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## **Specific dihydropyridines may affect gating properties of certain subsets of adenosin-triphosphate-dependent K-channels in myocardial tissue and hence modulate its response to ischaemia**

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# Specific Dihydropyridines May Affect Gating Properties of Certain Subsets of Adenosin-Triphosphate-Dependent K-Channels in Myocardial Tissue and Hence Modulate its Response to Ischaemia

H. Köppel, S. Vidalli, R. Schöllnast

It has been shown that dihydropyridines exert a cardio-protective effect during experimental ischaemia. This effect is reflected in a reduced K-efflux from the ischaemic tissue. Recently we have shown that ischaemic K-efflux is largely mediated by ATP-dependent potassium channels.

Using K-selective microelectrodes we studied the effect of nisoldipine on K-efflux during simulated ischaemia. While ischaemic K-efflux was Ca-dependent in stimulated preparations, surface K ( $K_o$ ) after 3 minutes of simulated ischaemia at one Hertz in the presence of 2.5 and 0 mM Ca was  $7.0 \pm 0.1$  and  $6.6 \pm 0.1$  mM respectively ( $n = 5$ ), it was independent of extracellular Ca in resting preparations. After 3 minutes of simulated ischaemia at rest in the presence of 2.5 and 0 mM Calcium  $K_o$  rose by  $2.1 \pm 0.0$  and  $2.1 \pm 0.0$  respectively ( $n = 5$ ) in the same preparation. In contrast,  $10^{-5}$  mM nisoldipine inhibited ischaemic K-efflux both in stimulated and resting preparations ( $K_o$  rose from 4.5 mM to  $7.1 \pm 0.1$  mM within 3 minutes of simulated ischaemia;  $n = 5$ ,  $\pm$  SEM, field stimulation 1 Hz), whereas in the presence of  $10^{-5}$  mM nisoldipine the same preparation showed a  $K_o$  of  $6.0 \pm 0.2$  after 3 minutes of simulated ischaemia.  $K_o$  after 3 minutes of simulated ischaemia in resting preparations without nisoldipine was  $6.7 \pm 0.1$  and  $5.5 \pm 0.1$  respectively ( $p < 0.0001$ ).

Our results show a cardioprotective action of nisoldipine during simulated ischaemia which leads to an inhibition of ischaemic K-efflux. We suggest a direct effect of nisoldipine on the  $K_{ATP}$ -channel. The latter is mainly responsible for ischaemic K-loss. *J Clin Basic Cardiol 2000; 3: 133–4.*

**Key words:** dihydropyridines,  $K_{ATP}$ -channels, myocardial ischaemia

It has been shown in many publications that calcium antagonists are protective against ischaemic injury [1–4]. In experimental studies nisoldipine was able to improve ventricular function [5–7]. Effects were reduction of infarct size, recovery of myocardial contractility, preservation of myocardial ultrastructure, an increased number of surviving myocytes, high energy phosphate concentrations and reduction of ischaemia-induced potassium efflux [8–10]. It has been shown that cardioprotective drugs reduce K-efflux from ischaemic myocardial cells. The present paper demonstrates this inhibitory action of nisoldipine on ischaemic guinea-pig papillary muscles.

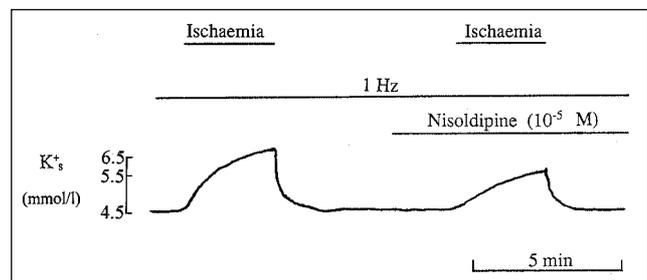
## Methods

In our experiments we used isolated guinea-pig papillary muscle superfused with normal Tyrode solution containing in mM: 140 NaCl, 4.5 KCl, 2.5 CaCl<sub>2</sub>, 1.0 MgCl<sub>2</sub>, Glucose 10, HEPES 20. The solution was adjusted to pH 7.4 by titration using 4 mM NaOH. Ion-selective microelectrodes were made as described in our earlier paper [11]. Values are quoted as  $\pm$  SEM,  $n = 3$  (at least) for all quoted experiments. In order to simulate ischaemia we used a modified version of the model first described by De Hemptinne and co-workers where the preparation was immersed in paraffin-oil. This was achieved by floating a drop of paraffin-oil on top of the meniscus in the experimental chamber, while maintaining a constant solution flow. The level of the aqueous-oil interface in the bath was then reduced electronically using a servo-controlled level device. For details see [11].

## Results

We found that after 3 minutes of ischaemia  $K_o$  rose from 4.5 to 7.0 mM and returned to 4.5 mM upon reperfusion. Nisoldipine at a concentration of  $10^{-5}$  mM led to a reduction of  $K_o$ -accumulation by approximately 30 % (see Fig. 1).  $K_o$  rose in 5 similar experiments from 4.5 to  $7.1 \pm 0.1$  ( $\pm$  SEM) under control conditions, in the presence of  $10 \mu$ M nisoldipine  $K_o$  rose to  $6.0 \pm 0.2$  in the same set of experiments ( $\pm$  SEM,  $n = 5$ ,  $p < 0.0001$ ).

While ischaemic K-efflux was Ca-dependent in stimulated preparations surface K ( $K_o$ ) after 3 minutes of simulated ischaemia at one Hertz in the presence of 2.5 and 0 Ca<sub>o</sub>



**Figure 1.** Potassium recordings on the surface of an isolated guinea pig papillary muscle in NT-solution. Ischaemic episodes are indicated with time bars. The preparation is stimulated at a frequency of 1 Hz. Surface recordings show the accumulation of potassium during simulated ischaemia with a subsequent decrease of surface potassium ( $K_s$ ) upon reperfusion. In the presence of nisoldipine potassium rises to a much lesser extent than in the presence of the drug.

was  $7.0 \pm 0.1$  and  $6.6 \pm 0.1$  mM respectively ( $n = 5$ ), it was independent of extracellular Ca in resting preparations (Fig. 2). After 3 minutes of simulated ischaemia at rest in the presence of 2.5 and 0 mM calcium  $K_o$  rose by  $2.1 \pm 0.0$  and  $2.1 \pm 0.0$  respectively ( $n = 5$ ) in the same preparation. In contrast,  $10^{-5}$  mM nisoldipine inhibited ischaemic K-efflux both in stimulated and resting preparations ( $K_o$  rose from 4.5 mM to  $7.1 \pm 0.1$  mM within 3 minutes of simulated ischaemia;  $n = 5$ ,  $\pm$  SEM, field stimulation 1 Hz), whereas in the presence of  $10^{-5}$  mM nisoldipine the same preparation showed a  $K_o$  of  $6.0 \pm 0.2$  after 3 minutes of simulated ischaemia.  $K_o$  after 3 minutes of simulated ischaemia in resting preparations without nisoldipine was  $6.7 \pm 0.1$  and  $5.5 \pm 0.1$  respectively ( $p < 0.0001$ ).

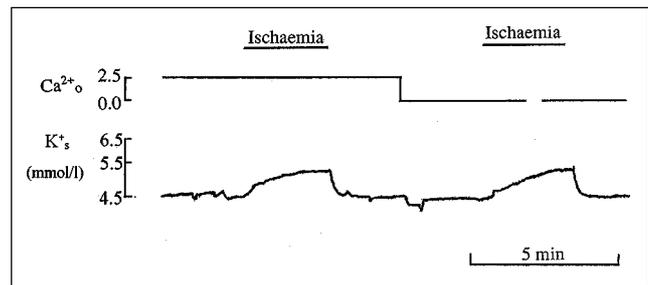
### Discussion

Our main finding is that extracellular potassium accumulation during simulated ischaemia is largely prevented by the dihydropyridine calcium antagonist nisoldipine. We find that nisoldipine reduces K-accumulation in stimulated as well as in unstimulated preparations. We also show that ischaemic K-efflux is rate dependent and depends also on the presence of calcium in stimulated preparations. We conclude that the reduction of ischaemia-induced K-efflux cannot be a result of inhibition of calcium-influx by nisoldipine but must be due to a direct effect of the drug on the pathway which mediates ischaemic K-efflux. The conclusion derives from the observation that in resting preparations reduced extracellular Ca to 0 mM does not inhibit K-efflux, whereas the addition of nisoldipine does.

The main mechanism of myocardial protection by calcium antagonists seems to vary among the different types of calcium antagonists. However, decreased myocardial oxygen demand (decreased afterload, decreased heart rate and a negative inotropic effect), a favourable redistribution of blood flow to the ischaemic areas and a direct cellular anti-ischaemic effect play the main roles. While our experiments do not look at effects on the coronary arteries, we are likely to look at effects such as decreased myocardial oxygen demand and direct cellular anti-ischaemic effects. A reduced oxygen consumption as a result of decreased Ca-influx will necessarily lead to both reduced oxygen demand and a minimised high energy phosphate depletion.

Calcium antagonists have a complex mode of action as far as reducing ischaemia-induced injury is concerned. Besides the mentioned energy-sparing effect of decreased contractility and decreased heart rate, they also show the loss of adenosine precursors. Calcium antagonists slow the release of lysosomal enzymes and exert a direct protective effect on the sarcolemma. The reduction of calcium entry into the cell before and during ischaemia also prevents excessive activation of calcium-dependent ATPases in the contractile apparatus, the sarcoplasmic reticulum and mitochondria which would enhance ATP-consumption. Calcium antagonists may also prevent overstimulation of Ca-activated phospholipases and specific proteases, which, apart from oxygen free radicals, are mainly responsible for cell necrosis and mitochondrial disintegration.

It has been stated that transmembrane K-conductance is partially dependent on intracellular calcium. Furthermore,



**Figure 2.** In a resting papillary muscle recordings of  $K_s$  show equal amounts of K-accumulation in the presence as well as in the absence of calcium (+EGTA).

the decrease of intracellular calcium resulting from calcium-antagonistic action has been associated with cellular K-leakage that occurs during myocardial ischaemia. The latter has been taken as a measure for ischaemic injury. However, in quiescent papillary muscles the removal of extracellular calcium does not affect ischaemic K-efflux, whereas nisoldipine does. This observation strongly argues in favour of a direct action of nisoldipine on ATP-dependent K-channels. The possibility of such an action receives further support by the observation of Charnet et al. [12], who found that dihydropyridines show unspecific K-channel inhibition, a phenomenon already seen by Kass and Tsien [13]. From our observations we conclude that ischaemic K-accumulation and its inhibition may not be an ideal measure for ischaemic injury or myocardial protection. The effects of Ca-antagonists on ischaemic K-efflux are likely to be direct unspecified actions of the drugs on K-efflux pathways.

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