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THEORETICAL ANALYSIS OF HUMAN MUSCLE MEMBRANE BEHAVIOR IN HYPOKALEMIC PERIODIC PARALYSIS

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Abstract– **Computer simulations were performed to investigate the behavior of human muscle membrane with membrane defects supposed to be present in the muscular disease Hypokalemic Periodic Paralysis (HOPP). The model used for simulation was a Hodgkin-Huxley model. The T-tubular system was also incorporated. It was studied whether the membrane defects caused the following recorded HOPP phenomena: a slight depolarization of a HOPP muscle cell when serum potassium is normal and a strong depolarization to -50 mV when serum potassium is low. In our model a constant small sodium leak conductance slightly depolarized the cell, whereas a small fraction of noninactivating sodium channels caused a strong depolarization. In the case of a dependency of this fraction on serum potassium according to a Boltzmann relation such a depolarization occurred only when serum potassium was low. In our simulations, the resting membrane potential moved from -90 mV to -30 mV after a single action potential when 8% or more of the sodium channels did not inactivate. Our results were qualitatively similar when the T-tubular system was decoupled.**

I. Introduction

Hypokalemic Periodic Paralysis (HOPP) is a muscular disease causing periodic muscle weaknesses. During an attack, the cell is depolarized to -50 mV [1]. Consequently, the sodium channels are in the inactivated state, which is the cause of the paralysis. Serum potassium is lower than normal during an attack. Serum potassium and Resting Membrane Potential (RMP) for normal and HOPP conditions are shown in Table 1.

The Goldman-Hodgkin-Katz equation predicts a hyperpolarization on reduction of serum potassium, so the depolarization in HOPP is an anomaly. It is thought to arise as a result of defects in membrane channels. The most important defects that were mentioned in earlier research [1] are: a. a decreased potassium conductance, b. an increased sodium conductance and c. an increased activity of the Na-K-pump. It was investigated whether these defects could account for the experimental data listed in Table 1.

Table 1: Serum potassium ($[K^+]_o$) and the RMP for normal and HOPP conditions [1].

		normal	HOPP
$[K^+]_o$	no attack	4 mM	4 mM
	attack	not appl.	2 mM
RMP	no attack	-85 mV	-75 mV
	attack	not appl.	-50 mV

II. Methods

A model of the electrical behavior of a human muscle cell membrane was taken from [2]. The model contained for both sarcolemma and T-tubule membrane a. the capacitive current, b. the delayed rectifier potassium conductance, c. the regenerative sodium conductance and d. a leak conductance. The coupling between the T-tubular system and the extracellular medium was modeled by an access resistance. With the model, current-voltage-curves (I-V-curves) in the quasi-steady state were calculated. The intersections of the I-V-curves with the voltage axis, being the membrane equilibrium potentials, were analyzed. Their stability was determined to investigate whether they were RMPs. In addition, the behavior of the membrane potential in time was investigated.

III. Results

A decreased potassium conductance hardly influenced the I-V-curve under normal conditions. An increased pump activity hyperpolarized the cell. A small constant sodium conductance slightly depolarized the cell when serum potassium was normal and low. A small constant fraction of noninactivating sodium channels introduced two extra equilibrium potentials (Fig.1), the right one being an extra RMP. The two extra equilibrium potentials disappeared when serum potassium was decreased (Fig.2), in contrast with the observations in HOPP. When a dependency of the fraction of noninactivating sodium channels on serum potassium as

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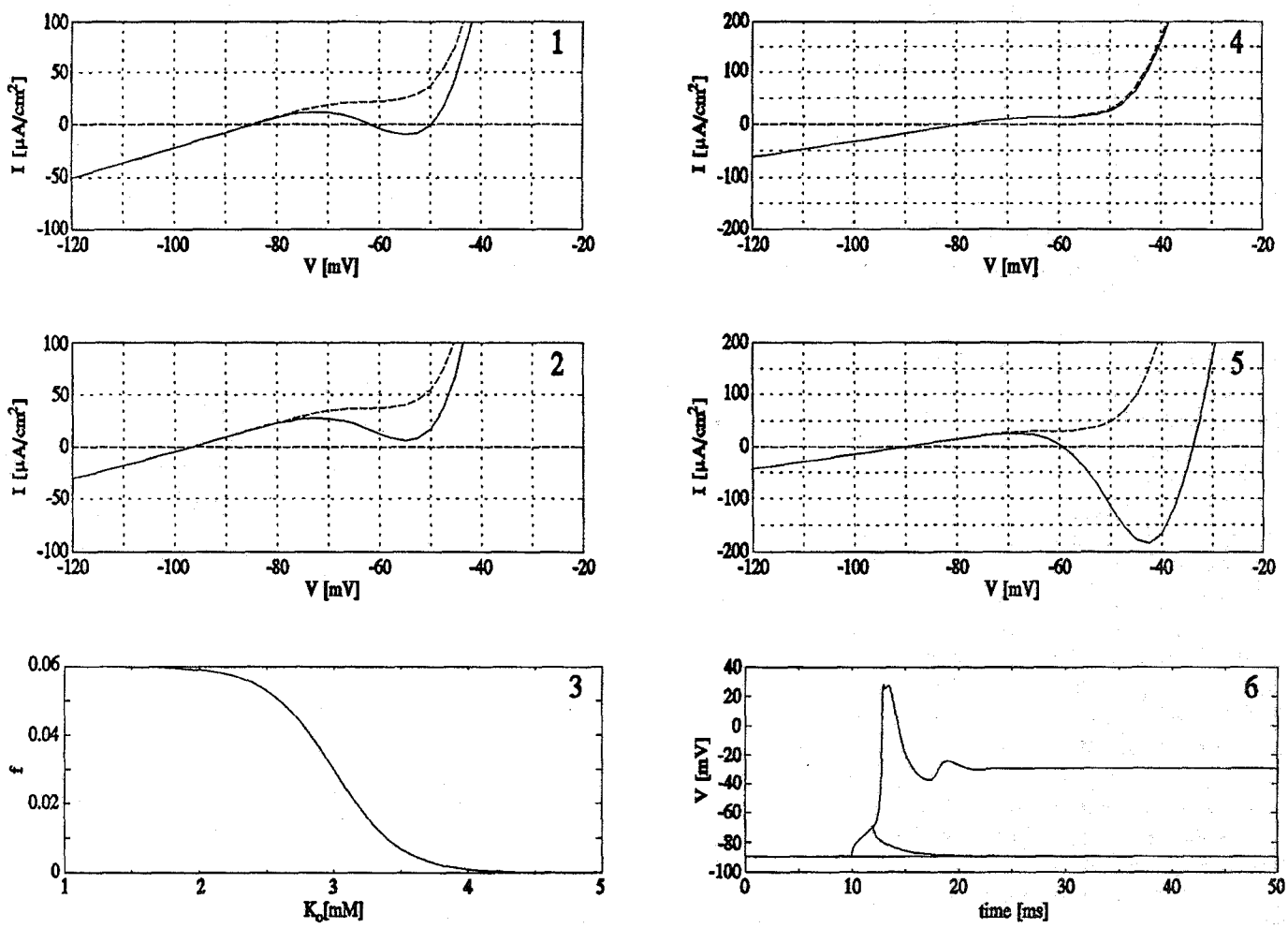

Fig.1-6: Simulation results. Fig.1 and 2 show the I-V-curves under normal conditions (–) and with 1.3% noninactivating sodium channels (–) when serum potassium was 4 mM and 2 mM respectively. Fig.3 shows the assumed dependency of the noninactivating fraction of sodium channels (f) on serum potassium and Fig.4 and 5 show the I-V-curves without (–) and with (–) this dependency when serum potassium was 4 mM and 2 mM respectively. Fig.6 shows the membrane potential in time resulting from stimuli just below and just above threshold when serum potassium was 2 mM and 8% of the sodium channels was noninactivating.

plotted in Fig.3 was used, it could bring about two extra equilibrium potentials. When serum potassium was normal, one RMP was present (Fig.4). When serum potassium was low, two more equilibrium potentials arose (Fig.5). The less negative one was an RMP, being a phenomenon corresponding to observations in HOPP. Moreover, the membrane potential moved from the most negative RMP to the less negative RMP after one action potential (Fig.6). Simulations of electrically isolated T-tubule membranes by means of an increased access resistance yielded qualitatively similar phenomena (not shown).

IV. Conclusions

In the simulations a small leak sodium conductance brought about a slight depolarization. A constant fraction of inactivated sodium channels could not account for a strong depolarization on reduction of serum potassium, but a fraction dependent on serum potassium as supposed could. When this fraction was great enough, the membrane potential moved from the more negative RMP to the less negative RMP after a single action potential.

V. References

[1] Links, T. P., "Familial hypokalemic periodic paralysis", Doctoral Thesis, University of Groningen, The Netherlands, 1992.

[2] Cannon, S. C., Brown, R. H., Jr., Corey, D. P., "Theoretical reconstruction of myotonia and paralysis caused by incomplete inactivation of sodium channels", *Biophysical Journal*, vol. 65, pp. 270-288, 1993.