The HMGB1/MAPKs/Nrf2 Signaling Arbitrates Hepatoprotection Conferred by Celecoxib in Preeclamptic Weaning Rats

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Preeclampsia (PE) is often associated with multiple organ damage that remains noticeable long beyond gestation. Here, we tested the hypotheses that antenatal therapy with nonsteroidal antiinflammatory drugs (NSAIDs), namely celecoxib, diclofenac, or naproxen, refashions liver damage induced by PE in weaning rats and that the high mobility group box 1 (HMGB1) and downstream inflammatory and oxidative effectors modulate this interaction. PE was induced by pharmacologic nitric oxide deprivation during the last week of gestation (N\textsuperscript{\textordfntwo}-nitro-L-arginine methyl ester, L-NAME, 50 mg/kg/day, via oral gavage). Compared with control rats, weaning PE rats (3 weeks post-labor) revealed substantial rises in serum transaminases together with clear histopathological signs of hepatic cytoplasmic changes, portal inflammation, and central vein dilation. While gestational NSAIDs reversed the elevated transaminases, they had no effects (celecoxib, naproxen) or even worsened (diclofenac) the structural damage. Molecularly, celecoxib was the most effective NSAID in: (i) reversing PE-evoked upregulation of hepatic gene expression of proinflammatory HMGB1 and downstream inflammatory and oxidative markers, such as EMAPK\textsubscript{ERK} and MAPK\textsubscript{p38}, respectively, and (ii) elevating and suppressing serum interleukin-10 and TNF-\textalpha, respectively. Amendments caused by PE in protein expression of the antioxidant transcription factor Nrf2 (decreases) and its negative modulator Keap-1 (increases) were also notably ameliorated by celecoxib. Alternatively, rises in serum IL-1\textbeta and shifts in macrophage polarization towards an inflammatory phenotype caused by PE were comparably diminished by all NSAIDs. Together, the data disclose an advantageous therapeutic potential for gestational celecoxib over diclofenac or naproxen in controlling hepatic dysfunction and HMGB1-interrelated inflammatory and oxidative sequelae of PE.