The Influence of the Extracellular Potassium Concentration on the Glycoside Effects Upon Contractile Force and Action Potential Duration of the Guinea-Pig Papillary Muscle

Previous investigations have shown that the positive inotropic effect of cardiac active glycosides, such as that caused by a diminution of the extracellular potassium concentration to 1.2 mM or less, depends upon the sodium concentration in the extracellular fluid[1,2], in contrast to the inotropic effects of epinephrine and xanthine derivatives[4]. Both sodium-dependent inotropic effects are accompanied by a shortening of the plateau of the action potential (AP)[2,3].

A variation in the potassium concentration in the suspension medium of between 2.4 and 9.6 mM also strongly affects the inotropic action of 1 and $2 \cdot 10^{-5} M$ dihydro-ouabain upon the papillary muscle of the guinea-pig (Figure 1). The force of contraction as observed in a medium with 4.8 mM K^+ is not changed by an increase in the potassium concentration to 9.6 mM; it is slightly increased, however, by a diminution of $[K^+]$ to 2.4 mM (Figure 1a). The guinea-pig papillary muscle, therefore, is similar to the cat's papillary muscle in its response to a change in the extracellular $[K^+]$[5]. As the potassium concentration is lowered from 9.6 mM to 2.4 mM, the inotropic effect of the glycoside increases considerably and almost inversely proportional to the potassium concentration (Figures 1a and b). Experiments with epinephrine have shown that its positive inotropic action does not increase if the potassium concentration is lowered.

The increment in the inotropic glycoside effect is paralleled by an increase in the shortening of the action potential duration (Figures 1c and 2). This is greatest at the plateau phase (30% repolarization).

The shortening of the plateau of the AP indicates a change in the ionic conductance of the cellular membrane. The question arises as to whether a change in membrane conductance can enlarge the degree of activation of the muscle and thereby lead to an inotropic effect. It is during the time of the early plateau phase that the papillary muscle starts to develop tension (Figure 2); and the activation of the papillary muscle increases until about half of the peak tension is reached[6]. One explanation for such a mechanism would be the assumption that

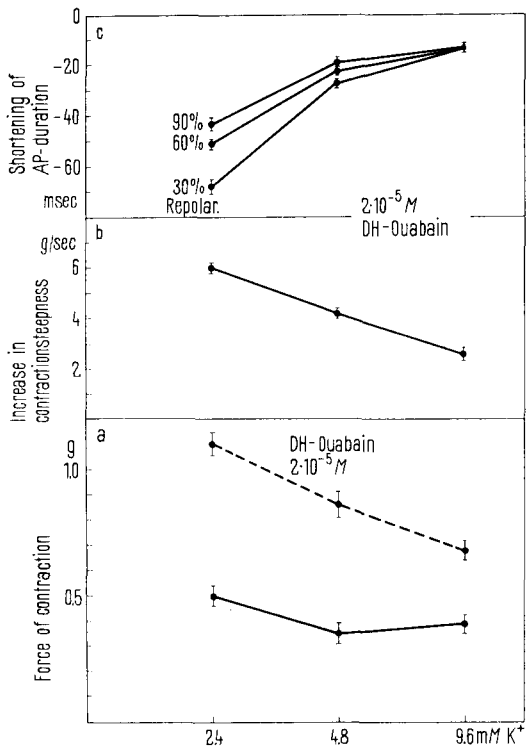

Fig. 1. The action of dihydro-ouabain ($2 \cdot 10^{-5} M$) upon force of contraction and action potential duration of the guinea-pig papillary muscle as affected by the extracellular potassium concentration. Mean values of 6 different papillary muscles. Krebs-Henseleit solution with 140 mM Na^+ and 3.2 mM Ca^{++}. Potassium concentration as indicated on the abscissa. Frequency of stimulation 1 c/sec. Temperature 35 °C. (a) Absolute values of force of contraction before and after the addition of the glycoside (mean values ± standard error). (b) Inotropic action of the glycoside expressed as the increase in contraction steepness (g/sec). (c) Shortening of the AP-duration (msec) at different stages of repolarization (30%, 60% and 90%, as indicated in the graph).

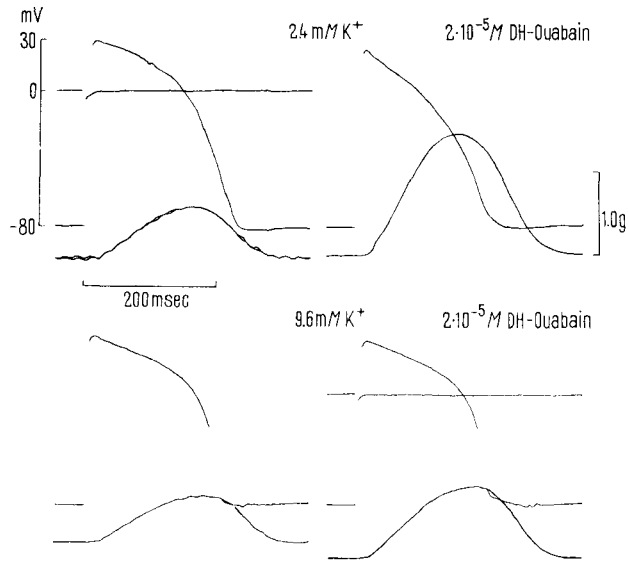

Fig. 2. The influence of dihydro-ouabain ($2 \cdot 10^{-5} M$) on the isometric contraction curve and the action potential of the guinea-pig papillary muscle at 2 different potassium concentrations (2.4 mM and 9.6 mM, as indicated). Papillary muscle of the right ventricle, length 6.0 mm, diameter 0.71 mm, resting tension 0.4 g. Stimulation frequency 1 c/sec. Temperature 35 °C. Krebs-Henseleit solution with 140 mM Na^+ and 3.2 mM Ca^{++}.

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the change in ionic conductance leads to an increase of the net influx of calcium ions due to the reduction of a backward flux of calcium during the time the papillary muscle is depolarized.

Zusammenfassung. Eine Verringerung der extrazellulären Kaliumkonzentration im Bereich zwischen 9,6 und 2,4 m*M* führt zu einer Zunahme der positiv inotropen Glykosidwirkung am Meerschweinchenpapillarmuskel; die Wirkung des Adrenalins wird nicht beeinflusst. Die Vergrösserung der inotropen Wirkung geht parallel einer starken Zunahme der Verkürzung der Aktionspotentialdauer, besonders in Höhe des Plateaus (30% Repolarisation).

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Post-Irradiation Induced Sensitization of Inhibition of Oxidative Phosphorylation by Iodoacetamide

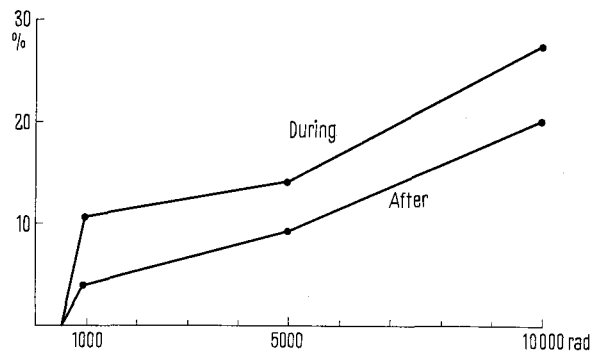
The potent sulphydryl poison iodoacetamide (IAA) and the related iodoacetate are known as radiosensitizers on death of mammals[1], inactivation of bacteria[2], loss of intracellular potassium and hemolysis of erythrocytes[3], etc. The mechanism of action is still largely unknown. With the aim of investigating the possibility that iodoacetamide inhibits post-irradiation repair processes[2], we investigated the effect of IAA on the oxidative phosphorylation during and after irradiation of rat liver mitochondria in vitro.

Method. The mitochondria of rat liver were isolated in the manner described earlier[4], diluted in tris buffer and irradiated by a Philips-MG 150 apparatus (6670 rad/min). After irradiation the mitochondria were reconcentrated and placed immediately in the incubation mixture. (Each flask contained in 3.95 ml: 24 μ moles $MgCl_2$; 39 μ moles KF; 5.76 μ moles DPN; 6.0 μ moles tris buffer, pH 7.4–7.5; 59 μ moles phosphate buffer; 30 μ moles AMP; 0.6 mg cytochrome c; 30 μ moles α-ketoglutarate; 0.5 mg hexokinase; 38.9 μ moles glucose; 5 μ moles ATP.) In one part of the experiments iodoacetamide was added during the irradiation at different concentrations to the mitochondrial suspension in buffer (pH 7.4 or 7.8). In another part IAA was given after irradiation, either immediately in the buffer with mitochondria or in the reaction mixture of the Warburg vessels. Oxygen consumption and loss of inorganic phosphate[4] was tested for 30 min at 20 °C (equilibration time 10 min).

A marked inhibition of oxidative phosphorylation can be seen when IAA is present during the irradiation of the mitochondrial suspension diluted in tris buffer and after removal from the suspension (total exposition time: 15 min) (Table I). IAA is known, like the iodoacetate, as an uncoupler of oxidative phosphorylation[5] and an inhibitor of oxygen uptake[6], but, with the concentration used of 1 m*M* IAA, the P:O ratios are not deeper than the ratios of non-treated controls. Irradiation with 10,000 rad alone alters only slightly the P:O ratio (inhibition 3–4%). The sensitization is largely dependent on the irradiation dose (Figure 1). When the IAA was given immediately after irradiation in the diluted suspension and removed after 10 min, we also observed a depression of the P:O ratios (Table II). The effect still remains when IAA is added 10 min after irradiation, but the P:O ratio of unirradiated sample is also depressed. The sensitizing effect is rever-

Table I. Application of IAA (concentration 1 m*M*, total 12 ml suspension) during the irradiation

Dose (rad)	No. of measurements	Change (%) in O_2 uptake	P:O ratio		Change (%) in P:O ratio
			Unirradiated	Irradiated	
500	6	− 35.9	2.35	2.36	–
1,000	6	+ 13.5	2.39	2.14	− 10.5
5,000	6	− 14.4	2.85	2.45	− 14
10,000 without IAA	18	− 12	2.08	1.53	− 27.4
10,000	18	− 16	2.25	2.17	− 3.6



Irradiation dose dependency of the sensitizing effect of IAA during (Table I) and after (Table II) irradiation.

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