Deciphering the physiological roles of COX-2

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Even though blocking the formation of prostaglandins has been used as a therapeutic strategy against inflammation and rheumatism for more than 3,500 years (16), it is only 30 years ago that cyclooxygenase (COX) was identified as the underlying molecular target (15). COX catalyzes the biosynthesis of prostaglandin H2 from arachidonic acid and is the rate-limiting enzyme of prostaglandin production. For centuries, extracts of herbs or plants, such as willow bark, were used to block COX activity. After the discovery of paracetamol, phenacetin, and aspirin at the end of the 19th century, the use of natural products has been replaced by non-steroidal anti-inflammatory drugs (NSAIDs). Today, NSAIDs belong to the most commonly used drugs worldwide (18).

In addition to their unequivocal therapeutic benefits, NSAIDs are useful tools to identify the physiological functions of prostaglandins. These range from cytoprotection in the gastric mucosa, platelet aggregation, temperature regulation, central sensory processing, induction of uterine contractions during labor, and vasorelaxation, to salt and water homeostasis (17). Due to these many normal functions of prostaglandins, NSAIDs can exert severe side effects, most notably gastrointestinal bleeding and renal dysfunction. Therefore, the discovery of a second, inducible form of COX in the early 1990s (9, 13, 19) was welcomed with great enthusiasm. In contrast to the constitutively expressed classical COX, now termed COX-1, this new isoform (COX-2) was found to be selectively upregulated in inflammatory states by bacterial endotoxins, cytokines, and growth factors (8). This led to the hypothesis that specific inhibition of COX-2 will preserve the therapeutic potential of NSAIDs without inducing their notorious side effects, and highly selective COX-2 antagonists were developed.

Soon after its cloning, it became clear that COX-2 is not only present after induction but that it is also constitutively expressed in the adult mammalian organism such as in the brain and kidney. In the kidneys of different species, COX-2 is detected in blood vessels, in the cortical thick ascending limb of the loop of Henle including the macula densa region, in intraglomerular podocytes, medullary interstitial cells, and in inner medullary collecting duct cells (5). Moreover, renal expression of COX-2 is regulated in response to a variety of physiological stimuli, for example the rate of salt intake (5). The expression of COX-2 in the thick ascending limb and the macula densa and its interaction with nitric oxide have recently attracted particular interest (2–4, 6, 7, 11, 14). Both prostaglandins and nitric oxide are important locally generated vasodilators that counteract vasoconstriction induced by increased levels of ANG II or renal sympathetic activity, and an excessive renal vasoconstrictor tone sensitizes the kidney to the side effects of NSAIDs. Accordingly, COX-2-derived prostaglandins may physiologically function as safeguards of an adequate renal perfusion.

It is this important function that is addressed by Lopez and colleagues (12) in their paper in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. The authors assess the effects of selective or combined pharmacological inhibition of nitric oxide synthase and COX-2 on the renal hemodynamic responses to graded increments of exogenous norepinephrine in anesthetized dogs. Renal blood flow and glomerular filtration nearly cease even at the lowest dose of norepinephrine during combined blockade of nitric oxide formation and COX-2. The same dose of norepinephrine barely affects renal hemodynamics in control animals. Moreover, the marked renal vasoconstriction during combined blockade is largely attenuated by coadministered angiotensin AT1 receptor blockade. This suggests that ANG II contributes significantly to the excessive renal vasoconstriction under these conditions. Remarkably, the effect of the combined blockade is over-additive as compared with blockade of nitric oxide synthase or COX-2 alone. A possible explanation for this finding may be that norepinephrine activates COX-2 and that this activation is dependent on nitric oxide. In addition, previous studies have demonstrated that nitric oxide elevates intracellular cAMP levels by inhibiting the activity of the cAMP phosphodiesterase PDE-3 (10). COX-2-derived prostaglandins can also elevate...
intracellular cAMP levels, however, by directly stimulating adenyl cyclase. Thus a parallel activation of both pathways will result in a potentiation of intracellular cAMP levels, which ultimately causes vasorelaxation. Nevertheless, there are other possibilities and the seeming interaction may simply result from the fact that both treatments target the same intrarenal vessel.

Whatever the answer will be, the data from the study by Lopez and colleagues (12) strongly support the concept that COX-2-derived prostaglandins help to protect the renal vasculature against excessive vasoconstrictor influences. These results confirm that COX-2 has physiological functions in addition to its multiple roles in inflammatory processes. They do also provide a rationale for understanding why the nephrotoxic potential of selective COX-2 inhibitors appears to be similar to that of nonselective NSAIDs (1). It seems likely that future studies will uncover many more physiological roles for COX-2-derived prostaglandins.

REFERENCES