Recent findings in prevention and treatment of Alzheimer's disease with anti-inflammatory drugs

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SUMMARY: While cure for Alzheimer's disease is still unknown, many medications whose primary function is to ease the symptoms of AD are in a widespread use. Some epidemiological studies have shown the possibility of various anti-inflammatory drugs to belong to that group of medications. Nonsteroidal anti-inflammatory drugs have been thought as drugs with most potential in the prevention and treatment of AD, since many studies involved patients who suffered not only from AD, but also from some inflammatory illness that was treated precisely with NSAIDs. However, clinical trials demonstrated almost exclusively negative results, in strong contrast with previous findings, both in prevention and treatment of AD. Even though the criticism of both clinical and epidemiological studies exists, there is still not enough data to conclusively approve or disprove either of them.

KEYWORDS: Anti-inflammatory drugs, Alzheimer's disease, NSAIDs, Clinical trials, Preventive trials, Epidemiological studies

Given the unfortunate fact there is still no cure for Alzheimer's disease (AD), most of efforts are directed at finding the medication to ease and/or delay the very onset of the disease. There are many suspected causes for Alzheimer's cases, so naturally several hypotheses about its mechanism of development exist, such as tau, amyloid and cholinergic. Even though the environmental factors and age are thought to play a causal role in AD, genetics is, however, considered as a predominant factor, with the inheritance of E4 allele of apoliprotein E being probably the best known risk factor[1]. Most of today's drug therapies are based on cholinergic hypothesis, which postulates that Alzheimer's disease is caused by the lack of neurotransmitter acetylcholine[2]. Donepezil, one of those medications, aims to block the enzyme which would normally breakdown acetylcholine.[3] Memantine, on the other hand, acts as a NMDA receptor antagonist on the glutamatergic system[4]. Glutamate, although an important neurotransmitter, can lead to an unwanted excitotoxicity if it accumulates in excessive amounts in the brain[5]. Those drugs had moderate success, due to several side-effects, and in most cases are administrated together, with only donepezil showing benefits when used to treat advanced AD[6]. Additionally, recent studies have demonstrated the possibility of the role anti-inflammatory drugs could play in treatment, and also prevention, of Alzheimer's disease.

Overview of NSAID mechanism of action

Nonsteroidal anti-inflammatory drugs, commonly known as NSAIDs, are a class of drugs that provide wide range of effects, including antipyretic, analgesic and of course, anti-inflammatory. Their main mechanism of action is inhibition of enzyme cyclooxygenase (COX), which then leads to the inhibition of prostaglandins synthesis. Cyclooxygenase exists in two major isoforms, COX-1 and COX-2, while COX-3 has been described as a splice variant of COX-1.[7,8] Both COX-1 and COX-2 are very similar in structure, the main difference being that COX-1 is constitutively expressed in tissue, when COX-2 is not expressed under normal circumstances (COX-2 expression is a part of inflammatory response). Furthermore, different levels of these isoforms are present at different stages of AD, and it was suggested that COX-2 might be involved in regenerative pathways in the brain, while COX-1 could play a role in inflammatory pathway [7,9].

Based on these isoforms are also two classes of NSAIDs, one which acts as a non-selective COX-inhibitors (aspirin, ibuprofen, naproxen, indomethacin) and another which specifically targets COX-2 (celecoxib, rofecoxib)[9].

Effects of anti-inflammatory drugs on AD

Even though not all anti-inflammatory drugs are NSAIDs, most of studies directed at this matter focused primarly on them, due to their availabilty and known mechanism. Other drugs will also be mentioned in this article, in contrast, or more likely, in confirmation of their potential in treatment, as well as prevention, of AD.

When it comes to NSAIDs, it seems that the type of drug plays rather important role. NSAIDs without aspirin compunds have been proven to show more protective effects when compared to the patients who were using aspirin[9]. Moreover, a cohort study published in 2004, that followed 1301 dementia-free participants over the course of 6 years, showed that subjects administered with non-aspirin NSAIDs for around three years did not developed AD in the next three years[10]. Most studies that include NSAIDs involve patients who suffer not only from AD but also from inflammatory diseases such as arthritis. The study

Drug	Treatment duration	Dose (mg/day)	No. patients	Main outcome	Reference
Indomethacin	6 months	100-150	44	Beneficial effects	Rogers et al. (1993)
Indomethacin	1 year	100	51	Beneficial effects	De Jong et al. (2008)
Diclofenac	6 months	50	41	Beneficial effects	Schaarf et al. (1999)
Nimesulide	3 months	200	40	Neutral effects	Aisen et al. (2002)
Prednisone	1 year	10	138	Neutral effects	Aisen et al. (2000)
Dapsone	1 year	100	201	Neutral effects	Bain (2002)
Hydroxychloroquine	18 months	200-400	168	Neutral effects	Van Gool et al. (2001)
Celecxoib	1 year	400	285	Neutral effects	Sainati et al. (2000)
Celecoxib	1 year	400	425	Neutral effects	Soininen et al. (2007)
Rofecoxib	1 year	25	351	Neutral effects	Aisen et al. (2003)
Rofecoxib	1 year	25	692	Neutral effects	Reines et al. (2004)
Naproxen	1 year	440	351	Neutral effects	Aisen et al. (2003)
Ibuprofen	1 year	800	132	Neutral effects	Pasqualetti et al. (2009)
Tarenflurbil	1 year	800-1600	210	Neutral effects	Wilcock et al. (2008)
Tarenflurbil	18 months	1600	1684	Neutral effects	Green et al. (2009)
Tarenflurbil	18 months	1600	840	Neutral effects	Wilcock (2009)

of McGreer et al, published in 1990, reviewed 7490 hospital discharges and insinuated the idea that anti-inflammatory drugs, corticosteroids and other anti-inflammatory agents help ease the effects and the irreversible neurodegenerative process of AD. In addition, Japanese patients who suffered from leprosy also exhibited lower incidence of AD, which is atributed to them being treated with dapsone, an antibiotic whose mechanism of action also includes anti-inflammatory activity[8]. Also significant to mention is the study from 1994 by Chui et al that showed lower levels of beta-amyloid plaques in patients who suffer from both AD and leprosy.[11] Another important study, conducted at Johns Hopkins Alzheimer's Disease Research Center in 1995 showed that patients who were taking NSAIDs on a daily basis at a study entry[12], not only experienced later onset of symptoms, but also showed reduced severity of symptoms after adjustment for age and duration of disease and – most interestingly – displayed slower progression of symptoms upon longitudinal evaluation of wide variety of neuropsychological measures[8]. As many of those studies mainly focused on reviews and documentation of patient's history, the need of clinical trials arose.

One of those trials, conducted in 1993 by Rogers et al, was double-blind, placebo controlled study in which patients were administrated 100-150mg of indomethacin over a course of 6 months. The study was concluded with positive results, however since high number of patients receiving indomethacin abandoned the trial, the results could be considered biased or rather problematic to explain[13,8]. Subsequent studies followed, but due to a low number of participants and, again, high number of desertion of active group recipients, the studies showed only favourable indications[8]. Another important study was 1-year long double-blind, placebo controlled study which primarily concentrated on celecoxib, but the drug did not show any ability to slow down cognitive decline. What's more, no other study carried out so far hasn't had a positive result linking any of selective COX-2 inhibitors and beneficial treatment they may have in AD. Additionally, long-term studies with non-selective COX inhibitors also haven't given positive results in patients with mild to moderate Alzheimer's disease[9]. Tarenflurbil underwent extensive clinical trials, all of which conclusively showed no relation whatsoever between the administration of the drug and its supposable beneficial potential.[9,14] Also, studies with other anti-inflammatory agents produced completely negative results as well[9].

Preventive studies of NSAIDs have similarly produced negative results, despite being designed to last for longer period of time and having evidently more participants[9]. Possibly the largest of those studies was a trial conducted in 2001 with more than 2500 partakers who were all at risk for AD. They were divided in three groups, one of which received naproxen, another celecoxib, while third group took placebo. Although planned to last for 7 years, the trial ended after only 3, and analyses showed increased hazard ratios for AD compared to placebo with both celecoxib and naproxen[9,15]. However, recent analysis showed that people from naproxen group were actually protected from the onset of AD when compared to those in placebo group. Those results refer to people whose brain was still disease free in the beginning of the trial, and were taking naproxen for 1 to 3 years. On the other hand, taking NSAIDs turned out to be not only futile, but also to aggravate the condition of people, in whose brain the disease process has already started, no matter if symptomatic or not[9].

Conclusion

Even though all long-term clinical trials failed to produce wanted results, those failures could be attributed to wrong timing, low doses and wrong class of drug administrated, or perhaps, too short time to conduct a significant study. One theory suggest that anti-inflammatory drugs cannot reduce effects of AD once the disease starts, even when the disease still shows no symptoms at all. In addition, NSAIDs have considerably severe gastro-intestinal side-effects, which occurred in already mentioned studies with tarenflurbil[9].

To sum up, it's hard to give a final conclusion about the role anti-inflammatory drugs play in treatment and prevention of Alzheimer's disease, mainly because almost all published studies contradict themselves in one way or another. While epidemiological studies have shown that prolonged exposure to NSAIDs

may lead to delayed onset and serve as a protective factor in AD, clinical studies paint rather grim picture and show us that some of the anti-inflammatory drugs could even worsen the symptoms[9]. However, it's important to notice that ibuprofen, the most promising subject of epidemiological studies16, has been studied only in a single small trial with patients who suffer from AD[17], and no preventive trial has been conducted. So even though these results may seem discouraging, many new trials should be established in order to conclusively determine the role anti-inflammatory drugs play in the process of Alzheimer's disease.

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Noviji pronalasci u prevenciji i liječenju Alzheimerove bolesti s protuupalnim lijekovima

SAŽETAK: Iako ne posotji apsolutni lijek za Alzheimerovu bolest (AB), koriste se mnogi lijekovi s kojima se mogu smanjiti simptomi te bolesti. Neke epidemiološke studije su pokazale mogućnosti za različite protuupalne lijekove koji bi se mogli koristiti u tu svrhu. Smatralo se da nesteroidni antiinflamatorni lijekovi (NSAIL) posjeduju najviše potencijala za prevenciju i liječenje AB te su u brojne studije bili uključeni pacijenti koji su koristili terapiju NSAIL-ima zbog neke druge upalne bolesti. Ipak, klinička istraživanja su pokazala gotovo isključivo negativne rezultate za prevenciju i liječenje AB i što je protivno prijašnjim pronalascima. Usprkos kriticizmu koji postoji i za klinička i epidemiološka istraživanja, još uvijek ne postoji dovoljno podataka za konačno odluku o upotrebi ili odbacivanju ove skupine lijekova.

KLJUČNE RIJEČI: Protuupalni lijekovi, Alzheimerova bolest, NSAIL, klinička istraživanja, preventivna istraživanja, epidemiološke studije