Endothelial Nitric Oxide Synthase, Cyclooxygenase-2, and Essential Hypertension: Is There an Interaction?

To the Editor:

Nitric oxide (NO), prostacyclin (PGI₂), and thromboxane (TxA₂) are produced by NO synthase (NOS) and cyclooxygenase (ie, COX-1 and COX-2) isoforms, respectively. They are highly potent vasoactive molecules. NOS and COX pathways are assumed to interact and modulate each other. Both NOS and COX can produce superoxide which may react with NO to produce peroxynitrite (ONOO⁻), thus diminishing NO bioactivity. Peroxynitrite may decrease NOS activity, but its action on COX is 2 sided; it may enhance or decrease COX activity depending on its concentration. Using experimental COX-1 and COX-2 selective inhibitors, Virdis et al¹ reported that in essential hypertension COX-2 decreased the bioavailability of endothelial NOS (eNOS)–derived NO and uncoupled eNOS in small arteries by increasing oxidative stress. In newly diagnosed mild uncomplicated patients with essential hypertension, we found that PGI₂ synthesis and oxidative stress are not altered compared with healthy normotensives,² whereas NO synthesis is slightly (27%) decreased, suggesting that NO biosynthesis but not NO bioavailability is diminished in essential hypertension. A possible explanation for the finding by Virdis et al¹ on involvement of COX-2–derived oxidative stress in essential hypertension may be that COX inhibitors act distinctly different on oxidative stress and PGI₂, and TxA₂ synthesis. In vivo in healthy humans, celecoxib (a COX-2 selective inhibitor) and indomethacin (a COX-unselective inhibitor) decreased oxidative stress (Figure) and PGI₂ synthesis,³ whereas indomethacin but not celecoxib inhibited TxA₂ synthesis.³

Taken together, COX-2 inhibition by nonsteroidal anti-inflammatory drugs is associated with oxidative stress decrease but this does not translate into cardiovascular protection. The cardiovascular risk of COX-unselective and selective COX-2 inhibitors is well established.⁴,⁵

Disclosures

None.

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