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PGI$_2$ and TXA$_2$in vascular injury

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Keywords

cardiovascular disease, COX-2, NSAIDs, prostacyclin, thromboxane

Context

Cyclooxygenases participate in the pathogenesis of atherothrombotic lesions by two opposing mechanisms. Platelet cyclooxygenase-1 (COX-1) participates in the synthesis of thromboxane A_2 (TxA_2), a potent vasoconstrictor and platelet activator, and endothelial cyclooxygenase-2 (COX-2) mediates the synthesis of prostacyclin (PGI_2), a vasodilator and platelet inhibitor. Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin exert differential effects on platelet-endothelium interactions that are dependent upon their relative capacity to inhibit COX-1 and COX-2 isoenzymes. Potent and sustained inhibition of COX-1 by low dose aspirin provides efficient anti-thrombotic prophylaxis. Different NSAIDs can induce transient and variable inhibition of COX-1-dependent TxA_2 synthesis, and all NSAIDs and COX-2 selective drugs inhibit COX-2 dependent PGI_2 synthesis, but the clinical relevance of both effects is still unclear. These authors explored the role of TxA2/PGI2 balance in the response to vascular injury using TxA_2 and PGI_2 receptor knockout mice.

Significant findings

Catheter-induced vascular injury was enhanced in mice genetically deficient in the PGI_2 receptor, whereas it was depressed in those mice genetically deficient in the TxA_2 receptor or treated with a TxA_2 receptor antagonist. The augmented response to vascular injury was abolished in mice deficient in both receptors.

Comments

The results of Cheng *et al.* are consistent with the well known role of TxA_2 in vascular disease and demonstrate a role in counterbalancing TxA_2 platelet activation for PGI_2 synthesized in response to vascular injury. However, the authors' extrapolation regarding the clinical use of NSAIDs versus COX-2 selective inhibitors is not clear because most NSAIDs lack the potent inhibition and anti-platelet effect provided by aspirin. These data in knockout mice remind us of the need to ensure anti-platelet prophylaxis in patients with cardiovascular disease, particularly before using either NSAIDs or COX inhibitors, but further studies on the potential clinical effects of PGI_2 inhibition by both types of drugs are still warranted.

Methods

Carotid-induced injury, histomorphometric analyses.

References

1. Cheng Y, Austin SC, Rocca B, Koller BH, Coffman TM, Grosser T, Lawson JA, Fitzgerald GA: Role of Prostacyclin in the Cardiovascular Response to Thromboxane A_2 . Science . 2002, 296: 539-541. ,