i_{St} = 0$). This results in the sum of the ionic current densities

$$i_{ion} = i_{Na} + i_K + i_L = 0, \quad (3)$$

where i_{Na} is the sodium, i_K the potassium and i_L the leakage current density including the chloride ionic density i_{Cl}. Each ionic current density is dependent on the density of the ionic channels, the gradient of the ionic concentration and the membrane potential. The detailed description of the ionic currents can be written in the form

$$g_{Na} \cdot m^3 \cdot h \cdot (V - E_{Na}) + g_k \cdot n^4 \cdot (V - E_K) + g_L \cdot (V - E_L) = 0, \quad (4)$$

where V is the membrane potential, g_{Na}, g_K and g_L are the maximum sodium, potassium and leakage conductivities, E_{Na}, E_K and E_L are the sodium, potassium and leakage equilibrium potentials and m, n and h are the opening and closing probabilities of the ionic channels.

After denervation the fall of chloride conductivity means, that the amount of Cl-channels decreases. At the same time, the intracellular ionic concentration of chloride rises and the chloride equilibrium potential (E_{Cl}), which is included in the leakage equilibrium potential (E_L), moves towards depolarization for about $\Delta E_L = 15mV$. The rise of AChR synthesis leads to an increase of the Na-channel density and results in a higher Na-conductivity. Actually, the AChR is a different type of Na-channel (type 2) compared to the normal (type 1) Na-channel, but referred to their voltage sensitivity they have similar behavior [10]. For that reason ionic channels of type 1 and type 2 can be added to a higher amount of normal Na-channels.

AChR and Cl-channels are reacting in an indirect relation (Fig. 1). If the level of AChR is high, the level of Cl-conductivity is low and vice versa. After denervation of a skeletal muscle the amount of AChR increases and the Cl-conductivity or the amount of Cl-channels decreases, respectively. Functional electric stimulation (FES) of denervated muscle brings the Cl-conductivity up to normal level and AChR will disappear.

With the assumption that the changes in the muscle fiber membrane of AChR and Cl-conductivity are in the same rate of percentage, a membrane condition parameter (P_{mc}) can be introduced. The increase in the rate of AChR synthesis leads to an increase of sodium conductivity up to an estimated maximum of 150%. The changes referred to chloride result in a decrease of leakage conductivity down to 50% as well as a shift of leakage equilibrium potential towards depolarization up to 15mV.

In order to describe different states of muscle fiber after denervation, the parameter P_{mc} is used. If the day of denervation is a long time ago and no FES has been applied during this period, the membrane condition parameter ($P_{mc} = 1$) indicates 100% of denervation changes. After a period of applied FES, when the membrane has changed back to normal conditions, the membrane condition parameter ($P_{mc} = 0$) represents 0% of changes after denervation. The parameter P_{mc} can be tuned to the current state of membrane changes between 0 and 1.

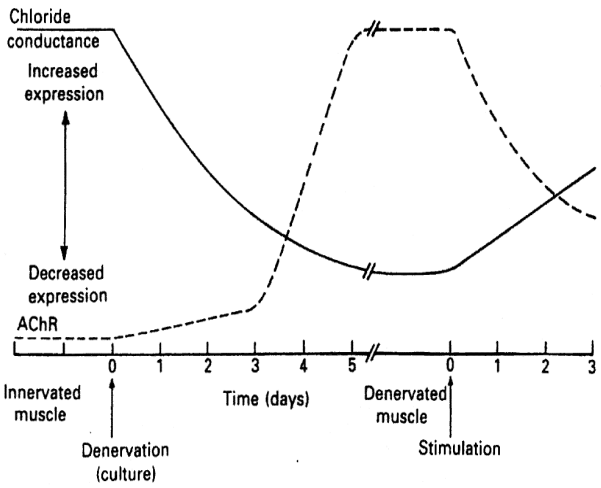

Fig. 1: Anticoordinate expression of chloride conductance and AChR. The diagram indicates the time course and relative magnitude of the changes seen in the experiment of [8]. The innervated muscle has a high chloride conductance, which decreases evenly after a few days of denervation to a lower level and keeps there at a stationary state. Soon after denervation AChR synthesis rises very slow but later the slope becomes steeper until a stationary state at the end is reached. After applying of FES both levels start to move back to the initial position (innervated muscle).

Considering this assumptions, the sum of the ionic current densities (3) can be rearranged, with the help of (4) by including the membrane condition parameter P_{mc}, to the form

$$\left(1 + \frac{P_{mc}}{2}\right) \cdot i_{Na} + i_K + \left(1 - \frac{P_{mc}}{2}\right) \cdot (i_L + \cdot g_L \cdot P_{cm} \cdot \Delta E_L) = 0, \quad (5)$$

where the influence of the sodium or the leakage current can be increased or decreased up to 50%, respectively.

3. Results

Caused by the dependence of membrane voltage of the stationary opening probabilities (m_∞ , n_∞ and h_∞) of the Hodgkin-Huxley type membrane model [9], the resting membrane potential V_{rest} cannot explicitly be calculated from (5). Instead of the explicit calculation an implicit method, like numerically iteration for finding zeros or graphically zero investigation, has to be considered.

In the course of this work, discrete membrane states from $P_{mc} = 0$ to 1 in steps of 0.1 has been calculated. To visualize the investigation of the resting membrane

condition, 2 cases for $P_{mc} = 0.1$ (case 1) and $P_{mc} = 0.9$ (case 2) are shown in Fig. 2.

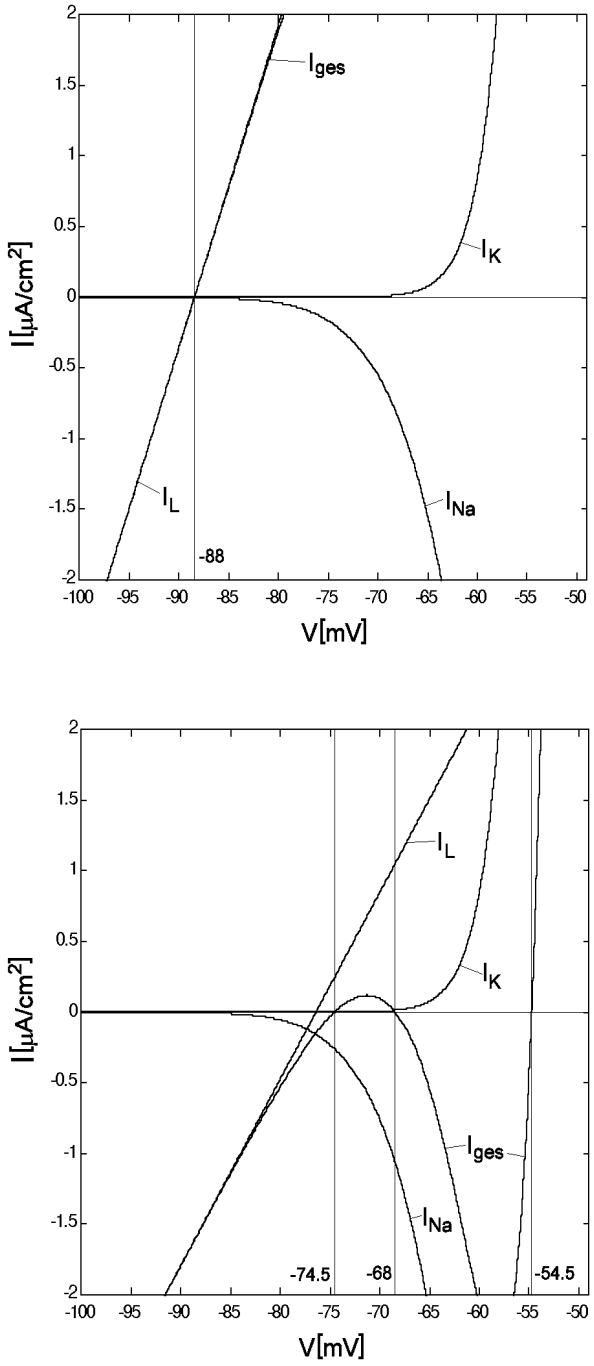

Fig. 2: Ionic currents in the area of V_{rest} for $P_{mc} = 0.1$ (upper picture) and $P_{mc} = 0.9$ (lower picture), where the sum of all currents $I_{ges} = 0$ is located at $V = -88mV$ in the upper and at $V = -74.5$, -68 and $-54.5mV$ in the lower case. The resting membrane potentials are –88 and –74.5mV, because the other solutions are above threshold voltage and not stable.

In case 1 ($P_{mc} = 0.1$) the resting membrane potential is only dependent on leakage or chloride current, respectively and can be determined at $-88mV$. In case 2 ($P_{mc} = 0.9$) an additional influence of the sodium current is evident and 3 solutions at -74.5, -68 and $-54.5mV$ can be seen. But only the first solution is stable, because the other solutions are above the threshold potential and would result in an spontaneous action potential. In both cases the potassium current has no effect on the change in resting membrane potential.

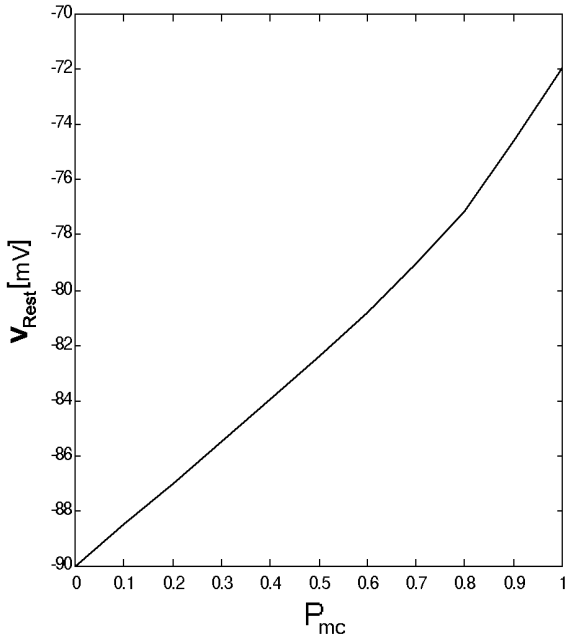

Fig. 3: Resting membrane potential V_{rest} dependent on the membrane state P_{mc}. Physiologically the membrane conditioning parameter is $P_{mc} = 0$ and for long term denervation $P_{mc} = 1$.

By collecting all stable solutions of the discrete membrane states mentioned above, the coherence between the membrane state P_{mc} and the resting membrane potential V_{rest} is shown in Fig. 3. The steeper ascent of V_{rest} for values of P_{mc} between 0.8 and 1can be explained by an increasing influence of sodium current.

In case of long term denervation ($P_{mc} = 1$) the resting membran potential is not stable, caused by a solution of (5) at a membrane potential above threshold potential. The result is the appearance of spontaneous action potentials (defibrillation potentials) in flaccid paralyzed skeletal muscle.

References

[1] Axelsson J & Thesleff S. (1959) A study of supersensitivity in denervated mammalian skeletal muscle. J. Physiol. Lond. 149:178-193.

[2] Miledi R. (1960) Junctional and extrajunctional ACh receptors in skeletal muscle fibers. J. Physiol. Lond. 151:24-30.

[3] Fambrough DM. (1979) Control of acetycholine receptors in skeletal muscle. Physiol. Rev. 59:165-227.

[4] Westgaard RH. (1975) Influence of activity on the passive electrical properties of denervated soleus muscle fibres in the rat. J. Physiol. Lond. 251:683-697.

[5] Camerino D & Bryant SH. (1976) Effects of denervation and colchicine treatment on the chloride conductance of rat skeletal muscle fibers. J. Neurobiol. 7:221-228.

[6] Lorkovic H and Tomanek RJ. (1977) Potassum and chloride conductances in normal and denervated rat muscle. Am. J. Physiol. 232(2):C109-C114.

[7] Harris GL & Betz WJ. (1987) Evidence for active chloride accumulation in normal and denervated rat lumbrical muscle. J. Gen. Physiol. 90:127-144.

[8] Heathcote RD. (1989) Acetylcholin-gated and chloride conductance channel expression in rat muscle membrane. J. Physiol. Lond. 414:473-497.

[9] Hodgkin AL and Huxley AF. (1952) A quantitative description of membrane current and ist application to conduction and excitation in nerve. J. Physiol. Lond. 117:500-544.

[10] Pappone PA. (1980) Voltage-Clamp experiments in normal and denervated mammalian skeletal muscle fibres. J. Physiol. Lond. 306:377-410.