Clinical and Experimental Pharmacology and Physiology (2015) **42**, 496–501 doi: 10.1111/1440-1681.12383

ORIGINAL ARTICLE

Preserved cardiac mitochondrial function and reduced ischaemia/reperfusion injury afforded by chronic continuous hypoxia: Role of opioid receptors

Leonid N Maslov,* Natalia V Naryzhnaya,* Ekaterina S Prokudina,* Frantisek Kolar,† Alexander S Gorbunov,* Yi Zhang,‡ Hongxin Wang,§ Sergey Yu Tsibulnikov,* Alla G Portnichenko,¶ Tatiana V Lasukova and Yury B Lishmanov***

**Laboratory of Experimental Cardiology, Federal State Budgetary Scientific Institution, Research Institute for Cardiology, Tomsk, Russia, †Department of Developmental Cardiology, Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic, ‡Department of Physiology, Hebei Medical University, Shijiazhuang, §Department of Pharmacology, Liaoning Medical College, Jinzhou City, China, ¶Bogomoletz Institute of Physiology, National Academy of Sciences of Ukraine, Kiev, Ukraine and **Tomsk State Pedagogical University, Tomsk, Russia*

SUMMARY

Chronic continuous normobaric hypoxia (CNH) increases cardiac tolerance to acute ischaemia/reperfusion injury. The objective of this study was to find out whether the cardioprotective effect of CNH mediated by opioid receptors is associated with preservation of mitochondrial function. Rats were adapted to CNH (12% oxygen) for 3 weeks. Isolated perfused hearts were subjected to 45 min of global ischaemia and 30 min of reperfusion; subgroups were pretreated with non-selective opioid receptor antagonist naloxone (300 nmol/L) for 10 min. Cardiac contractile function, creatine kinase activity in coronary effluent, mitochondrial respiration rate, and calcium retention capacity were assessed. Adaptation to CNH decreased myocardial creatine kinase release during reperfusion and improved the post-ischaemic recovery of contractile function, mitochondrial state 3 and uncoupled respiration rates, and calcium retention capacity compared to the normoxic group. These protective effects were completely abolished by naloxone. The contractile recovery positively correlated with state 3 respiration and calcium retention capacity. The results suggest that the preserved mitochondrial function contributes to the protected cardiac phenotype afforded by adaptation to CNH and point to an important role of opioid receptor activation.

Key words: cardioprotection, chronic hypoxia, ischaemia/reperfusion, mitochondrial function, opioid receptors.

INTRODUCTION

Heart function and viability critically depend on a continuous blood oxygen supply for energy production, such that a prolonged ischaemic insult with subsequent reperfusion results in irreversible myocardial injury. There is increasing evidence that mitochondria play a central role in myocardial susceptibility to ischaemia/reperfusion (I/R) injury, and that the preservation of mitochondrial function is essential for protecting the heart and its complete recovery from ischaemia.[1,2] Mitochondrial permeability transition pore (MPTP), a non-specific pore in the inner membrane, is now widely recognized as an important determinant of myocyte death or survival. Its full opening at early reperfusion, triggered by Ca^{2+} overload and a burst of reactive oxygen species production, disrupts the membrane permeability barrier and results in the uncoupling of oxidative phosphorylation, a drop in adenosine triphosphate (ATP) concentration, the activation of degradative enzymes, the release of pro-apoptotic factors, and finally in apoptotic and necrotic cell death.[3–5] The inhibition of MPTP opening, either with pharmacological agents directly targeting the pore component cyclophilin D or by interventions decreasing mitochondrial Ca^{2+} overload and oxidative stress associated with reperfusion, protects the heart from I/R injury.[6–9]

It has been well established that adaptation to various modes of chronic hypoxia confers an ischaemia-tolerant cardiac phenotype. Its important feature is that it persists much longer than conventional forms of cardioprotection. Rats adapted to intermittent hypoxia or neonatal rabbits raised in hypoxia exhibited an improved tolerance to I/R injury for several weeks after their transfer to a normoxic environment.[10,11] However, the precise mechanism underlying the cardioprotective effects of chronic hypoxia remains insufficiently understood, although a number of factors have been shown to play a role.[12] There is limited evidence that chronic intermittent hypoxia preserves myocardial Ca^{2+} handling, attenuates Ca^{2+} overload caused by I/R,[13–15] reduces lethal myocardial injury associated with Ca^{2+} paradox,[16] and inhibits MPTP opening induced by Ca^{2+} or reactive oxygen species.[17,18] However, it is unknown whether the inhibition of

Correspondence: Prof Leonid N Maslov, Laboratory of Experimental Cardiology, Federal State Budgetary Scientific Institution, Research Institute for Cardiology, Kyevskaya 111, Tomsk 634012, Russia.
Email: maslov@cardio-tomsk.ru

Received 31 October 2014; revision 12 December 2014; accepted 24 December 2014.