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

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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 (Kₐ) 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 Kₐ 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 (Kₐ 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 Kₐ of 6.0 ± 0.2 after 3 minutes of simulated ischaemia. Kₐ 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 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

Results

We found that after 3 minutes of ischaemia Kₐ 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 Kₐ-accumulation by approximately 30 % (see Fig. 1). Kₐ rose in 5 similar experiments from 4.5 to 7.1 ± 0.1 (± SEM) under control conditions, in the presence of 10⁻⁵ mM nisoldipine the same preparation showed a Kₐ of 6.0 ± 0.2 after 3 minutes of simulated ischaemia. Kₐ 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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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 K_o 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 (K_o 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 K_o of 6.0 ± 0.2 after 3 minutes of simulated ischaemia. K_o 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 extracellular potassium 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 specific K-channel inhibition, a phenomenon already seen by Kass and Tsen [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.

**References:**

7. Knorr AM. Why is nisoldipine a specific agent in ischemic left ventricular dysfuncion? Am J Cardiol 1983; 51: 363–40E.
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