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COX2 inhibitors for acquired brain injuries: Is the time ripe?*

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The timeliness of the results presented in “Cyclooxygenase-2 inhibition provides lasting protection against neonatal hypoxic-ischemic brain injury” by Fathali et al (1) pertains to our current lack of treatments for improving functional deficits after acquired brain injuries. Fathali and colleagues examine the relationships between perinatal hypoxic/ ischemic brain injury, COX2 inhibition, and functional recovery, brain/body morphometrics, and the inflammatory response induced after hypoxic brain injury in neonatal rats. This work provides the basis for a better understanding of the molecular effectors of neuroinflammation, and the effects of COX2 inhibitors (coxibs) on those effectors.

The results show an increase in COX2 after brain injury that could be reversed by early posthypoxia intervention with superanalgesic doses of the COX2 inhibitor NS-398. Consistent with other neuroprotection studies, this high-dose regimen reduced subacute mortality from hypoxic/ischemic insult, stabilized chronic brain and body weight loss, and improved functional recovery in both neurologic and cognitive testing paradigms.

The evidence that prolonged elevations of COX2 expression and activity in the brain is detrimental to outcomes is overwhelming reviewed in our earlier work (2). The induction by and contribution of COX2 to inflammation in the brain has been well documented (3–5). However, there may be a case for an initial benefit of the acute COX2 response. In our brain injury studies, some data indicated (albeit indirectly) that acute COX2 activity may be beneficial (6). A few studies suggested prostaglandins may be neuroprotective, but the preponderance of data show the opposite. The effects of prostaglandin E₂ in neural excitotoxicity models are limited to subacute reductions in nuclear dye uptake; no protection was seen after 48 hrs (7). McCullough et al showed that the protective effects of prostaglandin E₂ in primarily neuronal cell cultures diminished significantly in cultured brain slices, likely because of the preservation of astrocytic/neuronal interactions in organotypic cultures (8). Prostaglandin E₂, likely via the EP2 receptor, mediates reduced neuroinflammatory responses in cultured neurons, but not in the presence of glia (8). Interestingly, one study has provided evidence that COX2 prostaglandins, rather than reactive oxygen species, are responsible for COX2-mediated neurotoxicity (9). Importantly, the studies in which prostanoids (or their EP2 receptors) are characterized as neuroprotective have never shown improvements in functional outcomes.

By contrast, COX2 inhibitors (e.g., 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl)phenyl-2(5H)-furanone [DFU] and nimesulide) reduced inflammation and cell death, and improved behavioral recovery even when administered hours after brain injury (6, 10–12). These findings provide evidence that COX2 inhibitors have an extended window of opportunity to protect vulnerable brain tissue from secondary damage.

*See also p. 572.

Furthermore, our studies suggest that coxibs do more than just reduce prostaglandins and free radicals. COX2 inhibition after brain injury causes arachidonic acid shunting, increasing hydroxyeicosatetraenoic acids and epoxyeicosatrienoic acids levels in the injured brain (6, 13). These cytochrome P450 epoxygenase metabolites of arachidonic acid are prime candidates for neuroprotective eicosanoids. Hydroxyeicosatetraenoic acids have been shown to block glutamate-mediated excitotoxicity in cultured neurons (14). Epoxyeicosatrienoic acids block activation of inflammatory gene induction and reduce adhesion molecule expression in endothelial cells both *in vitro* and *in vivo* (15).

It is apparent from this study by Fathali et al (1) that there are minimal age-related differences in the benefit of coxibs to the injured brain. The coxib-related risks of adverse cardiovascular events (16–21) are containable, if not insignificant, in the perinatal population. Thus, this work also represents a potential therapeutic approach after perinatal hypoxia that could improve the quality of life for children and their families.

Yet, the lack of treatments to block COX2 or its induction specifically after brain injury is due, in my opinion, to a popular collective expectation in this country of a life free from risk, rather than to any failings of researchers to provide proof-of-principle or in BioPharma's considerable efforts to develop and make available helpful tools for this indication. There are still critical questions that remain with regard to the coxibs' mechanisms of action, or whether there is any gender dependence in their utility (or risk of adverse effects).

But if the current beneficial use of thalidomide after decades of disuse (due, admittedly, to its dreadful side effects on human fetuses) is any example, it will be a long time before drugs like rofecoxib or parecoxib can be revived. Only a grass-roots consciousness-raising effort by professional and patient advocates can change the repetition of a long, long wait for these potentially valuable agents in the treatment of brain injuries.

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