Glucocorticoid Protection Against Myocardial Ischemia-Reperfusion Injury
Central Role for the PGD₂-Nrf2 Pathway

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Endogenous glucocorticoids have long been recognized to play a pivotal role in orchestrating an adaptive response of the host to stress, from trauma and infection to inflammation. Therefore, it is not surprising that glucocorticoids received considerable attention as potential therapeutic agents for acute myocardial infarction. Numerous studies documented their ability to protect the heart from ischemia-reperfusion injury in many animal and in vitro models. However, clinical trials with glucocorticoids for the treatment of acute myocardial infarction have yielded inconsistent results, with both a small beneficial effect on mortality and adverse influence on longer term remodeling being reported. A likely explanation for these discrepant observations is that the benefits of local anti-inflammatory actions of glucocorticoids in the ischemic heart are offset by adverse systemic effects. Thus, understanding of the mechanisms underlying local protective actions of glucocorticoids is of particular importance. In most cell types, glucocorticoids suppress prostaglandin biosynthesis that contributes to dampening of inflammation. By contrast, glucocorticoids were found to upregulate cyclooxygenase-2 expression in rodent cardiomyocytes, suggesting that it may also evoke Nrf2 activation in the heart in vivo. 15d-PGJ₂ is a well-characterized degradation product of cyclooxygenase-2 (COX-2)–like 2 (Nrf2) pathway. Nrf2 is a basic leucine-zipper transcription factor that regulates transcription of genes coding for a multitude of antioxidant enzymes. The Nrf2 pathway is the primary cellular defense against the cytotoxic actions of oxidative stress. The activity of Nrf2 is regulated via its interaction with Kelch-like ECH–associated protein 1 (Keap1) that directs its proteosomal degradation and to a lesser extent via phosphorylation by various protein kinases and epigenetic factors. Using an elegant combination of receptor-knockout mice, pharmacological tools, and siRNA technology, Katsumata et al demonstrate convincingly that PGD₂ and its spontaneous dehydration product 15-deoxy-D12,14-prostaglandin J₂ (15d-PGJ₂) bind to different receptors, prostaglandin F₂α receptor (FP) and peroxisome proliferator-activated receptor γ (PPARγ), respectively, rather than the canonical PGD₂ receptors, DP1 or DP2, to activate Nrf2.

An unexpected observation was that 15d-PGJ₂ induced Nrf2 activation much faster than the parent molecule, suggesting that rapid metabolism of PGD₂ may be required for initial cardioprotection. 15d-PGJ₂ has 2 reactive carbonyl groups that can initiate irreversible alkylation of cysteine residues of Keap1, thereby allowing Nrf2 to escape proteosomal degradation. Furthermore, among its other actions, 15d-PGJ₂ was found to modify proteins important for NF-κB signaling covalently, thereby likely contributing to reducing inflammation. However, these actions would not require receptor-mediated signaling. Whether biologically significant amounts of PGD₂ are converted into 15d-PGJ₂ in vivo has been a subject to controversy. Katsumata et al now show that 15d-PGJ₂ at low nanomolar concentrations that can be detected in tissues could stimulate expression of Nrf2 target genes in cultured cardiomyocytes, suggesting that it may also evoke Nrf2 activation in the heart in vivo. 15d-PGJ₂ is a well-characterized ligand for PPARγ and does not bind to prostaglandin F₂α receptor or DP1. Previous studies documented the ability of PPARγ agonists other than 15d-PGJ₂ to attenuate injury to cardiomyocytes but did not address the involvement of the Nrf2 pathway. The different kinetics of Nrf2 activation by PGD₂ and 15d-PGJ₂ is consistent with sustained Nrf2 activation in the heart in response to dexamethasone treatment although it remains to be investigated whether PGD₂ and 15d-PGJ₂ evoke simultaneous or sequential Nrf2 activation. Likewise, additional studies are needed to assess the impact (if any) of dexamethasone on PGD₂ metabolism.

The data presented by Katsumata et al clearly demonstrate a critical role for Nrf2 activation in protecting the mouse heart against ischemia-reperfusion injury, noting enhanced Nrf2 activation with associated augmentation of transcription of several genes encoding for proteins that are crucial for antioxidant defense. Consistently, dexamethasone-induced improvement of functional recovery after ischemia-reperfusion injury was markedly blunted in Nrf2 null and in prostaglandin F₂α receptor–deficient mice, as well...
Although the study of Katsumata et al. identifies Nrf2 as a potential target for therapy of myocardial ischemia-reperfusion injury, several important questions about the PGD$_2$-Nrf2 pathway remain to be resolved. Is dexamethasone-evoked PPAR$\gamma$-mediated increase in Nrf2 mRNA a prerequisite for subsequent activation of Nrf2 protein by PGD$_2$ via FP? Is FP expression altered during myocardial ischemia-reperfusion and, therefore, the explanation for relative PGD$_2$ specificity for cardiomyocytes? Does PGD$_2$ bind simultaneously to DR1 and FP, leading to enhanced cardioprotection? Would dexamethasone stimulate PGD$_2$ biosynthesis and exert cardioprotective actions when administered as a treatment (i.e., during ischemia)? From a mechanistic perspective, it will be interesting to see future studies about involvement of Keap1, various protein kinases, and epigenetic factors in regulating PGD$_2$ and 15d-PGJ$_2$ in other cell types/tissues, it remains a future challenge to investigate whether therapeutic interventions aimed to enhance myocardial Nrf2 activation selectively without mimicking the effects of glucocorticoids on innate and adaptive immunity could have clinical benefits.

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None.

**References**

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