

Activation of peroxisome-proliferator-receptor α and γ mediates remote ischemic preconditioning against myocardial infarction

Although vast improvements have been made in the clinical care of patients suffering from an acute myocardial infarction, heart attacks still remain the number one cause of death in the Western world. A promising approach in overcoming this troublesome issue is to make use of an innate cardioprotective response: the ability of short ischemic episodes to precondition the heart against a subsequent prolonged ischemic insult. This powerful form of protection not only reduces the resultant damage up to 50%, but can also be initiated from a distance, such as by using repetitive blood-pressure cuff inflations and deflations, a phenomenon known as remote ischemic preconditioning (remote IPC). In the work published on page 113 of this issue of *Experimental Biology and Medicine*, Dr Lotz and co-workers used a clinically relevant animal model of remote IPC, as well as distinct biochemical markers to demonstrate an important role for the nuclear transcription factors peroxisome-proliferator-receptor (PPAR) α and γ within the signal paradigms of this powerful form of cardioprotection. Tobias Tischer-Zeitz, as part of his MD thesis, together with Christopher Lotz and other colleagues, carried out the work at the University of Würzburg, Germany.

Dr Lotz stated 'Remote ischemic preconditioning seems to be much easier to translate into the clinical setting compared to other forms of cardiac protection, in particular where the ischemic event can be anticipated, such as during cardiovascular surgery. However, to achieve a maximum benefit with minimal side-effects it is crucial to identify the molecular players governing the protective phenotype. This will allow a careful consideration of which cardioprotective intervention suits each individual patient.'

In the current study, Dr Lotz and his fellow researchers utilized repetitive cycles of renal ischemia/reperfusion as a remote stimulus to highlight PPAR α and γ as novel signaling elements of remote IPC. The data indicate that both nuclear receptors afford the protective effects of remote

IPC, as evidenced not only by increased PPAR-DNA-binding, but also by the loss of protection subsequent to their specific pharmacological blockade. Furthermore, the research team was able to link the activation of PPAR α and PPAR γ to increased myocardial mRNA levels of inducible nitric oxide synthase (iNOS), indicating the activation of a PPAR α /PPAR γ /NOS pathway to govern the production of the well-established preconditioning-mimetic nitric oxide (NO).

Dr Lotz said 'The study highlights a new signaling aspect of remote IPC, linking nuclear transcription factor signaling to a common and indispensable preconditioning mimetic, the production of NO. This not only helps to add another piece to the puzzle of cardioprotective signaling, but also speaks to the still controversial question of whether the activation of the PPARs benefits the ischemic heart.'

Remote IPC has shown promising results in recent clinical trials and although data from large multicenter trials are not available to date, it may soon prove to be an indispensable, as well as easily applicable tool to protect the ischemic heart. In this regard, it is important to shed light on the participating signaling networks as well as their inter-relationship. The current study comes into play here, establishing a novel link between PPAR signaling and NO during remote IPC, advancing the understanding of the molecular interactions leading to a reduced myocardial infarct size.

Steven R Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said 'Tischer-Zeitz, Lotz and colleagues have shed significant light on the molecular mechanisms behind the cardioprotection resulting from remote ischemic preconditioning. They have convincingly demonstrated a role for the nuclear transcription factors PPAR α and γ and their activation related induction of iNOS in this process.'

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