REMIFENTANIL AND CARDIAC PRECONDITIONING

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Cardiac preconditioning represents the most potent and consistently reproducible method of rescuing heart tissue from undergoing irreversible ischaemic damage. Major milestones regarding the elucidation of this phenomenon have been passed in the last two decades. Volatile anaesthetics and opioids effectively elicit pharmacological preconditioning. Anaesthetic-induced preconditioning and ischaemic preconditioning (IPC) share many fundamental steps, including activation of G-protein-coupled receptors, multiple protein kinases and ATP-sensitive potassium channels (KATP channels). Opioids activate δ and κ opioid receptors, and this leads to protein kinase C (PKC) activation. Activated PKC acts as an amplifier of the preconditioning stimulus and stabilizes, by phosphorylation, the open state of the mitochondrial KATP channel (the main end-effector in anaesthetic preconditioning) and the sarcolemmal KATP channel. The opening of KATP channels ultimately elicits cytoprotection by decreasing cytosolic and mitochondrial Ca2+ overload.

There is compelling evidence that preconditioning occurs in humans. However, there are conflicting reports on the efficacy of preconditioning in the diseased and aged myocardium. In addition, many anaesthetics and a significant number of perioperatively administered drugs affect the activity of cardiac sarcolemmal and mitochondrial KATP channels, the end-effectors of cardiac preconditioning, and thereby markedly modulate preconditioning effects in myocardial tissue. Although these modulatory effects on KATP channels have been investigated almost exclusively in laboratory investigations, they may have potential implications in clinical medicine. Important questions regarding the clinical utility and applicability of perioperative cardiac preconditioning remain unresolved and need more experimental work and randomized controlled clinical trials.

Remifentanil is a potent ultra-short-acting phenylpiperidine opioid that can be used in high doses for anaesthesia yet facilitating rapid recovery which makes it attractive as a practical preconditioning agent. In an animal preconditioning model we found a dose related reduction in infarct size after treatment with remifentanil that was similar to IPC. This effect was prevented or significantly attenuated by co administration of a μ, κ or δ-opioid receptor (OR) antagonist. The infarct sparing effect of ischemic preconditioning was abolished by blockade of κ - or δ - OR, but not μ -OR. Remifentanil mimics cardioprotection via all three ORs and this differs from IPC, which confers cardioprotection via κ- and δ-, but not μ-ORs. Part of remifentanil's protective effect may be produced by μ agonist activity outside the heart.

References

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