The Janus Face of Cyclooxygenase-2 in Ischemic Stroke
Shifting Toward Downstream Targets

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COX-2 and the Brain: Roles in Models of Ischemic Injury

In the normal brain, COX-2 is expressed predominantly in dendritic profiles of glutamatergic neurons, a localization consistent with its role in synaptic function and neurovascular regulation. In rodents as in humans, cerebral ischemia upregulates COX-2 expression in neurons, glia, vascular cells, and in inflammatory cells invading the ischemic brain. Inhibition of COX-2 attenuates ischemic injury after middle cerebral artery occlusion with a relatively wide therapeutic window (6 to 24 hours). In addition, ischemic injury is attenuated in COX-2-deficient mice and is exacerbated in transgenic mice overexpressing COX-2. The mechanisms of the deleterious effects of COX-2 are multifactorial. On the one hand, COX-2 reaction products contribute to glutamate excitotoxicity, a major factor in the Ca²⁺ dysregulation initiating the ischemic cascade. On the other hand, COX-2 contributes to the deleterious effects of the inflammatory reaction involving the ischemic brain. Therefore, COX-2 is an attractive target for stroke therapy.

COX-2 Mediated Neurotoxicity: Quest for Downstream Effectors

Recent studies have focused on the specific mediators of the deleterious effects of COX-2 in ischemic brain injury. COX-2 produces prostanoids and free radicals, both of which could mediate tissue damage. Data in excitotoxicity models suggest that prostanoids, mainly prostaglandin E₂ (PGE₂), and not free radicals are the pathogenic factors mediating brain injury. PGE₂ activates 4 receptors termed EP₁ through EP₄ (Figure). Although limited data are available on the role of EP receptors in cerebral ischemia, evidence suggests that EP₁ receptors are protective. Therefore, EP₁ receptors are unlikely to mediate the neurotoxicity of COX-2. Preliminary evidence suggests that activation of EP₁ receptors is deleterious in models of excitotoxicity and oxygen–glucose deprivation. Therefore, activation of EP₁ receptors by PGE₂ may be a factor responsible for the toxicity exerted by COX-2, but further studies are required to establish this point more firmly.
From Bench to Bedside: COX-2 Inhibitors in Clinical Practice

In the 1970s, Vane suggested that the biological effects of nonsteroidal anti-inflammatory drugs (NSAIDS) were mediated by COX. After the discovery of the different isoforms of COX, studies revealed that the analgesic and anti-inflammatory effects of these drugs were mediated by their ability to block COX-2. However, nonselective NSAIDS might be harmful because they also block COX-1, leading to altered gastrointestinal function, mucosal ulceration, pain, and bleeding. The development of selective COX-2 inhibitors promised to relieve pain and inflammation without the adverse events associated with COX-1 inhibition. In the United States, celecoxib and rofecoxib were the first COX-2 inhibitors approved for use by the FDA. Celecoxib was labeled for treatment of RA and rofecoxib for treatment of acute pain and menstrual pain. COX-2 inhibitors were studied rigorously to determine whether they provided anti-inflammatory and analgesic effects without gastrointestinal complications. In a study of patients with RA, Celecoxib (100 to 400 mg BID) was effective, with lower incidence of endoscopic ulcers compared with naproxen. Another study in patients with RA and osteoarthritis examined whether celecoxib was associated with a lower incidence of significant gastrointestinal complications and other adverse effects compared with conventional NSAIDS. Celecoxib at high doses (400 mg BID) was associated with a lower incidence of gastrointestinal side effects and other complications compared with the NSAIDS ibuprofen and diclofenac. Similarly, rofecoxib was shown to have a favorable gastrointestinal profile when compared with naproxen. The successes of the COX-2 inhibitors led to the popularity of these drugs and billions of dollars in sales per year. Was there an ominous adverse event signal that had been ignored?

Trouble in Paradise: Cardiovascular Complications of COX-2 Inhibitors

Coincident with the FDA approval of rofecoxib and celecoxib, FitzGerald et al reported that these drugs suppress the formation of prostacyclin (PGI2), leaving the production of thromboxane A2 (TXA2) unaltered. PGI2 is a key COX product in the endothelium that inhibits platelet aggregation, causes vasodilatation, and prevents proliferation of vascular smooth muscle cells. Evidence was also provided that PGI2...
production in vivo was COX-2 dependent, possibly through COX-2 induction in endothelial cells by shear stress. In contrast to PGI₂, the COX-1–derived prostanoid TXA₂ causes platelet aggregation, vasoconstriction, and vascular proliferation. FitzGerald et al speculated that suppression of COX-2–dependent formation of PGI₂ by the COX-2 inhibitors left TXA₂ generation unopposed, promoting vasoconstriction, thrombosis, and atherogenesis. A number of publications began to surface suggesting that the COX-2 inhibitors might be associated with an increased risk of cardiovascular events. For example, a critical review of the Vioxx Gastrointestinal Outcomes Research Study (VIGOR), the Celecoxib Long-term Arthritis Safety Study (CLASS), and 2 smaller trials showed that the relative risk of a thrombotic cardiovascular event, including myocardial infarction, ischemic stroke, and transient ischemic attack, with rofecoxib treatment was $\approx 2.4$% compared with naproxen ($P=0.002$). In the Tennessee Medicaid program (TennCare) study, high-dose rofecoxib users were $\approx 1.7$x more likely than nonusers to have coronary heart disease. There was no evidence of increased risk at doses of $\leq 25$ mg of rofecoxib. Other analyses had raised similar concerns about rofecoxib, and one study suggested a higher risk of admission for congestive heart failure in rofecoxib users and nonselective NSAID users, but not with celecoxib, relative to non-NSAID controls. The safety of parecoxib and valdecoxib in relation to serious adverse events has also been challenged, whereas a large trial comparing lumiracoxib with naproxen and ibuprofen suggested that lumiracoxib might be safe from a cardiovascular standpoint. On September 30, 2004, Merck, the manufacturer of rofecoxib, withdrew the drug from the market because of an excess risk of myocardial infarctions and strokes. This action occurred after the results of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, a study to determine the effect of rofecoxib treatment was $\approx 3.9$-fold increase in the incidence of serious thromboembolic adverse events in the group receiving 25 mg of rofecoxib compared with placebo, and the incidence of myocardial infarction and thrombotic stroke diverged progressively after $\approx 1$ year of treatment. Is there a unifying explanation for this troublesome cardiovascular event profile with administration of at least certain COX-2 inhibitors? One possibility is that the depression of PGI₂ formation caused by the inhibitors led to elevation of blood pressure, accelerated atherogenesis, and exaggerated thrombotic response to atherosclerotic plaque rupture.

Conclusions

The COX-2 pathway is a valuable therapeutic target for ischemic brain injury. However, the available clinical and experimental evidence suggests that, although COX-2 inhibitors are able to attenuate injury in stroke models, they also produce an unbalance in prostanoid synthesis that promotes deleterious vascular effects. Indeed, clinical trials have demonstrated that chronic inhibition of COX-2 increases the incidence of serious thromboembolic complications that would be devastating in patients with stroke. Therefore, inhibition of the COX-2 pathway with most of the drugs available today does not seem a viable option for stroke treatment. COX-2 inhibitors with a safer cardiovascular profile, such as lumiracoxib, and third-generation inhibitors might prove to be more suitable. In addition, new therapeutic strategies targeting the factors mediating the damage downstream of COX-2 offer great promise. These approaches provide the opportunity to block the specific receptors mediating COX-2–dependent neurotoxicity without altering the homeostatic balance between COX-2–derived prostanoids. These novel clinical and experimental approaches, if successful, may offer stroke patients powerful new tools to ameliorate brain damage and improve their functional outcome.

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