Naringenin, a *Citrus* flavonoid, promotes cardioprotective effects, through the activation of mitochondrial BK channels

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Naringenin, flavonoid abundant in many fruits of the genus *Citrus* such as grapefruit and orange, exhibits endothelium-independent vasorelaxing effects on rat thoracic aorta and porcine coronary arteries, interacting, at least in part, with the sarcolemmal large-conductance calcium-activated potassium channels (BK) (Saponara et al., 2006; Kunaze et al., 2007).
Although no specific mechanism of action has been identified, anti-ischemic effects of *Citrus* extracts have been described in experimental models of ischemia/reperfusion (I/R) (Testai et al., 2013). Moreover in humans, the association between the dietary intake of *Citrus* fruits and a lower rates of acute coronary events has been reported (Yamada et al., 2011).
Recently, Cao et al. demonstrated that activators of BK channels expressed in cardiac mitochondria (mitoBK) trigger protective effects in several models of myocardial I/R (Cao et al., 2005).
Actually no study has been undertaken to investigate the possible interaction between BK-activating flavonoids and mitoBK channels. In this work we evaluated the potential cardioprotective activity of naringenin, and the involvement of mitoBK channels.
In an in vivo model of acute infarct in rats, naringenin (100 mg/Kg i.p.) significantly reduced the heart injury induced by I/R; this effect was antagonized by the selective BK-blocker paxilline. Noteworthy, this dose led to plasma concentration of naringenin in the low micromolar range, in agreement with the usual dietary consumption of *Citrus* fruits. Such a cardioprotective dose of naringenin did not cause significant effects on the blood pressure. The results obtained in Langendorff-perfused rat hearts submitted to I/R, were fully consistent with those observed in the vivo model, in fact naringenin led to the improvement of the post-ischemic functional parameters and to lower extension of myocardial injury.
In order to identify the possible role of mitoBK channels, further studies on isolated rat cardiac mitochondria have been carried out, by electropotentiometric and spectrofluorimetric methods. On these organelles, naringenin caused a concentration-dependent depolarization of mitochondrial membrane. Naringenin activated a trans-membrane flow of thallium (potassium-mimetic cation). Both these effects were antagonized by selective blockers of BK channels, paxilline and iberiotoxin, indicating that the effects evoked by this flavanone are largely due to activation of BK-mediated trans-membrane K^+ flows. Finally, naringenin also half-reduced the calcium uptake into the matrix of cardiac mitochondria exposed to high calcium concentrations. In conclusion, although a possible involvement of other mechanisms typical of most flavonoids cannot be excluded, this study demonstrated that naringenin exerts anti-ischemic effects through a 'pharmacological preconditioning' that it is likely to be mediated by the activation of mitoBK channels.

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