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Role of the MPTP in conditioning the heart - Translatability and mechanism

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Abstract

© 2014 The Authors. British Journal of Pharmacology published by John Wiley Sons Ltd on behalf of The British Pharmacological Society. Mitochondria have long been known to be the gatekeepers of cell fate. This is particularly so in the response to acute ischaemia-reperfusion injury (IRI). Following an acute episode of sustained myocardial ischaemia, the opening of the mitochondrial permeability transition pore (MPTP) in the first few minutes of reperfusion, mediates cell death. Preventing MPTP opening at the onset of reperfusion using either pharmacological inhibitors [such as cyclosporin A (CsA)] or genetic ablation has been reported to reduce myocardial infarct (MI) size in animal models of acute IRI. Interestingly, the endogenous cardioprotective intervention of ischaemic conditioning, in which the heart is protected against MI by applying cycles of brief ischaemia and reperfusion to either the heart itself or a remote organ or tissue, appears to be mediated through the inhibition of MPTP opening at reperfusion. Small proof-of-concept clinical studies have demonstrated the translatability of this therapeutic approach to target MPTP opening using CsA in clinical settings of acute myocardial IRI. However, given that CsA is a not a specific MPTP inhibitor, more novel and specific inhibitors of the MPTP need to be discovered - the molecular identification of the MPTP should facilitate this. In this paper, we review the role of the MPTP as a target for cardioprotection, the potential mechanisms underlying MPTP inhibition in the setting of ischaemic conditioning, and the translatability of MPTP inhibition as a therapeutic approach in the clinical setting.

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