Renal hemodynamic effects elicited by acute cyclooxygenase-2 inhibition are not related to angiotensin II levels

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Numerous studies have demonstrated that cyclooxygenase-2 (COX-2) is involved in the regulation of renal function. It has also been shown that renal COX-2 expression and activity change in response to physiological stimuli, such as variations in sodium intake, and in response to changes in several vasoactive hormones (6, 9). The importance of COX-2-derived metabolites in regulating renal function in volume-contracted states is supported by studies showing that COX-2 expression is enhanced in the renal cortex (16) and demonstrating that the renal vasoconstriction elicited by the acute and prolonged COX-2 inhibition is greater when sodium intake is low than when it is normal or elevated (12, 13, 15). These findings have clinical implications because dietary sodium restriction is extensively used in the management of patients with impaired sodium conservation mechanisms and hypertension. Therefore, COX-2 inhibitors should be used with caution in these patients for the treatment of inflammatory diseases. The renal vasoconstriction elicited by COX-2 inhibition when extracellular volume is reduced may be secondary not only to a decrease in prostaglandins (PGs) (10) but also may be mediated by the effects of other regulatory mechanisms such as ANG II (4, 7), leucotrienes (LTs) (2, 5), 20-HETE (3), and renal sympathetic activity (8).

The possible involvement of ANG II in mediating the renal vasoconstriction elicited by the administration of a COX-2 inhibitor when sodium intake is low is supported by studies showing that ANG II and COX-2 activity are elevated (10, 13, 16) and that the ANG II-induced renal vasoconstriction is modulated by endogenous PGs (4, 7). It has also been demonstrated that COX-2 inhibitors enhance the pressor effect of ANG II and that COX-2-derived metabolites modulate the vasoconstrictor effect of ANG II on medullary circulation (11). However, it was unknown whether the renal hemodynamic changes elicited by COX-2 inhibition are mediated by ANG II levels when sodium intake is low. With an elegant and imaginative approach, the study published by Green et al. (4a) in an issue of the American Journal of Physiology-Renal Physiology has tested the hypothesis that the renal effects elicited by COX-2 inhibition are positively correlated to the endogenous renin-angiotensin system activity. The renal vasoconstriction would be secondary not only to the withdrawal of PG vasodilatory influence but also to the greater unopposed ANG II effects. The authors’ hypothesis was tested by evaluating the renal effects induced by the administration of a COX-2 inhibitor in rats with normal or low sodium intake, and in rats treated with a converting enzyme inhibitor (CEI). Sodium restriction and CEI treatment induced a significant elevation in PG synthesis and COX-2 expression. However, ANG II levels are enhanced in rats with low sodium intake and reduced in CEI-treated rats. The results obtained support the notion that the renal hemodynamic effects induced by the acute administration of a COX-2 inhibitor are not related to the endogenous ANG II levels because the administration of nimesulide induced a similar renal vasoconstriction in both groups of rats.

Green et al. (4a) also found that the acute administration of nimesulide leads to a significant reduction in renal excretory ability when sodium intake is low and that only sodium excretion is ANG II dependent. The decrease in sodium excretion was not dependent on changes in medullary blood flow and seems to be an acute effect because sodium retention is not observed when COX-2 activity is reduced during several consecutive days (9, 12, 13). The transitory effect on sodium excretion could be explained by a change in other regulatory mechanisms that compensate the sodium-retaining effects induced by COX-2 inhibition. As reported in previous studies (11), Green et al. (4a) also found that the PGs involved in the regulation of medullary blood flow are COX-2 dependent. These findings are important since medullary blood flow is a determinant of sodium excretion, and its reduction could contribute to the sodium retention and hypertension observed with the clinical use of COX-2 inhibitors (15). Furthermore, reduction of blood supply to renal papilla by COX-2 inhibition may also contribute to the papillary necrosis associated with long-term use of nonsteroidal anti-inflammatory drugs (1).

The interaction between COX-1- and COX-2-derived metabolites in the acute regulation of renal function has also been examined in the study performed by Green et al. (4a). The results obtained suggest that both isoforms have opposite effects on renal hemodynamics when COX-2 expression is enhanced. Since there are conflicting data in the studies already published (6, 9, 11–13), and it is an interesting and clinically relevant area of research, new studies defining the interaction between both isoforms in the regulation of renal function are needed.

In summary the results reported by Green et al. (4a) clearly suggest that the renal vasoconstriction elicited by acute COX-2 inhibition is not ANG II dependent. Further studies are needed to examine whether this renal vasoconstriction is only secondary to a reduction in PGs or also mediated by other regulatory mechanisms such as 20-HETE or LTs. The possible involvement of LTs in mediating the renal vasoconstriction elicited by COX-2 inhibitors is supported by studies suggesting that these drugs may redirect arachidonic acid metabolism to the 5-lipoxygenase pathway, thus increasing the formation of LTs (2) and showing that LTs elicit an important renal vasoconstriction (5).
GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES