Role of mitochondrial KATP channels in the reduced cardiac tolerance to ischemic injury in the ageing

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Mitochondria play a critical role in the mechanisms of cardioprotection. In particular, the mitochondrial ATP-sensitive potassium channels (mitoKATP) represent an attractive target to develop novel strategies aimed at triggering mitochondrion-mediated pharmacological preconditioning (Testai et al., 2007).
Many experimental and epidemiological data correlate an increase of deaths due to myocardial injury with the age, suggesting that ageing compromises the cardiac resistance against the ischemic insult and reduces the endogenous cardioprotective defenses (Boengler et al., 2009). Ageing-related mitochondrial dysfunction, largely due to the oxidative stress, is likely to account for such an unsuccessfully cardioprotection. Furthermore, attenuated function of cardiac mitoKATP channel is observed in ageing mitochondria. Even if the cause (changes in channel density, responsiveness to stress stimuli or defective respiratory chain) is yet unknown (Liu et al., 2011), such a ion channel dysfunction might result in an ineffective KATP-mediated cardioprotection in ageing hearts.
On these bases, this work evaluated the possible different age-related behavior of rat cardiac mitochondria, exposed to the treatment with two mitoKATP openers, diazoxide (the reference mitoKATP opener) and compound A, a novel mitoKATP opener (Calderone et al., 2010).
Cardiac mitochondria were isolated from young (12-16 weeks) and aged rats (40-44 weeks), by differential centrifugations. Potentiometric and spectrofluorimetric methods were used, in order to evaluate the changes of mitochondrial membrane potential, as well as calcium and potassium ions movements across the organelle membranes.
The basal membrane potential was more depolarized in 'aged mitochondria', even if uncoupling agents showed a similar profile, suggesting that this dysfunction is not due to compromised oxidative phosphorylation.
On 'young mitochondria', both the mitoKATP openers induced a mild concentration-dependent membrane depolarization, a massive reduction of the driving force for the calcium up-take by the mitochondrial matrix. The use of thallium-sensitive fluorescence probe showed that the mitoKATP openers activated strong trans-membrane flow of thallium ions (thallium is a potassium-mimetic cation). A massive trans-membrane thallium flow was also induced in 'young mitochondria' by the potassium ionophore valinomycin. In contrast, on 'aged mitochondria', the mitoKATP openers did not produce significant changes in the membrane potential and did not affect the calcium ion movements. Noteworthy, even the valinomycin-induced thallium-flow was markedly reduced (by about 75%) in 'aged mitochondria'. This result suggests that a) 'aged mitochondria' show impaired KATP-mediated potassium currents and reduced pharmacological responses to mitoKATP-activators, and b) such a reduction in KATP-mediated potassium currents is unlikely to be related to a decreased density or efficiency of these channels, but is more probably due to an attenuated driving force for potassium entry into the matrix.

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