Letter to the Editor

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

The issues raised by Tsikas and Stichtenoth1 in their letter with regard to our article2 fall into 2 areas: (1) the possible endothelial NOS (eNOS)–cyclooxygenase (COX)-2 interaction and products of COX-2 activation; (2) the cardiovascular protection by coxibs. Concerning the first issue, we agree that a cross-talk between eNOS and COX-2 exists. Vascular eNOS expression was not investigated because it was beyond the scope of our study. Nevertheless, our functional experiments indirectly indicate that the decreased eNOS activity secondary oxidative stress generation, if occurring, is a surmountable and temporary phenomenon. Indeed, the sensitivity to L-NAME was acutely restored when vascular oxidative stress was inhibited by the scavenger ascorbic acid or COX-2 blockade, suggesting that NO production is quickly restored after stress excess removal. At this point, the statement that in our article “COX-2 decreased the vascular uncoupled eNOS” is not correct. Actually, the uncoupled eNOS, tested by the BH4 precursor sepiapterin, was exclusively investigated (and then excluded) as a possible source of oxidative stress. However, a demodulated eNOS activity does not necessarily exclude the presence of a reduced NO availability as a consequence of oxidative stress-induced NO breakdown. This opens the question on the role of oxidative stress in essential hypertension. Basically, hypertension accelerates the age-related endothelial dysfunction. In normotensive subjects, age-related endothelial dysfunction is detectable after 30 years and is progressively caused by a defect in the L-arginine-NO pathway. After 60 years, COX-derived oxidative stress becomes the main contributor. Essential hypertension anticipates the same mechanisms, which characterize age-related endothelial dysfunction. In particular, ≤45 years of age, patients with essential hypertension show an exclusive alteration in the L-arginine-NO pathway, whereas oxidative stress does not occur. COX-derived oxidative stress starts at 45 years of age, progressively increasing with advancing age.3 Thus, it is not surprising that in their previous article, conducted in young (age, 39±10 years) patients with uncomplicated hypertensive, oxidative stress was not increased.

Stichtenoth et al2 propose that oxidative stress and prostacyclin (PGI2) are produced by COX-2, whereas thromboxane (TxA2) is COX-1 derived. Our results, conducted in different experimental conditions (patients with hypertensive versus healthy subjects; vascular experiments versus urinary markers of prostanoids), agree with the hypothesis that oxidative stress is COX-2 derived. PGI2 was not measured in our study. However, when considering the vasorelaxing property of PGI2, a missing reduced vascular relaxation under COX-1 or COX-2 blockade argues against the possibility that PGI2 contributes to vascular dysfunction. Similarly, TP receptor blockade unaffected the relaxation to acetylcholine, thus ruling out any involvement of TxA2. If so, being oxidative stress, but not PGI2 or TxA2, the only COX-2–derived product, it might be speculated that the existence of a so-called uncoupled COX-2 status, as recently hypothesized.5 Finally, findings that COX-2 inhibition failed to exert a cardiovascular production, despite local vascular oxidative stress reduction, are consistent with the complex scenario behind COX activation in humans: a variety of prostanoids with opposite effects, protective or detrimental, tissue and district specific. Only when selective inhibitors for vascular COX-2 will become available, the clinical impact of such pathway will be more evident.

Disclosures

None.

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Agostino Virdis, Alessandra Bacca, Rocchina Colucci, Emiliano Duranti, Matteo Fornai, Gabriele Materazzi, Chiara Ippolito, Nunzia Bernardini, Corrado Blandizzi, Giampaolo Bernini and Stefano Taddei

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