P577

Allosteric modulation of 5-HT_{2B} receptors by celecoxib. Putative involvement in adverse drug reactions associated with coxibs.

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Selective inhibitors of cyclooxygenase-2 (COX-2) (coxibs) were developed to avoid the adverse effects associate to nonsteroidal anti-inflammatory drugs, however, the analysis of multiple clinical trials, has established a clear relationship between some coxibs and cardiotoxicity (Meade y cols., J Biol Chem 1993; 268:6610-6614).

Many drugs with demonstrated adverse cardiovascular effects (fenfluramine, pergolide, ..) share the ability to activate the serotonin (5-HT) 5-HT_{2B} receptor, whose activation, together with the inhibition of 5-HT transporter (5-HTT) plays an important role in the pathogenesis of heart valve disease (Fitzgerald y cols., Mol Pharmacol 2000; 57:75-81).

Based on the above, in the present study it is hypothesized that the adverse effects associated with coxibs may come mediated by its interaction with the 5-HT_{2B} receptor.

We characterized the interaction of a currently marketed coxib (celecoxib) with 5-HT_{2B} receptor by radioligand binding and functional (*in vitro* and *ex vivo*) assays. Moreover, we also evaluated the modulation of 5-HT_{2B} receptor expression and function after celecoxib treatment with doses equivalent to the human therapeutic ones.

Celecoxib showed low affinity and efficacy in binding and functional assays for human 5-HT_{2B} receptor (Ki>10 µM). When this compound was administered in presence of 5-HT, it produced a significative ($P<0.05$, Student t test) increase in its potency and /or efficacy (EC_{50} from 118 to 65.9nM and E_{max} from 100 to 118%).

Thus, after 21 days treatment, the immunohistochemical results showed no alterations in both expression and localization of 5-HT_{2B} receptor in rat stomach fundus. However, the response to endogenous agonist, 5-HT, is clearly increased in rats treated (%E_{max} treated vs control = 140%).

The data obtained are compatible with a behaviour of celecoxib as positive allosteric modulator of 5-HT at this receptor, increasing the sensitivity and potency of 5-HT at 5-HT_{2B}. This interaction would explain at least some of the adverse reactions associated with these compounds.

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