

Can NSAIDs contribute to Alzheimer's disease?

Several years ago it was discovered that some NSAIDs lower the levels of amyloid β peptide ($A\beta$). This peptide is a key component of neuritic plaques, which, along with neurofibrillary tangles and cerebral atrophy, are a pathologic hallmark of Alzheimer's disease. Not all NSAIDs produce this result, however, and new research reveals that some cyclooxygenase-2 (COX-2) inhibitors actually increase the production of $A\beta$, an effect comparable to that of mutations thought to cause Alzheimer's disease.¹

There are several forms of $A\beta$; the one with 42 amino acids ($A\beta_{42}$) is the insoluble form found in neuritic plaques. The deposition of $A\beta_{42}$ is thought to play an important role in the cascade of events leading to the formation of neurofibrillary tangles and the eventual degeneration of neurons. The production of $A\beta_{42}$ is catalyzed by β - and γ -secretases. In 2001, Weggen and colleagues found that the NSAIDs ibuprofen, indomethacin and sulindac sulfide decrease the levels of $A\beta_{42}$ in cells, in some cases by as much as 80%.² This decrease appears not to be due to an effect on cyclooxygenase, the primary target of NSAIDs. Instead, these drugs appear to modulate the ability of γ -secretase to produce $A\beta_{42}$.

The results of a number of epidemiological studies that preceded the study by Weggen and colleagues suggested that people using NSAIDs had a reduced incidence of Alzheimer's disease. This led to speculation that NSAIDs may aid in preventing this disease. However, clinical trials with rofecoxib and naproxen showed no benefit. A prevention trial for Alzheimer's disease using celecoxib was recently halted because COX-2

inhibitors were coming under fire for increasing the risk of adverse cardiovascular events.³

Mimicking Alzheimer's disease

In a recent study, Kukar and colleagues tested over 300 compounds, including COX-2 selective NSAIDs, NSAID derivatives and several novel compounds, with the goal of finding drugs that had little effect on cyclooxygenase but decreased the production of $A\beta_{42}$.¹ They exposed cultured H4 neuroglioma cells to various drugs and measured production of $A\beta$.

Their results were surprising. Although they discovered that one NSAID, R-flurbiprofen, lacked cyclooxygenase activity and reduced $A\beta_{42}$ levels, many of the COX-2 inhibitors, including tilmacoxib and valdecoxib, increased the production of $A\beta_{42}$. In particular, celecoxib raised $A\beta_{42}$ levels by almost 200%. Rofecoxib and lumiracoxib only slightly influenced $A\beta_{42}$ levels, even at high doses. The COX-2 selective NSAIDs appeared to exert their effects on $A\beta_{42}$ production by targeting γ -secretase. This is similar to the mechanism by which autosomal dominant mutations linked to Alzheimer's disease are known to function.

NSAIDs are not the only class of drug that affects $A\beta_{42}$ production. Fenofibrate, a lipid-lowering drug, increased the $A\beta_{42}$ levels in cultured H4 cells by over 300% in a dose-dependent fashion. In contrast, fenofibric acid, the active metabolite of fenofibrate, did not raise $A\beta_{42}$ levels, which suggests that the effect was specific to the drug.

The clinical implications of these findings are not clear, as the authors point out.¹ In particular, it is uncertain whether celecoxib and the other drugs

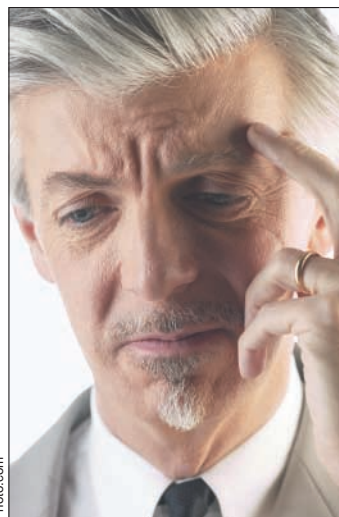


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used in the study have the same effects in the human brain as they did in the mouse model used in the study. If they do, it is conceivable that they may have an impact on the pathology of Alzheimer's disease, which raises several issues for future study. The in vivo effects of COX-2 inhibitors on $A\beta_{42}$ levels and subsequent neuritic plaque formation need to be ascertained. An understanding of how these NSAIDs modulate the activity of γ -secretase may one day contribute to the design of drugs that inhibit the production of $A\beta$.³ Finally, whether the drug-induced alteration of $A\beta_{42}$ levels is a new risk factor for Alzheimer's disease needs further research. — David Secko, Vancouver

References

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