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Review - Part of the Special Issue: Alzheimer's Disease - Amyloid, Tau and Beyond

Therapeutic implications of the prostaglandin pathway in Alzheimer's disease

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ABSTRACT

An important pathologic hallmark of Alzheimer's disease (AD) is neuroinflammation, a process characterized in AD by disproportionate activation of cells (microglia and astrocytes, primarily) of the non-specific innate immune system within the CNS. While inflammation itself is not intrinsically detrimental, a delicate balance of pro- and anti-inflammatory signals must be maintained to ensure that long-term exaggerated responses do not damage the brain over time. Non-steroidal anti-inflammatory drugs (NSAIDs) represent a broad class of powerful therapeutics that temper inflammation by inhibiting cyclooxygenase-mediated signaling pathways including prostaglandins, which are the principal mediators of CNS neuroinflammation. While historically used to treat discrete or systemic inflammatory conditions, epidemiologic evidence suggests that protracted NSAID use may delay AD onset, as well as decrease disease severity and rate of progression. Unfortunately, clinical trials with NSAIDs have thus far yielded disappointing results, including premature discontinuation of a large-scale prevention trial due to unexpected cardiovascular side effects. Here we review the literature and make the argument that more targeted exploitation of downstream prostaglandin signaling pathways may offer significant therapeutic benefits for AD while minimizing adverse side effects. Directed strategies such as these may ultimately help to delay the deleterious consequences of brain aging and might someday lead to new therapies for AD and other chronic neurodegenerative diseases.

Contents

1. Neuroinflammation in AD

Alzheimer's disease (AD) is an incurable neurodegenerative disorder affecting tens of millions of Americans and their families. Sporadic, or late onset, AD (LOAD) is slowly progressive, with age representing the single greatest risk factor. While the neuropathologic hallmarks of the disease include both intra- and extracellular aggregation of neurotoxic peptides within discrete brain regions, widespread neuroinflammation prominently accompanies these lesions [1–4]. Indeed, inflammatory molecules, including prostaglandins and cytokines, increase in cerebral spinal fluid (CSF) and brain parenchyma with age [5–8] and are associated with age-dependent cognitive impairment [9–11], suggesting that exacerbated or persistent neuroinflammation is a potentially significant driver of pathogenesis and disease progression in age-related neurodegenerative diseases [12], and

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especially in AD [13]. Furthermore, this inflammatory milieu is present in both the initial asymptomatic latent disease phase [14] in addition to more advanced stages of AD, supporting the development of targeted anti-inflammatory pharmacotherapy approaches aimed at prevention as well as treatment [15].

2. NSAIDs and AD: Epidemiology

Anti-inflammatory drugs are widely used for a variety of conditions, from simple headaches and fevers to serious autoimmune disorders such as rheumatoid arthritis (RA). Noting that various molecular signatures of inflammation are markedly increased in the brains of AD subjects [1,16,17], more than twenty years ago McGeer, Rogers, and colleagues observed that coincidence of AD and RA was significantly below the levels expected in the general population, implicating anti-inflammatory drugs as potentially neuroprotective. Specifically, the authors calculated general AD prevalence to be 2.7% in patients older than 64 years, and according to hospital discharge statistics, found that a diagnosis of AD and RA in the same patient existed in 29 of 13,246 individuals (0.2%) [18]. Furthermore, only 2 of 169 autopsied putative AD cases were documented to have preexisting RA, and the coincidence of both disorders was less than 0.5% (6 of 1332) in RA and AD clinics [18]. They inferred from this association that chronic anti-inflammatory treatment may provide a significant preventive or therapeutic intervention for AD.

3. NSAIDs and AD: Clinical trials

Although epidemiological findings were ultimately met with skepticism because of the unusually low AD prevalence cited compared to other reported observations [19], Rogers et al. conducted a short-term double-blind placebo-controlled clinical trial using the non-steroidal anti-inflammatory drug (NSAID) indomethacin [20]. They reported reduced cognitive impairment in patients prescribed 100 to 150 mg/d of indomethacin after six months of treatment compared to controls [20]. Unfortunately, the study was hampered by poor tolerance of drug side effects and significant participant dropout, and did not address the effects of NSAIDs during the prodromal asymptomatic phase of AD since inclusion criteria for study subjects included previous AD diagnosis. Several clinical trials followed mostly in patients with clinical AD with varying limited success [21–25]. Even so, administration of non-selective [26–31] and selective [26,32] COX inhibitors in various murine AD models results in significant reduction of amyloid pathology and associated neuroinflammation, as well as improved performance in cognitive testing. Combined with existing epidemiological evidence [1,16–18] supporting this protective role for NSAIDs in the development of AD, the ADAPT study tested the preventive efficacy of selective and non-selective COX inhibitors in AD [33,34], but it was abruptly discontinued due to significant cardiovascular side effects [35,36]. Noteworthy, a subset of participants in that trial who did not develop AD early in the trial were shown to have a lower incidence of AD with long-term follow up, suggesting a subgroup in the study in whom NSAID administration may have provided a preventive benefit [36,37]. However, for others in the trial, NSAID administration was poorly tolerated and in others may have unmasked latent AD [35,36]. The study authors acknowledge that the therapeutic effect of NSAIDs likely varies as a function of AD stage and progression [33,34], confirming that increased efficacy might be achieved through prophylactic NSAID administration years in advance of clinical onset. Thus, while NSAIDs demonstrated neuroprotection in numerous experimental studies, there appeared to be limited clinical benefit for patients with AD (Table 1). Zahs and Ashe offer a possible explanation for this unfortunate contradiction, proposing that current animal models of AD more accurately reflect early latent phases of disease, failing to accurately capture the more clinically observed time course [38]. If true, this suggests that NSAID clinical trials should focus on prevention over intervention, a perspective supported by the original observation in RA subjects where NSAID regimens were likely initiated during latent disease phase in predisposed individuals. An additional consideration is the deleterious side effects associated with chronic NSAID use, especially selective COX-2 inhibitors like celecoxib and rofecoxib, in elderly patients [35,39]. Thus, a more effective, less toxic alternative is needed.

4. Cyclooxygenase and AD

NSAIDs inhibit cyclooxygenase (COX) enzymes, the rate-limiting mediators of prostanoid biosynthesis. Prostanoids are a broad class of arachidonic acid-derived paracrine signaling molecules that include thromboxanes, prostaglandins, and prostacyclins. Under normal conditions, a constitutive pool of prostanoids ubiquitously regulates a host of diverse physiological processes, including vasomotor tone, platelet aggregation, ovulation, and neonatal development [40–43]. However, a second highly responsive and inducible prostanoid pool of primarily prostaglandin E2 (PGE_2) mediates the initiation and propagation of inflammation, and is thought to contribute to the disproportionate inflammatory response in AD, and to many other pathological processes such as carcinogenesis and metastasis [44,45]. As endogenous lipid signaling molecules, the prostanoids are not proactively synthesized and stored within cells for future release, but are rather generated *on demand* in response to a variety of

Table 1
Results from randomized, double-blinded, placebo-controlled clinical trials using currently prescribed NSAIDs. ADAS-cog (Alzheimer Disease Assessment Scale- Cognitive); CIBIC+ (Clinician's Interview Based Impression of Change with caregiver input); AD (Alzheimer's disease); MCI (mild cognitive impairment).

Drugs	No. of subjects	Primary outcome measure	Results	Pre-treatment state	References
Celecoxib	425	[a]ADAS-cog and [b]CIBIC+	Did not slow the progression	Mild-to-moderate AD	[126]
Celecoxib or Naproxen	2528	Incidence of AD	Reduction in AD incidence among asymptomatic enrollees who were given naproxen. High incidence of adverse side effects for both drugs	Symptomatic AD	[37]
Ibuprofen	132	[a]ADAS-cog	Did not slow the progression	Mild-to-moderate AD	[127]
Prednisone	138	[a]ADAS-cog	Did not slow the progression	Probable AD	[128]
Rofecoxib	692	[a]ADAS-cog and [b]CIBIC+	Did not slow the progression	Mild-to-moderate AD	[129]
Rofecoxib	1457	Percentage of patients with a clinical diagnosis of AD	Did not slow the progression	MCI	[130]
Rofecoxib or Naproxen	351	[a]ADAS-cog	Did not slow the progression	Mild-to-moderate AD	[131]
Triflusal	257	[a]ADAS-cog	Triflusal therapy was associated with a significant lower rate of conversion to dementia	MCI	[132]