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5-Lipoxygenase as a Putative Mechanism of NSAID-Related Psychiatric Adverse Events

In a recent article, Onder et al.[1] summarised the evidence for NSAID-related psychiatric adverse effects, which adds to the mounting evidence of cardiovascular adverse effects of these drugs. Initially, it was believed that only the cyclo-oxygenase (COX)-2 inhibitors increase risk for heart attacks and stroke, but now it appears that mixed COX-1/COX-2 inhibitors, such as naproxen, may also cause the same risk. Hence, on 20 December 2004, the US FDA released a statement pointing to evidence for an increased risk of cardiovascular events in patients receiving naproxen when compared with those receiving placebo. The exact mechanisms of NSAID-triggered psychiatric and cardiovascular adverse effects are not clear. In a recent paper,[2] we discussed the possibility that 5-lipoxygenase might be involved in the comorbidity of psychiatric disorders such as anxiety and depression with cardiovascular pathologies. Here we propose that 5-lipoxygenase could participate in NSAID-related depression and anxiety.

For example, genetically modified mice that do not have a functional 5-lipoxygenase gene show attenuated anxiety- and depression-like behaviours,[2,3] suggesting that 5-lipoxygenase up-regulation may favour these behaviours. 5-Lipoxygenase and COX isozymes metabolise arachidonic acid into leukotrienes and prostaglandins, respectively. An inhibition of the COX pathway, for example by naproxen, up-regulates 5-lipoxygenase gene expression and leukotriene production.[4] In the paper by Onder et al.,[1] naproxen treatment was frequently associated with depression and anxiety. If 5-lipoxygenase is involved in these effects of NSAIDs, the naturally occurring variability in the 5-lipoxygenase gene could render some individuals more prone to 5-lipoxygenase up-regulation and more susceptible to psychiatric adverse effects. In a recent study,[5] it was found that about 6% of the general population has variant 5-lipoxygenase genotypes (lacking the common allele), and also has significantly increased mean carotid-artery intima-media thickness and elevated markers of inflammation compared with carriers of the common allele. It has been suggested that this[5] and other genetic variability[6] may result in an over-active 5-lipoxygenase pathway in some individuals. We propose that these individuals could be at greater risk for NSAID-related psychiatric adverse events. Our hypothesis could be tested in future clinical trials employing 5-lipoxygenase genotyping.

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