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

Köppel H, Schöllnast R, Vidalli S
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 (Ks) after 3 minutes of simulated ischaemia at one Hertz in the presence of 2.5 and 0 mM Ca was 7.0 ± 0.1 and 6.6 ± 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 Ks rose by 2.1 ± 0.0 and 2.1 ± 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 (Ks rose from 4.5 mM to 7.1 ± 0.1 mM within 3 minutes of simulated ischaemia; n = 5, ± SEM, field stimulation 1 Hz), whereas in the presence of 10⁻⁵ mM nisoldipine the same preparation showed a Ks of 6.0 ± 0.2 after 3 minutes of simulated ischaemia. Ks after 3 minutes of simulated ischaemia in resting preparations without nisoldipine was 6.7 ± 0.1 and 5.5 ± 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 Kₐ₅₆-channel. The latter is mainly responsible for ischaemic K-loss. J Clin Basic Cardiol 2000; 3: 133–4.

Key words: dihydropyridines, Kₐ₅₆-channels, myocardial ischaemia

Results

We found that after 3 minutes of ischaemia Ks 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-efflux from the ischaemic tissue. While ischaemic K-efflux was Ca-dependent in stimulated preparations, surface K (Ks) after 3 minutes of simulated ischaemia at one Hertz in the presence of 2.5 and 0 mM Calcium Ks was 7.0 ± 0.1 and 6.6 ± 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 Ks rose by 2.1 ± 0.0 and 2.1 ± 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 (Ks rose from 4.5 mM to 7.1 ± 0.1 mM within 3 minutes of simulated ischaemia; n = 5, ± SEM, field stimulation 1 Hz), whereas in the presence of 10⁻⁵ mM nisoldipine the same preparation showed a Ks of 6.0 ± 0.2 after 3 minutes of simulated ischaemia. Ks after 3 minutes of simulated ischaemia in resting preparations without nisoldipine was 6.7 ± 0.1 and 5.5 ± 0.1 respectively (p < 0.0001).

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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 (Ks) upon reperfusion. In the presence of nisoldipine potassium rises to a much lesser extent than in the presence of the drug.

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From the Experimental Cardiology Unit, Medizinische Universitätsklinik Graz, Austria.
Correspondence to: Herwig Köppel, MD, Experimental Cardiology Unit, Med. Univ.-Klinik Graz, Auenbruggerplatz 15, A-8036 Graz, Austria
was 7.0 ± 0.1 and 6.6 ± 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 Ks rose by 2.1 ± 0.0 and 2.1 ± 0.0 respectively (n = 5) in the same preparation. In contrast, 10^-5 M nisoldipine inhibited ischaemic K-efflux both in stimulated and resting preparations (Ks rose from 4.5 mM to 7.1 ± 0.1 mM within 3 minutes of simulated ischaemia; n = 5, ± SEM, field stimulation 1 Hz), whereas in the presence of 10^-5 M nisoldipine the same preparation showed a Ks of 6.0 ± 0.2 after 3 minutes of simulated ischaemia. Ks after 3 minutes of simulated ischaemia in resting preparations without nisoldipine was 6.7 ± 0.1 and 5.5 ± 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, 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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