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Focused issue on K_{ATP} channels

K_{ATP} channels and preconditioning: A re-examination of the role of mitochondrial K_{ATP} channels and an overview of alternative mechanisms

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Abstract

Preconditioning by one or several brief periods of ischemia activates an endogenous cardioprotective program that increases the resistance of cardiomyocytes to injury by subsequent prolonged periods of ischemia. Ischemic preconditioning can be mimicked by K^+ channel openers and various other substances, a phenomenon termed pharmacological preconditioning. Initially, ischemic preconditioning has been ascribed to the opening of ATP-sensitive K^+ channels at the surface membrane of cardiomyocytes. Since 1997, numerous publications have implicated mitochondrial ATP-sensitive K^+ channels (mK_{ATP}) as a major trigger and/or end effector of preconditioning. Diazoxide has been suggested to be a specific activator of mK_{ATP} channels, and the substituted fatty acid 5-hydroxydecanoate (5-HD) has been suggested to be a specific inhibitor. However, diazoxide and 5-HD have multiple K^+-channel-independent actions, and the experimental evidence for an obligatory role of mK_{ATP} channels in preconditioning, or even their existence, remains inconclusive. In contrast, surface K_{ATP} channels have been well characterized, and we summarize the evidence suggesting that they make a major contribution to preconditioning. We also discuss a number of other factors involved in preconditioning: (1) generation of reactive oxygen species, (2) impairment of fatty acid metabolism, and (3) opening of the mitochondrial permeability transition pore. In the light of these emerging concepts, we critically re-examine the evidence for and against a role of mK_{ATP} channels in ischemic and pharmacological preconditioning.

Keywords: Diazoxide; 5-Hydroxydecanoate; K_{ATP} channels; Ischemic preconditioning

1. Introduction

Preconditioning activates a powerful endogenous adaptive mechanism that increases the resistance of the heart to ischemia and could potentially increase the chances of survival under pathophysiological conditions. Two different types of ATP-sensitive potassium channels have been implicated in preconditioning: surface membrane K_{ATP} (sK_{ATP}) channels and mitochondrial K_{ATP} (mK_{ATP}) channels. The structure and function of sK_{ATP} channels have been investigated extensively, whereas the subunit composition and the gene(s) coding for putative mK_{ATP} channels are still unknown. Both channels are presumed to be regulated by changes in energy metabolism and to have cardioprotective effects.

The central question of this review is whether mK_{ATP}, sK_{ATP} or both of these channels play a role in ischemic and/or pharmacological preconditioning. We first provide an overview of the phenomenon of preconditioning and outline the concept of mK_{ATP} channels as a major mediator of preconditioning (Section 2). Despite a large body of work on intact hearts and on simplified models of preconditioning, doubts persists as to the plausibility of current hypotheses about mK_{ATP} channels as triggers and/or effectors of preconditioning. By nature of their localization, mK_{ATP} channels are difficult to study. We therefore discuss the experimental evidence for the presence of mK_{ATP} channels in the mitochondrial inner membrane in some detail and point out the merits and pitfalls of the different methodological approaches (Section 3).

The main tools for discriminating between mK_{ATP} channels and sK_{ATP} channels are the K^+ channel openers diazoxide, nicorandil and pinacidil and the blockers 5-hydroxy-

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decanoate (5-HD), HMR1098 and glibenclamide. However, several recent studies have questioned the usefulness of these substances for defining and characterizing mK_{ATP} channels. To assess the validity and limitations of the pharmacological approach to channel characterization, we provide an analysis of the effects of diazoxide and 5-HD on mK_{ATP} channels and on other targets (Section 4). On the basis of the available data we summarize our view of the role of mK_{ATP} channels in preconditioning. In addition, we discuss the possible role of other mitochondrial K^+-selective channels in regulating matrix volume and the potential of the mitochondrial inner membrane (Section 5).

The surface K_{ATP} channel is a sensor of the metabolic state of the cells that is modulated by a variety of metabolic intermediates. It is clear that it does contribute to the effects of preconditioning, but the extent of its contribution is still under debate. We discuss the mechanisms of regulation of the sK_{ATP} channel that may be relevant under conditions of ischemia, and we summarize the pharmacology of sK_{ATP} channels, emphasizing similarities and differences between sK_{ATP} and mK_{ATP} channels (Section 6). We then go on to summarize the information available about the role of sK_{ATP} channels in preconditioning (Section 7). Finally, we give an overview of the most important alternative mechanisms of preconditioning. In particular, the profound alterations of fatty acid metabolism occurring during ischemia and reperfusion, as well as the regulation of the mitochondrial permeability transition pore by reactive oxygen species may play a role as mediators or effectors of cardioprotection (Section 8).

The intention of this review is not to say that the current view of the mK_{ATP} channel as the principal mediator of preconditioning is necessarily incorrect, or that mK_{ATP} channels do not exist. In fact, there is ample evidence for the existence of K^+ channels in the mitochondrial inner membrane, and there is growing consensus that ion channels are involved in the regulation of matrix volume, matrix calcium and respiratory rate. Rather, we want to point out that the properties ascribed to mK_{ATP} channels on the basis of pharmacological experiments should not be considered as established facts. It is not yet clear whether the mitochondrial inner membrane is endowed with channels that bear any resemblance to surface K_{ATP} channels, and alternative hypotheses for the cellular defense mechanisms against ischemic damage also need to be considered. In the summary and conclusions of this review we try to weigh the evidence for and against a role of mK_{ATP} and sK_{ATP} channels in preconditioning in the light of recent findings, and we try to give an integrated picture of the mechanisms involved in protecting the heart against ischemic injury.

2. Studies of preconditioning in the intact heart

2.1. The phenomenon of preconditioning

The term ischemic preconditioning (IPC) refers to the observation that one or several intermittent periods of ischemia (lasting ~ 5 min) protect the myocardium against the injury caused by a subsequent, prolonged period of ischemia (lasting ~ 30 min), which is denoted index ischemia [1–4]. There are two windows of protection: the initial window which lasts 1–2 h after the preconditioning stimulus ("classic IPC") and the 'second window of protection' which is less effective but covers a longer period. It occurs about 24 h after the preconditioning stimulus and lasts about 72 h. The possible mechanisms underlying the second window of protection have been reviewed elsewhere [3,5,6] and will not be discussed here. The cardioprotective effect of brief periods of ischemia can be mimicked by exposing the heart to various drugs, a phenomenon termed pharmacological preconditioning (PPC). The drugs used for PPC include K^+ channel openers (diazoxide, pinacidil and nicorandil), volatile anesthetics (halothane, desflurane, isoflurane and sevoflurane) [7], various agonists of G protein-coupled receptors (adenosine, bradykinin, catecholamines and opioids) [6,8–13], succinate dehydrogenase blockers (3-nitropropionic acid) [14], carbonmonoxide releasing molecules [15] and Na^+/H^+ exchange blockers (cariporide and ethylisopropyl amiloride) [16]. In most cases, PPC produces a similar degree of protection against subsequent ischemic injury as IPC.

It is generally assumed that preconditioning activates endogenous intracellular defense mechanisms that increase the tolerance to injury [3,6]. These endogenous cell survival programs are probably highly complex and depend, among other factors, on mitochondrial and cytosolic energy metabolism and the electrical activity of the cells [3,17,18]. A schematic description of the protection afforded by IPC and PPC is given in Fig. 1, which shows that the activation of cardioprotective mechanisms does not prevent, but rather delays cellular death. When the optimal preconditioning stimulus (brief episodes of ischemia or application of cardioprotective drugs) and the optimal duration of the index ischemia (usually 30–40 min) are chosen, infarct size after reperfusion is substantially reduced as compared to control, i.e. the infarct size measured without preconditioning. However, with shorter or longer duration of the index ischemia the difference between hearts with and without preconditioning stimulus is much less conspicuous. In other words, the effectiveness of preconditioning (reduction of infarct size compared to control) depends critically on the duration of the index ischemia chosen. Furthermore, the effectiveness of preconditioning depends on the timing of the index ischemia. When the interval between the conditioning stimulus and the onset of the index ischemia is postponed, the cardioprotective effect becomes smaller and eventually disappears within 2 h, indicating the time course of the decay of the defense mechanisms involved in IPC.

It is likely that preconditioning also occurs in human heart [3,6,19], and the elucidation of the mechanisms underlying the increased tolerance to ischemia is of considerable clinical importance [3,20–24]. Although the most extensive studies of preconditioning have been carried out in the heart, similar protective phenomena induced by short periods of ischemia have also been reported for the brain, skeletal muscle [25–27], kidney [28] and liver [29,30].