PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

NSAIDs reduce Alzheimer's independently of COX activity

ArticleInfo		
ArticleID	:	290
ArticleDOI	:	10.1186/ar-2002-74550
ArticleCitationID	:	74550
ArticleSequenceNumber	:	43
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2002–1–15 Received : 2002–1–4 OnlineDate : 2002–1–15
ArticleCopyright	:	Biomed Central Ltd2002
ArticleGrants	:	
ArticleContext	:	130754411

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Keywords

Alzheimer's disease, COX inhibitor, ibuprofen, sulindac sulphide

Context

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of rheumatoid arthritis. NSAID users have previously been shown to have a reduced risk of developing Alzheimer's disease. The deposition of the 42-residue isomer of the amyloid-? peptide (A?42) is central to the pathogenesis of Alzheimer's disease. A?42 is generated by cleavage of the amyloid precursor protein (APP) by a ?-secretase that cleaves APP at different positions thereby generating peptides of different lengths. This study investigates the mechanism through which NSAIDs exert their protective effect against the development of Alzheimer's disease.

Significant findings

CHO cells, which do not normally express APP, were transfected with APP and a presenilin mutant that leads to elevated levels of A? peptide production. Treatment of these cells with the nonselective cyclooxygenase (COX) inhibitors sulindac sulphide, ibuprofen or indomethacin, led to a 50-70% decrease in A?42 levels. However, not all NSAIDs were capable of reducing A?42 levels: the nonselective COX inhibitor naproxen, the COX-2 specific inhibitor celecoxib and the COX-1 specific and COX-2 preferential inhibitors aspirin and meloxicam respectively all had no effect on A?42 levels, indicating that the A?42-lowering effect is independent of COX activity. Indeed, fibroblasts deficient in both COX-1 and COX-2 exhibited reduced levels of A?42 in response to sulindac sulphide. Ibuprofen, but not naproxen, also reduced brain A?42 levels by 39% in a mouse model of Alzheimer's disease. Mass spectrometric analysis showed that the reduction in A?42 levels following sulindac sulphide treatment was associated with a dose-dependent increase in the level of another APP-derived peptide A?(1-38). Therefore, NSAIDs are thought to subtly alter the activity of the APP-cleaving ?-secretase.

Comments

One may not expect to see a study identifying a potential cure for Alzheimer's disease reported within *Arthritis Research*, however it is of interest to the arthritis community as it identifies both a novel use and site of action for some NSAIDs. This novel mechanism can account for the epidemiological observation that NSAID users have a reduced risk of developing Alzheimer's disease, which was recently confirmed by a large trial (see Additional information). It had previously been thought that the anti-inflammatory properties of NSAIDs were responsible for this reduced risk, acting via COX inhibition; however, this study clearly demonstrates that the protective mechanism is independent of COX activity and potentially acts via a ?-secretase. Further investigation is required to establish the precise mechanism by which amyloidogenic peptide levels are reduced by certain NSAIDs. As more specific COX-2 inhibitors become available for the treatment of rheumatoid arthritis, the beneficial COX-independent effects of these broad-acting therapies must not be forgotten.

Methods

ELISA, western blotting, immunoprecipitation with mass spectrometry (IPMS)

Additional information

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