Role of p38 Mitogen-Activated Protein Kinases in Preconditioning

A Detrimental Factor or a Protective Kinase?

Peipei Ping, Elizabeth Murphy

Preconditioning, the phenomenon whereby brief episodes of ischemia or pharmacological agents protect the myocardium against subsequent ischemic injury, consists of an early and a late phase. The early phase develops immediately and disappears within 1 to 2 hours of ischemic preconditioning stimulus, whereas the late phase, also known as the “second window” of protection, becomes manifest after 12 to 24 hours and lasts for 3 to 4 days. An understanding of the signaling mechanisms that trigger and mediate this cardioprotective phenomenon would have vast physiological and pathological implications. Accordingly, many recent studies have focused on the characterization and delineation of the signal transduction pathways (molecules) underlying the development and manifestation of both the early and late phases of preconditioning. The general hypothesis is that the preconditioning stimulus will induce the activation of a cascade of stress-responsive kinases, which in turn transduce the stress signal into the generation of a protective protein or activation of a protective kinase. In this context, the p38 mitogen-activated protein kinases (MAPKs), a family of stress-activated MAPKs, have been examined as the candidate kinases during preconditioning.

In this issue of Circulation Research, Dana et al. report that the adenosine A₁ agonist 2-chloro-N'-cyclopentyladenosine (CCPA) induces a late phase of preconditioning in rabbit hearts. Twenty-four hours after the transient activation of the adenosine A₁ receptor, the myocardium exhibited a significant rise in the activity of p38 MAPK. The increased p38 MAPK activity was completely abolished when the infarct-sparing effect of CCPA was abrogated by either the protein kinase C (PKC) inhibitor chelerythrine or the tyrosine kinase inhibitor lavendustin A. This is a very provocative study, and it is also the first to demonstrate activation of the p38 MAPK 24 hours after preconditioning. The data are compatible with the hypothesis that p38 MAPKs may mediate the protective signaling pathways or function as protective kinases during the late phase of pharmacological preconditioning. However, this conclusion is based on the correlation between activation of p38 MAPK and protection. Before the role of p38 MAPK in late preconditioning can be definitely established, it is necessary to show that the inhibition of p38 MAPK blocks the protection. If activation of p38 MAPKs is a necessary signaling event for the protection to manifest on day 2, then inhibition of this kinase will lead to the abrogation of late preconditioning.

The role of the p38 MAPK signaling pathway in the early phase of preconditioning has been more extensively investigated. However, the published observations are inconsistent, and the role of p38 MAPKs in early preconditioning seems to be controversial. The two lines of studies performed thus far have sought to determine (1) whether preconditioning induces the activation of p38 MAPKs and (2) whether inhibition of p38 MAPKs abrogates the cardioprotective effect. Unfortunately, both have yielded conflicting results. In the first line of studies, it remains uncertain whether ischemia/reperfusion induces sustained activation of p38 MAPKs. Ischemia stimulus has been shown to induce activation of p38 MAPKs. Furthermore, ischemic preconditioning activates MAPKAPK2, the downstream signaling substrate of p38 MAPK, demonstrating that activation of the p38 MAPK signaling cascade, not just one element of the MAPK module, is part of the signaling events involved in preconditioning. Although activation of p38 MAPK has been confirmed in several studies, the temporal aspects of the activation have been a point of debate. Several studies have reported that activation of p38 MAPKs during ischemia is transient and does not correlate with the preconditioning effect, thereby questioning the functional significance of this observation. In the second line of studies, at the center of the controversy are data obtained using the specific p38 MAPK inhibitors (SB 203580 or SB 202190). Inhibition of p38 MAPK was shown to completely block the cardioprotective phenomenon in several studies, indicating that activation of p38 MAPK is an essential signaling event in the genesis of preconditioning. In apparent contradiction to these findings, several recent studies report that SB 203580 and SB 202190 can function as cardioprotective compounds, implying that they improve posts ischemic functional recovery, delay myocardial cell death, and precondition cardiac myocytes against simulated ischemia. These studies suggest that, far from playing a protective role, activation of the stress kinase p38 MAPK may be detrimental to the heart and inhibition of this stress-activated kinase will protect the myocardium.
What could be the reasons for the discrepancies of these studies? One obvious explanation has to do with the experimental models and animal species. The experimental models used to test the role of p38 MAPKs are vastly different, ranging from isolated perfused rabbit hearts,6 rat hearts,5,10 and pig hearts,7,11 to cultured cardiac cells6,9 and biopsy tissue samples from human hearts.12 The preconditioning protocols differ among studies, and the endpoints examined are also different in each investigation. To a certain extent, these factors may have contributed to the conflicting observations. Nevertheless, a mechanism that is not conserved across species is arguably less significant than one that is manifest in multiple biological systems. The fact that the expression of p38 MAPKs is strikingly significant than one that is manifest in multiple biological mechanisms that is not conserved across species is arguably less important than one that is manifest in multiple biological systems. Thus, a second plausible explanation for the p38 MAPK controversy may be the differential actions of individual isoforms of the p38 MAPK family. One critical missing piece of the puzzle in all of the above reports is the effect of preconditioning on the activity of individual p38 MAPK isoforms and their corresponding downstream substrates. Characterization of the myocardial expression of all p38 MAPK isoforms and their downstream signaling targets would be necessary prerequisites for these studies. For example, selective activation of only one p38 isoform may result in an apparent lack of activation of the entire p38 MAPK family, a phenomenon that has been documented with the role of PKC isoforms in preconditioning. Indeed, one of the most powerful arguments against a role of PKC in preconditioning is the observation that total PKC activity did not increase after a preconditioning stimulus.15 However, it was found subsequently in rabbits that preconditioning induces selective activation of only 2 of the 11 known PKC isoforms (ε and η) and is insufficient to elevate total PKC activity.16 The third possibility for the inconsistencies resides in the efficacy and selectivity of the pyridinimidazole compound SB 203580. Although this agent has a potent effect on the activity of the p38α and p38β MAPKs, its efficacy for the p38γ and p38δ isoforms is low.17 Moreover, at a higher concentration (IC50 = 5 μmol/L), this compound will inhibit the c-Jun N-terminal kinase (JNK) family of MAPKs17 and phosphatidylinositol 3 (PI3) kinase/protein kinase B,18 and both the JNK and PI3 kinases have been shown to be recruited by ischemic preconditioning.13,19 It is difficult to assess the precise intracellular concentrations of this compound achieved in the isolated-perfused heart models; however, it is highly likely that the concentration of the inhibitor used may vary in different studies. This may have contributed to the inconsistent findings in the literature.

In summary, targeted activation or inhibition of individual p38 MAPK isoforms will be essential to provide conclusive evidence to either support or refute the role of p38 MAPKs in the early and late phases of preconditioning. The development of isoform-specific pharmacological inhibitors or transgenic mice expressing a cardiac-specific individual p38 MAPK isoform (in its active or trans-dominantly negative form) should provide important contributions to resolving this controversy.

References

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doi: 10.1161/01.RES.86.9.921

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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