Sodium-Potassium Movement and the Regulation of Cardiac Muscle Activity

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The changes in intracellular sodium activity and contractility produced by short-lasting application of a fast-acting cardiac glycoside were measured in guinea-pig ventricular muscle. It was found that under certain conditions the change in twitch tension paralleled the change in sodium activity. It is suggested that the electrogenic sodium pump may be involved in the regulation of both the mechanical and the electrical activity of cardiac muscle.

Two factors may contribute to the process of excitation concentration coupling in mammalian cardiac muscle: (i) the mechanism by which an action potential causes the release of Ca from intracellular stores and from the extracellular space into the sarcoplasm, and (ii) the mechanism by which the amount of releasable intracellular Ca is modulated. Of course these two factors are not independent of each other, but we think that it may be possible – and useful – to consider these two processes separately. The first process is still largely a matter of speculation. It is not yet clear (a) how the excitation of the T-system is transmitted to the sarcoplasmic reticulum [1, 2], (b) how the secondary inward current is related to the accompanying and the subsequent contractions [3 – 5], (c) what is the role of electrogenic Na/Ca-exchange during the plateau [6 – 8], (d) to which extent is Ca-induced Ca-release is involved [9].

Despite these uncertainties about the first process we think that our recent experimental results [10 – 12] may give some insight in the nature of the second process, *i.e.* the modulation of cardiac contractility.

The magnitude of the electrogenic pump current (I_p) in guinea-pig ventricular muscle was found to be about 1 μA/cm² in the steady state [10]. This suggests that the rate constant (k_{Na}) of the exchange of intracellular sodium in the steady state may be by an order of magnitude larger than assumed previously [13]. From the values of the surface/volume ratio of the cells [14], the coupling ratio of the Na/K-pump [15], the intracellular sodium activity (a_{Na}) [16, 17] and I_p [10] a value of 0.5 – 1 min^{-1} was calculated for k_{Na} [12].

Since the electrogenic pump current appears to be proportional to a_{Na} [15] one would expect a_{Na} to decay after an imposed Na load with a rate constant equal to k_{Na}. This prediction was tested by direct measurement of the rate of decay of a_{Na} with ion selective microelectrodes (liquid ion exchanger ETH 227). a_{Na} was first increased by inhibiting the electrogenic pump current with a fast-acting cardiac glycoside, dihydro-ouabain, for 2 – 3 min. After washout of the drug a_{Na} decayed to its resting value with a rate constant of 0.5 – 1 min^{-1} [11, 12], as predicted by our measurement of I_p.

These experiments with Na selective microelectrodes were carried out in unstimulated guinea-pig ventricular muscle. In subsequent experiments preparations of the same diameter (< 250 μm) were stimulated and the isometric force of contraction was measured with a piezoresistive transducer (Åkers). It was found that after washout of dihydro-ouabain contractility also decayed with a rate constant of 0.5 – 1 min^{-1} [12]. Furthermore after a sudden reduction of stimulation frequency the force of contraction approached its new steady-state value with a rate constant similar to k_{Na} ("descending staircase").

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The decay of contractility after a reduction of stimulation frequency was ascribed to the decay of the "positive inotropic effect of activation" (PIEA) by Blinks & Koch-Weser [18]. The rate constant (k_p) of the decay of the PIEA was found to be about $0.5-1\ min^{-1}$ a variety of animal species [19]. The striking similarity between k_{Na} and k_p makes it tempting to speculate that the PIEA may be associated with an increase of a_{Na}. This increase of a_{Na} may lead indirectly to an increase of the amount of Ca taken up by the SR, for example through its effect on the sarcolemmal Na/Ca exchange system [6, 12, 20, 21], or on the mitochondria [22]. Similar mechanisms have been suggested to explain the positive inotropic action of cardiac glycosides [12, 12, 23–28], of other cardioactive drugs [29–31], and the frequency-force relationship [13, 28].

If an increase of stimulation frequency does in fact lead to an increase in a_{Na} this is also expected to have a marked effect on action potential duration. This is so because the electrogenic pump current is large compared to the capacitive transmembrane current flowing at the plateau. Therefore any increase in a_{Na} – which leads to a change in I_p – would be expected to lead to a marked shortening of the action potential [32]. The idea that these mechanisms may have some functional importance is supported by the observation that under various experimental conditions changes in contractility are accompanied by inverse changes in action potential duration [33, 34].

Finally, it has been shown that cardiac pacemaker activity depends on a delicate balance of inward and outward currents [35–37]. The magnitude of the (hyperpolarizing) electrogenic pump current makes it very likely that any increase in a_{Na} – *e.g.* through an increase in heart rate – will influence this balances, and thus will tend to decrease pacemaker activity [38]. This may be a functionally important negative feedback loop.

This rather speculative review of the possible role of Na/K-exchange in the regulation of cardiac muscle activity may be summarized by the following points.

It is proposed that the Na/K-pump

(1) produces an electrogenic pump current of about $1\ \mu A/cm^2$ membrane in resting mammalian ventricular muscle,
(2) contributes about 6 mV to the resting potential in 3 mM external potassium,
(3) determines the rate and extent of the change in intracellular sodium activity following a change in heart rate,
(4) influences action potential duration through the effect of a_{Na} on the electrogenic pump current,
(5) influences cardiac contractility indirectly through the effect of a_{Na} on transmembrane Ca movements,
(6) may influence the generation of the heart rhythm through the effect of the electrogenic pump current on pacemaker activity.

In conclusion, it appears possible that the Na/K-ATPase simultaneously regulates the electrical and the mechanical activity of the heart.

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