Glucocorticoid Protection Against Myocardial Ischemia-Reperfusion Injury
Central Role for the PGD$_2$-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 and exert cytoprotective effects via activation of lipocalin-type prostaglandin D (PGD) synthase–mediated PGD$_2$ synthesis. However, PGD$_2$ receptors and downstream signaling pathways have not been characterized in this study.

In this issue of *Hypertension*, Katsumata et al$^4$ fill this important gap in our knowledge by demonstrating that the cardioprotective actions of endogenous PGD$_2$ are mediated predominantly through activation of the nuclear factor (erythroid-derived 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.$^8$ The activity of Nrf2 is regulated via its interaction with Kelch-like ECH–associated protein 1 (Keap1) that directs its proteasomal degradation and to a lesser extent via phosphorylation by various protein kinases and epigenetic factors.$^3$ Using an elegant combination of receptor-knockout mice, pharmacological tools, and siRNA technology, Katsumata et al$^4$ demonstrate convincingly that PGD$_2$ and its spontaneous dehydration product 15-deoxy-Δ12,14-prostaglandin J$_3$ (15d-PGJ$_2$) bind to different receptors, prostaglandin F$_{2\alpha}$ receptor (FP) and peroxisome proliferator-activated receptor $\gamma$ (PPAR$\gamma$), respectively, rather than the canonical PGD$_2$ receptors, DP1 or DP2, to activate Nrf2.

An unexpected observation was that 15d-PGJ$_2$ induced Nrf2 activation much faster than the parent molecule, suggesting that rapid metabolism of PGD$_2$ may be required for initial cardioprotection. 15d-PGJ$_2$ has 2 reactive carbonyl groups that can initiate irreversible alkylation of cysteine residues of Keap1, thereby allowing Nrf2 to escape proteasomal degradation.$^6$ Furthermore, among its other actions, 15d-PGJ$_2$ was found to modify proteins important for NF-$\kappa$B signaling covalently, thereby likely contributing to reducing inflammation.$^7$ However, these actions would not require receptor-mediated signaling. Whether biologically significant amounts of PGD$_2$ are converted into 15d-PGJ$_2$ in vivo has been a subject to controversy.$^9$ Katsumata et al$^4$ now show that 15d-PGJ$_2$ at low nanomolar concentrations that can be detected in tissues$^6$ could stimulate expression of Nrf2 target genes in cultured cardiomyocytes, suggesting that it may also evoke Nrf2 activation in the heart in vivo. 15d-PGJ$_2$ is a well-characterized ligand for PPAR$\gamma$ and does not bind to prostaglandin F$_{2\alpha}$ receptor or DP1. Previous studies documented the ability of PPAR$\gamma$ agonists other than 15d-PGJ$_2$ to attenuate injury to cardiomyocytes$^8$ but did not address the involvement of the Nrf2 pathway. The different kinetics of Nrf2 activation by PGD$_2$ and 15d-PGJ$_2$ is consistent with sustained Nrf2 activation in the heart in response to dexamethasone treatment although it remains to be investigated whether PGD$_2$ and 15d-PGJ$_2$ evoke simultaneous or sequential Nrf2 activation. Likewise, additional studies are needed to assess the impact (if any) of dexamethasone on PGD$_2$ metabolism.

The data presented by Katsumata et al$^4$ 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 F$_{2\alpha}$ receptor–deficient mice, as well as in mice treated with the
PPARγ antagonist GW9662. Of note, genetic deletion of Nrf2 may activate a yet unidentified compensatory mechanism that could partially protect the heart against acute ischemia-reperfusion injury while rendering the heart unresponsive to dexamethasone. These novel findings highlight the complexity of glucocorticoid-mediated cardioprotection and shed further insight into the underlying molecular mechanisms. Thus, glucocorticoids through stimulation of PGD2 synthesis (and perhaps metabolism) exert multipronged, predominantly Nrf2-mediated actions involving activation of multiple receptors to protect the heart from ischemia-reperfusion injury (Figure). The benefits of therapeutically targeting the Nrf2 pathway in fumarates were recently shown in preclinical models of neuronal injury, as well as in patients with psoriasis or multiple sclerosis. 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 PGD2-Nrf2 pathway remain to be resolved. Is dexamethasone-evoked PPARγ-mediated increase in Nrf2 mRNA a prerequisite for subsequent activation of Nrf2 protein by PGD2 via FP? Is FP expression altered during myocardial ischemia-reperfusion and, therefore, the explanation for relative PGD2 specificity for cardiomyocytes? Does PGD2 bind simultaneously to DR1 and FP, leading to enhanced cardioprotection? Would dexamethasone stimulate PGD2 biosynthesis and exert cardioprotective actions when administered as a treatment (ie, 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 FP and PPARγ-triggered Nrf2 activation. Considering the pro- and anti-inflammatory actions of PGD2, and 15d-PGJ2, 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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References
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