



# NSAIDs: how they work and their prospects as therapeutics in Alzheimer's disease

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There is significant epidemiological evidence to suggest that there are beneficial effects of treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in Alzheimer's disease, although these effects have not been reproduced in clinical trials. The failure of the clinical trials may be attributed to several possible facts: (1) NSAIDs may have been delivered too late to patients, as they may only be effective in early stages of the disease and possibly counterproductive in the late stages; (2) the beneficial effect may depend on the drug, because different NSAIDs may have different molecular targets; (3) the NSAID concentration reaching the brain and the duration of the treatment could also be critical, so increasing drug penetration is important in order to improve the efficacy and avoid secondary gastro-intestinal effects of the NSAIDs. In this report we analyze these different factors, with special emphasis on the role of NSAIDs in microglia activation over time.

**Keywords:** NSAIDs, Alzheimer's disease, microglia, PPAR $\gamma$ , amyloid

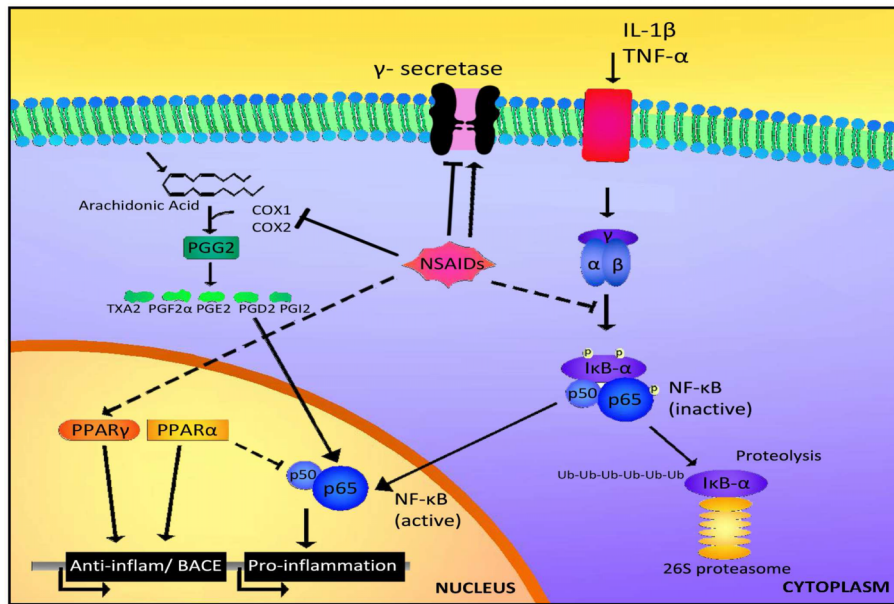
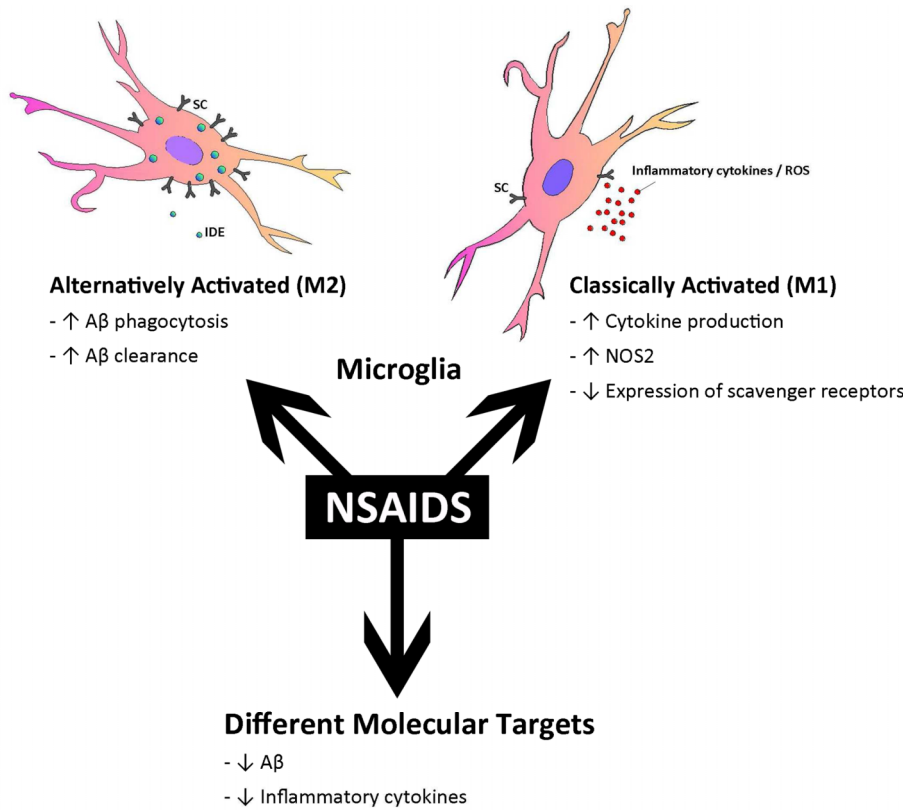
Many inflammatory pathways have been implicated in Alzheimer's disease (AD), yet these pathways are not sufficiently well delineated to define those processes and targets that may be pathogenic as opposed to those that may be protective. A clearer understanding of these distinctions is critical to the design of therapeutic strategies. The finding that treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced risk and age of onset of AD reinforces the hypothesis that modulating inflammation could have therapeutic efficacy. The beneficial effects of NSAIDs have also been associated with reductions in A $\beta$  generation, since experiments *in vitro* and in AD animal models indicate that certain NSAIDs are able to decrease A $\beta$  levels, plaque size and tau phosphorylation (Yoshiyama et al., 2007; El Khoury and Luster, 2008).

However, clinical trials have failed to reproduce the beneficial effects of NSAIDs in AD patients. This has led to further analysis of the previously published epidemiological data, which has revealed that the use of NSAIDs prevents cognitive decline in older adults if started in midlife (prior to age 65) rather than late in life (Hayden et al., 2007). In addition, it was recently shown that while NSAIDs may indeed protect those with healthier brains, they can accelerate AD pathogenesis in patients with advanced stages of the disease (Breitner et al., 2009). This is supported by studies in transgenic mice, in which NSAIDs can prevent the appearance of cell cycle protein markers in neurons in young mice, but not after cell cycle entry has been initiated (Varvel et al., 2009). Therefore, it seems that the protective effects of NSAIDs depend very much on the stage of the disease at which the medication is started as well as the duration of the treatment. Here we discuss four possible reasons why clinical trials with NSAIDs have been unsuccessful.

## TEMPORAL PROFILE OF MICROGLIAL ACTIVATION

A potential target of NSAIDs is thought to be the microglia associated with the senile plaques. This is supported by a study by Mackenzie and Munoz (1998) showing in non-demented patients that those treated with NSAIDs had three times less activated microglia as non-treated controls. These data have been confirmed by *in vivo* treatment with NSAIDs in mouse models of AD, which have shown decreases in microglial activation and in inflammatory mediators such as iNOS, COX and cytokines (Lim et al., 2000; Heneka et al., 2005). Experiments carried out in cultured microglia have revealed that incubation with NSAIDs decreased the secretion of pro-inflammatory cytokines and may increase A $\beta$  phagocytosis (Lleo et al., 2007). However, the reduction of activated microglia and astroglia by NSAIDs was not significant in AD patients, indicating an age or stage dependent difference in the glial response i.e. in their activation rate (Alafuzoff et al., 2000). Recently, these findings have been backed up by observations indicating that microglia may change from alternative to classical phenotype over time (Colton et al., 2006; Hickman et al., 2008; Jimenez et al., 2008; Lucin and Wyss-Coray, 2009), although probably there is a heterogeneous population. In addition, a paper of Meyer-Luehmann et al. (2008) using two-photon microscopy showed that microglia in the aged mouse brain is less motile and possess fewer processes. Therefore, the response of NSAIDs may differ in "young" vs "old" microglia (Figure 1).

It has been hypothesized that early microglial activation in AD delays disease progression by promoting clearance of A $\beta$  before formation of senile plaques. It is conceivable that glial activation is protective through mechanisms such as phagocytosis and clearance of A $\beta$  deposits (through release of insulin degrading enzyme, IDE), forming a protective barrier between A $\beta$  and neurons and



**FIGURE 1 | Different targets for NSAIDs.** The response to NSAIDs may differ depending on whether they are used in early stages of disease, in which microglia present an alternatively activated phenotype compared with late stages which is associated with a classical microglia phenotype. On the other

hand, different subsets of NSAIDs have different affinity for targets such as COX1, COX2, NFκB, PPARγ or γ-secretase, resulting in a range of effects including reductions in inflammatory mediators, such as cytokines and alterations in Aβ generation.

secretion of growth factors, early in the disease (Wyss-Coray et al., 2003; Maragakis et al., 2006; Wyss-Coray, 2006). In later stages, with persistent production of pro-inflammatory cytokines, microglia lose their protective effect (Hickman et al., 2008; Jimenez et al.,

2008) and may become detrimental through the release of cytokines and chemokines including IL-1β, IL-6, TNFα, IL-8 and MIP-1α (Hickman et al., 2008). These inflammatory mediators modulate immune and inflammatory function and may also alter neuronal

function. In addition, microglia from old transgenic mice have a decrease in the expression of the A $\beta$ -binding scavenger receptors A (SRA), CD36 and RAGE, and the A $\beta$  degrading enzymes IDE, neprilysin and MMP9, compared with wild-type controls (Hickman et al., 2008) (**Figure 1**). On the other hand, in aged human brain many microglia are dystrophic showing morphological features indicative of senescence, such as fragmented cytoplasmic processes (Streit et al., 2004). Therefore, overactivated and dysregulated microglia could cause uncontrolled inflammation that may drive the chronic progression of AD (Mrak and Griffin, 2005; Gao and Hong, 2008).

Microglia can be primed or desensitized by a stimulus (such as A $\beta$ ), which prepares the cells for an enhanced or decreased response to a second challenge (Gao and Hong, 2008). Microglia in aged or diseased brains are primed and usually behave differently to those in younger individuals (Gao and Hong, 2008). Thus, it is likely that microglia do not respond equally to anti-inflammatory therapy in old age and therefore, treatment of patients with NSAIDs in advanced stages of the disease may not produce any benefit.

One of the most controversial points is to establish whether microglia are "oversaturated" at a certain age or whether there is a loss of function. The debate on microglia function in AD progression has been intensified by a recent report showing that AD animal models with nearly complete ablation of microglia did not display differences in plaque formation (Grathwohl et al., 2009), raising questions as to whether inflammation may have an effect on neurodegeneration and cognitive decline rather than a direct role on A $\beta$  deposition. Furthermore, a study using two-photon microscopy in the intact brain of living AD mice has revealed an involvement of microglia in neuron elimination, indicated by locally increased number and migration velocity of microglia around lost neurons (Fuhrmann et al., 2010). Therefore, evidence has started to accumulate that the function of microglia is neuroprotection in young individuals (by secretion of neurotrophic factors and anti-inflammatory cytokines) and that "senescent" microglia contribute to the onset of sporadic AD (Streit et al., 2004, 2009).

Similarly, there are other factors that may change the risk for AD depending on the age, such as obesity or body mass index (BMI), which is an important predictor for late life dementia. However, in late life, low and declining BMI is associated with increased AD risk. Therefore, there is time frame for the beneficial effect of certain factors, and since AD is a disease with a long preclinical period, trials of short duration in severe cases of AD do not provide reliable information regarding development of AD (Bennett and Whitmer, 2009).

### MULTIPLE MOLECULAR TARGETS FOR NSAIDs

The type of NSAID appears to affect the outcome of the clinical trial (**Figure 1**). The inhibition of the canonical targets of NSAIDs, cyclooxygenase-1 and -2 (COX-1 and COX-2), do not seem to be responsible for the protective effect of NSAIDs in AD (see review Lleo et al., 2007). On the contrary, some COX-2 inhibitors may raise A $\beta$ 1-42 secretion (Kukar et al., 2005).

Interestingly, some NSAIDs and other small organic molecules have been found to modulate  $\gamma$ -secretase and to selectively reduce A $\beta$ 1-42 levels without affecting Notch cleavage. A subset of NSAIDs including ibuprofen, sulindac sulfide, and indomethacin have been

shown to decrease the levels of secreted A $\beta$ 42 in cells as well as in animal models of AD (Weggen et al., 2001; Eriksen et al., 2003). Importantly, the generation of A $\beta$ 40 was largely unaltered by these compounds, indicating that certain NSAIDs modulate rather than inhibit  $\gamma$ -secretase activity (Czirr and Weggen, 2006). In fact, NSAIDs seem to bind APP, instead of the  $\gamma$ -secretase (Kukar et al., 2008). Some positive effects on cognitive performance of AD patients have been observed with indomethacin and the (R)-enantiomer of flurbiprofen in phase-2 trials, while other NSAIDs without A $\beta$ 42 reducing activity did not show beneficial effects. However, recent clinical trials in mild AD cases revealed that R-flurbiprofen (tarenflurbil) does not slow cognitive decline or the loss of activities of daily living (Green et al., 2009). In addition, epidemiological studies report that the protective effect of NSAIDs seems to be independent of the A $\beta$ 42 reducing activity of the NSAID (Szekely et al., 2008a; Vlad et al., 2008).

Besides targeting molecules such as COX and  $\gamma$ -secretase, some NSAIDs such as ibuprofen, naproxen and indomethacin can activate PPAR $\gamma$  (Jaradat et al., 2001). PPAR $\gamma$  inhibition regulates the transcription of pro-inflammatory genes, such as IL1 $\beta$ ; therefore activation of PPAR $\gamma$  consequently inhibits the inflammatory response. In addition, we found that PPAR $\gamma$  activators are able to decrease total A $\beta$  levels under inflammatory conditions by affecting BACE1 transcription (Sastre et al., 2006b, 2008). Recently it was shown that ibuprofen is able to suppress RhoA activity in neuronal cells through PPAR $\gamma$  activation, promoting neurite elongation (Dill et al., 2010). Therefore, PPAR $\gamma$  activation could be beneficial in AD at several levels. A recent prospective randomized, open-controlled study with pioglitazone (a typical PPAR $\gamma$  agonist) has shown that at 6 months the WMS-R logical memory-I scores significantly increased in the pioglitazone group, but not in the control group (Hanyu et al., 2009). Another PPAR $\gamma$  agonist, rosiglitazone has been trialed with inconsistent results. In contrast to pioglitazone, rosiglitazone cannot cross the blood brain barrier (BBB) (Festuccia et al., 2008) and it was suggested that the protective effects are mediated through its effects on insulin and glucocorticoids that are able to penetrate into the brain.

Certain NSAIDs, such as flurbiprofen and indomethacin, inhibit the nuclear translocation of the transcription factor NF- $\kappa$ B. In addition, it was recently shown that R-flurbiprofen can interfere with the interaction between RXR $\alpha$  and 9-cis-retinoid acid, and that 9-cis-retinoid acid decreases (R)-flurbiprofen's reduction of A $\beta$  secretion (You et al., 2009). R-flurbiprofen has been shown to upregulate NGF and BDNF *in vitro*, which could potentially offer neuroprotection (Zhao et al., 2008). However, as mentioned above, R-flurbiprofen trials have not been successful, perhaps because of its low permeability into the brain and its weak pharmacological activity (Imbimbo, 2009).

### DURATION AND DOSE

The duration of the treatment could also influence the magnitude of the effect. A meta-analysis of nine studies revealed that the benefit of the NSAID treatment was greater in long-term users than in intermediate users (Etminan et al., 2003). Moreover, it has been suggested that at least 2 years of exposure are necessary to obtain full benefit, so the benefits may be greater the longer NSAIDs are used (Sastre et al., 2006a). The effect of NSAIDs in mice has

been reviewed extensively by Imbimbo (2009). Short term studies (3- to 7-days treatment) in transgenic mice revealed decreases in A $\beta$  levels, particularly in the A $\beta$ 42 isoform and activated microglia, although some studies have shown no changes, depending on the drug and the animal model (Eriksen et al., 2003; Heneka et al., 2005; Lanz et al., 2005). Long-term administration has demonstrated protective effects predominantly using ibuprofen and indomethacin treatments, in both types of A $\beta$ , as well as brain plaque load and inflammation (see Imbimbo, 2009). However, chronic R-flurbiprofen produced weak effects on A $\beta$  deposition, and was more effective as a preventive rather than a therapeutic treatment (Kukar et al., 2007). This is in line with the results obtained in clinical trials using flurbiprofen.

The dose and permeability of the drug could be relevant, although some epidemiological studies suggest that the daily dose is not important. In't Veld et al. (2001) noted that low doses had effects equal to those of the higher doses typically prescribed for osteoarthritis and other inflammatory conditions. However, the failure of some clinical trials has been associated with the low permeability of certain drugs such as R-flurbiprofen and rosiglitazone. In addition, there is some conflict between the potency of certain NSAIDs to decrease A $\beta$ 42 *in vitro* (reaching 300  $\mu$ M) and the effective drug concentration in the brain. Active concentrations of NSAIDs found in human plasma and cerebrospinal fluid are in the lower  $\mu$ M range (Bannwarth et al., 1990, 1995), which could not account for the effects on  $\gamma$ -secretase cleavage. Unfortunately, the clinical dose is limited because of adverse effects such as irritation and ulceration of the gastro-intestinal (GI) mucosa. There is growing interest in improving absorption and BBB permeability of certain NSAIDs in order to allow the administration of lower doses of these drugs. Another point that has to be borne in mind is that the barrier may be compromised in neurodegenerative diseases, permitting the diffusion of molecules that usually have no access to the brain parenchyma, therefore the dose reaching the brain can be different in AD patients compared with healthy controls (Nguyen et al., 2002).

## ApoE GENOTYPE

Another possible confounding factor in NSAID trials is the genotype of the patients being treated, most notably in relation to ApoE. The majority of prospective studies appear to show greater benefits in those with an ApoE  $\epsilon$ 4 allele (Hayden et al., 2007; Szekely et al., 2008b). In a recent trial, the ApoE  $\epsilon$ 4 carriers treated with ibuprofen were the only group without cognitive decline (Pasqualetti et al.,

2009). Similar positive effects in ApoE4 carriers have also been seen when the NSAIDs have been taken in conjunction with Vit E (Fotuhia et al., 2008). In addition, the influence of NSAID use in microglia activation has been noted in all ApoE genotypes however the trend of lower counts of glial cells with regular NSAID use was more marked in patients carrying the ApoE $\epsilon$ 4/4 alleles (Alafuzoff et al., 2000).

By contrast, results from clinical trials with rosiglitazone suggest that those without an APOE  $\epsilon$ 4 allele exhibit cognitive and functional improvement in response to rosiglitazone, while those that do carry the allele carriers showed no improvement and some decline was noted (Risner et al., 2006). ApoE4 and C-terminal-truncated fragments of apoE4 [apoE4(1–272), lacking the C-terminal 27 aa] impair cytoskeletal structure and mitochondrial function and it seems that rosiglitazone reverses this effect.

## CONCLUSIONS

There is still controversy regarding the reasons why clinical trials with NSAIDs have provided such disappointing results. Here we suggest that the short duration of the trials, the use of drugs targeting the wrong molecule, the wrong timing of the treatment (patients too old or too severely ill), the low levels of the drugs reaching the CNS and the genetic variability of the patients may all have contributed to the failures.

It is still unclear whether NSAIDs are beneficial because of their effects on reducing A $\beta$  or whether it is because of their anti-inflammatory action or the interaction between both (reducing inflammation may decrease A $\beta$  generation and the other way around). It would be helpful in the future to determine whether patients involved in trials experience changes in biomarkers in blood or CSF (such as A $\beta$  levels, tau or inflammatory markers) and whether those correlate with cognitive performance.

Taking all the currently available evidence together, NSAIDs should be used as preventive treatment rather than a therapeutic option and this would make more sense in a disease with a long pre-clinical period, with evidence that microglial/cytokine events take place years or even decades before plaques or tangles are detected (Griffin et al., 1989; Cagnin et al., 2001).

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