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Review

NSAIDs and Alzheimer disease: Epidemiological, animal model and clinical studies

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Abstract

This review reports correlations between four independent fields related to inflammation and Alzheimer disease: fundamental pathology, epidemiology, transgenic animal studies and clinical trials. Activated microglia, along with a spectrum of inflammatory mediators, have been identified in association with the lesions of Alzheimer disease (AD), suggesting that antiinflammatory agents such as NSAIDs should protect against the disease. In multiple epidemiological investigations testing this hypothesis, a significant risk reduction, or a trend towards such a reduction has been observed in long term as opposed to short term users of traditional NSAIDs. In studies where such NSAIDs have been administered to AD transgenic mice, a dose dependent reduction in pathology was observed. The selective C0X-2 inhibitors were ineffective. Results of clinical investigations have so far been disappointing but have nevertheless correlated with fundamental pathological findings and with transgenic mouse results. Four clinical trials using selective COX-2 inhibitors failed which is in keeping with the animal results and is consistent with pathological findings demonstrating that COX-1 and not COX-2 is the appropriate target in activated human microglia. A low dose trial of the traditional NSAID naproxen also failed, but pilot trials using therapeutically established doses of indomethacin and diclofenac/misoprostol showed promise. Further clinical investigations with relatively high doses of traditional NSAIDs might be warranted, although significant side effects should be anticipated.

Keywords: Activated microglia; Inflammation; Transgenic mice; COX-1; COX-2; Amyloid; Neurofibrillary tangles

1. Introduction

The concept that antiinflammatory agents might play a role in the prevention and treatment of Alzheimer disease (AD) originated with the discovery that activated microglia were strongly associated with the characteristic lesions of senile plaques and neurofibrillary tangles [36,49]. Subsequently, many neuroinflammatory mediators were found to be upregulated in affected areas of AD brain. These include, but are not limited to, prostaglandins, pentraxins, complement components, anaphylotoxins, cytokines, chemokines, proteases, protease inhibitors, adhesion molecules and free radicals. The degree of inflammation is intense, since comparisons of inflammatory marker levels showed greater upregulation in AD hippocampus than in surgically replaced joints, infarcted heart or atherosclerotic plaques [38].

The immunohistochemical findings led to the hypothesis that individuals on long term antiinflammatory drugs might inadvertently be combating the consequences of brain inflammation in AD [40]. Rheumatoid arthritics were an obvious population for evaluating this hypothesis since the typical age of onset is lower than in AD, and since high doses of antiinflammatory drugs are typically used on a sustained basis. An estimated six-fold sparing of AD was found in this population compared with age-matched general populations [39]. In addition, seven case control studies were conducted where arthritis in general was considered as the risk factor. Six of these studies showed a sparing of AD (reviewed in [41]),

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strongly suggesting that long term use of antiinflammatories might protect against AD.

Since nonsteroidal antiinflammatory drugs (NSAIDs) are the most commonly used of all antiinflammatory agents, these studies naturally led to investigations as to whether NSAIDs might have protective effects. Numerous epidemiological studies have been conducted in which the use of NSAIDs has been evaluated as a modifying factor for AD, dementia generally, or cognitive decline (for recent reviews see [9,11,12,19,60]).

NSAIDs are widely used agents, a number of which are available as non-prescription drugs. In order to evaluate more clearly whether they have a role to play in AD, we correlate here published data from four independent but related fields concerning NSAIDs and AD: fundamental neuropathology, epidemiology, transgenic animal studies and clinical trials. The combined data strongly support the hypothesis that NSAIDs play a protective role in AD and that well designed clinical trials may demonstrate a therapeutic role as well.

2. NSAIDs and the fundamental pathology of Alzheimer disease

Senile plaques (SPs) and neurofibrillary tangles (NFTs) are the pathological hallmarks of AD. Plaque material consists mostly of extracellular aggregations of beta-amyloid protein (Aβ), while NFTs consist mostly of intracellular aggregations of phosphorylated tau. Severe inflammation develops around Aβ deposits as well as extracellular NFTs (for reviews see [19,37,44]). Consolidated Aβ is a powerful activator of the complement system [48]. The terminal complement components assemble to form the membrane attack complex (MAC) which can insert itself into host cells in a process known as bystander lysis. This has been observed in AD [42,63]. Activated microglia produce a variety of other toxic materials, including oxygen free radicals and various proteases. Secretions of activated microglia cause death of neuronal cell lines in vitro, and this is reduced by exposure of the microglia to NSAIDs [26,27].

In accord with these basic findings, therapeutic strategies should be directed at reducing the level of inflammation. To achieve this, the toxic actions of over stimulated microglia should be attenuated. That is the presumed role of antiinflammatory agents, including NSAIDs. Evidence favoring this concept was obtained by Mackenzie [34] who found on postmortem examination that patients who had been using traditional NSAIDs showed significantly fewer activated microglia in their postmortem brains than non-users.

The main activity of NSAIDs is to inhibit cyclooxygenase (COX) activity. There are two forms, COX-1 and COX-2, and NSAIDs vary in their ability to inhibit these two forms [25]. Traditional NSAIDs inhibit COX-1 and have variable actions against COX-2. Newer agents such as celecoxib and rofecoxib have a selective action against COX-2 and have become popular because of their lower gastrointestinal side effects. It has been emphasized in the literature that COX-1 is a constitutive enzyme, while COX-2 is induced by inflammation and thus is the most appropriate target for antiinflammatory action. But this is an oversimplification which is inappropriate for brain. COX-2 is constitutively expressed at high levels in brain [55] and is specifically concentrated in pyramidal neurons which are vulnerable to AD pathology [67,68]. On the other hand, COX-1 is not constitutively expressed in brain at high levels [55] but is upregulated in reactive microglia, the target for inflammatory suppression [18]. So far, COX-2 has not been detected in astrocytes and microglia in AD and is barely induced by the inflammatory mediators in AD [19]. It would be anticipated, therefore, that NSAIDs with inhibitory activity against COX-1 rather than COX-2 would be more likely to reduce brain inflammation selectively.

Other mechanisms of action have been proposed for activity of certain NSAIDs such as inhibition of Aβ formation [64] and PPAR-γ agonism [17,30]. However, these activities are selective and are observed only at concentrations considerably higher than those anticipated from normal therapeutic doses. Nevertheless, it cannot be assumed that equivalent activity will be observed in brain and periphery for any given NSAID, particularly in view of the paucity of information regarding the ability of these agents to cross the blood brain barrier.

3. Epidemiological studies

The key results of major epidemiological studies examining the effects of NSAIDs against AD or dementia generally are shown in Table 1. The data are highly condensed and details need to be sought in the original publications. All of the studies involved traditional NSAIDs since selective COX-2 inhibitors have not been in use long enough for epidemiological data to be collected.

The most informative studies are those where the incidence of AD has been tracked in defined populations and where the consumption of NSAIDs has been carefully documented. In the Rotterdam study [21], a cohort of 6989 individuals aged 55 or older was repeatedly assessed. Drug use was documented from prescription records. For those using NSAIDs longer than 24 months, the relative risk of AD was reduced to 0.2 (95% CI 0.05–0.83). For those exposed from 1 to 23 months, there was a non-significant reduction to 0.83 (95% CI 0.62–1.11), and for those exposed for less than 1 month, there was no effect. It is noteworthy that no association was found between the use of NSAIDs and the risk of vascular dementia. A distinction between AD and vascular dementia has not always been made in epidemiological studies. The most commonly used NSAIDs were diclofenac with 43.2% of prescriptions and ibuprofen with 21.6% of prescriptions.

The Baltimore longitudinal study of aging [56] tracked the incidence of AD in a cohort of 1686 participants followed for many years. Drug use was obtained only by interview and thus