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Thinking outside the box about COX-1 in Alzheimer's disease

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Abstract

This article from Coma et al. shows that a salicylic acid derivative Triflusal, a platelet aggregation inhibitor and irreversible inhibitor of COX-1, can correct defects in axonal curvature and cognition in an AD transgenic mouse model (Tg2576) (Coma et al., 2010). Here we discuss the controversy over the role of COX-1 in AD, which has not been considered carefully in part due to the presumed adverse gastrointestinal effects of COX-1 antagonism. However, recent clinical data from this group as well as other groups challenges this assumption that COX-1 antagonism will be associated with side effects. Most importantly this article raises critical questions about the role of COX-1, versus COX-2 versus both in A β pathogenesis. The animal model data in this article as well as the recently published trial data suggest that COX-1 may play an important role in early pathogenesis and should not be ignored as a potential target for early intervention.

Keywords

COX-1; COX-2; NSAIDs; MCI; Tg2576

The salicylic acid derivative Triflusal, a platelet aggregation inhibitor and irreversible inhibitor of COX-1, was effective in reducing cognitive deficits and indices of neurodegeneration. As with other NSAID effects observed in animal models, longer duration of Triflusal treatment appeared more effective, exerting a greater impact on reducing dense cored-plaque load and associated, glial cell proliferation, pro-inflammatory cytokine levels and abnormal axonal curvature, and the better the correction of cognitive deficits. The small Triflusal effects on amyloid burden (reducing dense cored plaques but not total burden) was somewhat surprising, considering that mixed COX inhibitors, including ibuprofen, have been reported to have a much more pronounced effect on reducing amyloid burden in AD models, provided intervention was pre-pathology and long duration (Choi et al., 2009; Heneka et al., 2005; Jantzen et al., 2002; Lim et al., 2000, 2001; McKee et al., 2008; Morihara et al., 2005; Weggen et al., 2001; Yan et al., 2003). Indomethacin, which like Triflusal, has more specificity for COX-1, exerted a similarly weak (but significant) anti-amyloid effect reducing amyloid burden by 20%. In contrast, NCX-2216,

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nitro-S-flurbiprofen (also preferential COX-1) had an intermediate effect on reducing amyloid burden (Jantzen et al., 2002). This may indicate that some of the anti-A β effects of mixed COX inhibitors like ibuprofen, indomethacin and flurbiprofen also benefit from pleiotropic actions including γ -secretase modulation (Weggen et al., 2001), anti-aggregation (Agdeppa et al., 2002) and share significant COX-related mechanisms involving cytokine modulation (e.g. phospholipase A2, inducible nitric oxide synthase, interleukin-1, and α -1 anti-chymotrypsin) (Moriwara et al., 2005).

Trials in MCI or AD using a drug selective for COX-2 such as rofecoxib clearly failed (Aisen et al., 2008). Ultimately, COX-2 inhibitors have not worked in clinical trials after onset of cognitive deficits, for example, the COX-2 inhibitor rofecoxib was even associated with increased AD in a trial with MCI patients (Aisen et al., 2008). Similarly, a COX-2 inhibitor did not work for primary prevention in the ADAPT which was enriched with subjects with first degree relatives of AD patients (Laino, 2009). The anti-inflammatory steroid agent prednisolone failed (Aisen et al., 2000), which may relate to a known effect of glucocorticoids in inhibiting COX-2 in astrocytes (O'Banion et al., 1996).

Non selective COX inhibitors such as indomethacin (Rogers et al., 1993) and diclofenac (Scharf et al., 1999) showed preferential inhibition of COX-1 and possible positive clinical findings in AD trials. These "some what positive" trials were underpowered and full of safety issues including low tolerability. But with the positive results and good safety trial with Triflusal (Gomez-Isla et al., 2008), does that mean we should dismiss COX-2 as a target for prevention? Well the answer to that question requires a better understanding of stage-dependent pathogenesis. For example, COX-2 is elevated early in AD brain (Hoozemans et al., 2008). In AD models, COX-2 inhibitors can correct early deficits in LTP and cognition (Kotilinek et al., 2008) and early intervention trials (preMCI) with COX-2 specific inhibitor celecoxib showed a cognitive benefit with mild memory complaints and glucose utilization measured by FDG PET (Small et al., 2008). COX-1 and COX-2 are hypothesized to play different roles at different stages in AD (Hoozemans et al., 2008), which may explain why COX-2 antagonists can help if intervention is preMCI, while COX-1 antagonism may be somewhat effective up to MCI, but still probably not a viable target for AD. COX-2 has been associated with excitotoxicity but now it is known that COX-1 can also play a role in excitotoxicity (Pepicelli et al., 2005) that may have been inhibited by Triflusal in this Coma et al. report where it was associated with restoration of BDNF. Because neuronal COX-2 plays a critical role in memory retention (Rall et al., 2003), intervention with COX-2 antagonists at later stages could be detrimental after onset of neuron loss. In addition, some COX-2 inhibitors even increase amyloid burden (Jantzen et al., 2002; Xiang et al., 2002) or production (Kukar et al., 2007). Another reason not to dismiss COX-2 entirely as a target for prevention is that mixed COX inhibitors like ibuprofen, which has a better safety profile than naproxen, generally have a more robust impact on A β pathogenesis in AD models (Choi et al., 2009; Heneka et al., 2005; Jantzen et al., 2002; Lim et al., 2000, 2001; McKee et al., 2008; Morihara et al., 2005; Weggen et al., 2001; Yan et al., 2003) than Triflusal had in this AD model study.

The new data presented in this manuscript showing efficacy of Triflusal in an AD model (Coma et al., 2010) along with some positive results and good safety profile from the recent

MCI trial with Triflusal (Gomez-Isla et al., 2008) renews discussions about COX-1 and GI side effects. Although COX-1 inhibitors are generally considered to be associated with adverse side effects, it should be mentioned that this is not necessarily the case for Triflusal (Gomez-Isla et al., 2008). Surprisingly, there were no serious adverse gastrointestinal effects with Triflusal, in contrast to serious intestinal bleeding with subjects on aspirin, diclofenac or indomethacin (Gomez-Isla et al., 2008). The dogma that COX-1 inhibition inevitably causes gastrointestinal toxicity has recently been questioned by reports that newer selective COX-1 inhibitors do not necessarily have significant GI side effects (Tanaka et al., 2009). COX-2 specific inhibitors also have issues, most notably increasing cardiovascular risk (Rao and Knaus, 2008). COX-2 inhibitors cause selective suppression of vasodilatory and antithrombotic prostracyclin (PGI₂) in vascular endothelial cells, so suppression of COX-2 can increase thromboxane (TxA₂) levels and thus platelet aggregation (Jespersen et al., 2009).

Interestingly, like indomethacin (Rogers et al., 1993) and diclofenac (Scharf et al., 1999) naproxen is a mixed (COX-1 and COX-2) inhibitor that is more preferential for COX-1 than COX-2. In the large ADAPT trial, naproxen appeared to prevent conversion to AD, improved CSF tau and A β 42 biomarkers and reduced conversion rates, but only in subjects with no cognitive defects prior to onset of study (Laino, 2009). Whether the early halting of the ADAPT trial was necessary for naproxen's prevention of conversion to MCI (median 1.5 years duration on naproxen, 2 years off) remains a major question. Naproxen appeared to have more of an adverse cognitive effect on subjects with baseline deficits (Laino, 2009) possibly because of a stage-dependent alteration in the cytokines or microglial function (Hoozemans et al., 2008; Streit et al., 2009; Walker et al., 2009), raising serious questions about the potential detrimental effects of late stage intervention. Adverse effects observed at late intervention (post-MCI) with mixed COX inhibitors may also be independent of inflammation, for example by interfering with neuronal COX-2 required for normal memory retention (Rall et al., 2003). Alternatively, COX-1 and/or COX-2 may not be the ideal inflammatory target, since highly specific COX-1 or COX-2 inhibitors may upregulate arachidonic acid, a substrate for lipoxygenase pathway, also implicated in AD pathogenesis (Yao et al., 2005; Ikonovic et al., 2008).

Although lagging effects of drug efficacy (such as seen in the ADAPT) would be missed unless trials could be followed up to 4 years or later, collectively results from AD trials support the hypothesis that targeting early steps of pathogenesis are unlikely to be helpful after onset of cognitive decline. For example, prior to cognitive decline there is a pro-dromal period of several years duration where plaque and tangle buildup occur and are followed by an increase in CSF tau/ A β 42 ratios. Immediately preceding memory decline, there is pronounced brain atrophy and dramatic post-synaptic protein loss (Jack et al., 2010).

Unfortunately the role of neuroinflammation in Alzheimer's disease and mild cognitive impairment is still "a field in its infancy", also a title of McGeer's recently published article (McGeer and McGeer, 2010). This is exemplified by the fact that ten years ago several experts in neuroinflammation convened to write a special issue on relevance of neuroinflammation to Alzheimer's, including prospects of the amyloid vaccine and other inflammatory mechanisms like complement activation (Akiyama et al., 2000). The

conclusions of this article were that inflammation in AD is complex and has beneficial as well as detrimental effects (Akiyama et al., 2000). Ten years later the field remains full of controversy in part because of the frustration with trials having negative or unspectacular findings (both vaccine and NSAIDs). This paper (Coma et al., 2010) is likely to reignite a more focused discussion to the role of COX-1 at or before MCI and for more research on stage specific effects of inflammatory pathways and drug targets. This study also reinforces the need for animal models in developing and planning trials. Nevertheless epidemiology with aspirin, which may have similar mechanisms to Triflusal, showed weak or negative effects in prevention, and the fact that mixed COX inhibitors may have more robust effects on amyloid than Triflusal raises concerns about whether mixed COX inhibitors may work better to prevent AD.

In summary, although it is conceivable that a target other than COX-1 could play a role in Triflusal mechanism, this paper along with previous literature supports the hypothesis that COX-1 may be playing a crucial role in cognitive loss and neuroinflammation in the AD model. These strong animal model data suggest that COX-1 might be a viable target in Alzheimer's for prevention or even at MCI, but not play a major role in A β pathogenesis. In addition the lack of adverse side effects with Triflusal in the previous positive clinical trial results as well as in the animal models is encouraging.

Abbreviations

AD	Alzheimer's disease
ADAPT	Alzheimer's Disease Anti-inflammatory Prevention Trial
ApoE	Apolipoprotein E
Aβ	β -amyloid peptide
COX	Cyclooxygenase
MCI	Mild cognitive impairment
NSAIDs	Nonsteroidal anti-inflammatory drugs

References

- Agdeppa ED, et al. In vitro detection of (S)-naproxen and ibuprofen binding to plaques in the Alzheimer's brain using the positron emission tomography molecular imaging probe 2-(1-[6-[(2-[(18F]fluoroethyl)(methyl)amino]-2-naphthyl]ethylidene) malononitrile. *Neuroscience*. 2002; 117:723–730. [PubMed: 12617976]
- Aisen PS, et al. A randomized controlled trial of prednisone in Alzheimer's disease. *Alzheimer's Disease Cooperative Study*. *Neurology*. 2000; 54:588–593. [PubMed: 10680787]
- Aisen PS, et al. Rofecoxib in patients with mild cognitive impairment: further analyses of data from a randomized, double-blind, trial. *Curr. Alzheimer Res*. 2008; 5:73–82. [PubMed: 18288935]
- Akiyama H, et al. Inflammation and Alzheimer's disease. *Neurobiol. Aging*. 2000; 21:383–421. [PubMed: 10858586]
- Choi JK, et al. Anti-inflammatory treatment in AD mice protects against neuronal pathology. *Exp. Neurol*. 2009 PMID 19679126.

- Coma M, et al. Triflusal reduces dense-core plaque load, associated axonal alterations and inflammatory changes, and rescues cognition in a transgenic mouse model of Alzheimer's disease. *Neurobiol. Dis.* 2010 (Electronic publication ahead of print). PMID: 20149872.
- Gomez-Isla T, et al. A randomized, double-blind, placebo controlled-trial of triflusal in mild cognitive impairment: the TRIMCI study. *Alzheimer Dis. Assoc. Disord.* 2008; 22:21–29. [PubMed: 18317243]
- Heneka MT, et al. Acute treatment with the PPARgamma agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta1-42 levels in APPV717I transgenic mice. *Brain.* 2005; 128:1442–1453. [PubMed: 15817521]
- Hoozemans JJ, et al. Cyclooxygenase-1 and-2 in the different stages of Alzheimer's disease pathology. *Curr. Pharm. Des.* 2008; 14:1419–1427. [PubMed: 18537664]
- Ikonomic MD, et al. Increased 5-lipoxygenase immunoreactivity in the hippocampus of patients with Alzheimer's disease. *J. Histochem. Cytochem.* 2008; 56:1065–1073. [PubMed: 18678882]
- Jack CR Jr, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol.* 2010; 9:119–128. [PubMed: 20083042]
- Jantzen PT, et al. Microglial activation and beta-amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. *J. Neurosci.* 2002; 22:2246–2254. [PubMed: 11896164]
- Jespersen B, et al. Differential effects of immunosuppressive drugs on COX-2 activity in vitro and in kidney transplant patients in vivo. *Nephrol. Dial. Transplant.* 2009; 24:1644–1655. [PubMed: 19193738]
- Kotilinek LA, et al. Cyclooxygenase-2 inhibition improves amyloid-beta-mediated suppression of memory and synaptic plasticity. *Brain.* 2008; 131:651–664. [PubMed: 18292081]
- Kukar T, et al. Chronic administration of R-flurbiprofen attenuates learning impairments in transgenic amyloid precursor protein mice. *BMC Neurosci.* 2007; 8:54. [PubMed: 17650315]
- Laino C. In follow-up analysis of clinical trial, NSAIDs seem to preserve cognitive function in patients with healthy brains. *Neurol. Today.* 2009; 9:21–22.
- Lim GP, et al. Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. *J. Neurosci.* 2000; 20(15):5709–5714. [PubMed: 10908610]
- Lim GP, et al. Ibuprofen effects on Alzheimer pathology and open field activity in APPsw transgenic mice. *Neurobiol. Aging.* 2001; 22:983–981. [PubMed: 11755007]
- McGeer EG, McGeer PL. Neuroinflammation in Alzheimer's disease and mild cognitive impairment: a field in its infancy. *J. Alzheimers Dis.* 2010; 19:355–361. [PubMed: 20061650]
- McKee AC, et al. Ibuprofen reduces Abeta, hyperphosphorylated tau and memory deficits in Alzheimer mice. *Brain Res.* 2008; 1207:225–236. [PubMed: 18374906]
- Moriyama T, et al. Ibuprofen suppresses interleukin-1beta induction of pro-amyloidogenic alpha1-antichymotrypsin to ameliorate beta-amyloid (Abeta) pathology in Alzheimer's models. *Neuropsychopharmacology.* 2005; 30:1111–1120. [PubMed: 15688088]
- O'Banion MK, et al. Interleukin-1 beta induces prostaglandin G/H synthase-2 (cyclooxygenase-2) in primary murine astrocyte cultures. *J. Neurochem.* 1996; 66:2532–2540. [PubMed: 8632179]
- Pepicelli O, et al. Cyclo-oxygenase-1 and-2 differently contribute to prostaglandin E2 synthesis and lipid peroxidation after in vivo activation of N-methyl-D-aspartate receptors in rat hippocampus. *J. Neurochem.* 2005; 93:1561–1567. [PubMed: 15935072]
- Rall JM, et al. Intrahippocampal infusion of a cyclooxygenase-2 inhibitor attenuates memory acquisition in rats. *Brain Res.* 2003; 968:273–276. [PubMed: 12663097]
- Rao P, Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. *J. Pharm. Pharm. Sci.* 2008; 11:81s–110s. [PubMed: 19203472]
- Rogers J, et al. Clinical trial of indomethacin in Alzheimer's disease. *Neurology.* 1993; 43:1609–1611. [PubMed: 8351023]
- Scharf S, et al. A double-blind, placebo-controlled trial of diclofenac/ misoprostol in Alzheimer's disease. *Neurology.* 1999; 53:197–201. [PubMed: 10408559]

- Small GW, et al. Cognitive and cerebral metabolic effects of celecoxib versus placebo in people with age-related memory loss: randomized controlled study. *Am. J. Geriatr. Psychiatry*. 2008; 16:999–1009. [PubMed: 19038899]
- Streit WJ, et al. Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. *Acta Neuropathol*. 2009; 118:475–485. [PubMed: 19513731]
- Tanaka K, et al. Inhibition of both COX-1 and COX-2 and resulting decrease in the level of prostaglandins E2 is responsible for non-steroidal anti-inflammatory drug (NSAID)-dependent exacerbation of colitis. *Eur. J. Pharmacol*. 2009; 603:120–132. [PubMed: 19101538]
- Walker DG, et al. Decreased expression of CD200 and CD200 receptor in Alzheimer's disease: a potential mechanism leading to chronic inflammation. *Exp. Neurol*. 2009; 215:5–19. [PubMed: 18938162]
- Weggen S, et al. A subset of NSAIDs lower amyloidogenic A β 42 independently of cyclooxygenase activity. *Nature*. 2001; 414:212–216. [PubMed: 11700559]
- Xiang Z, et al. Cyclooxygenase-2 promotes amyloid plaque deposition in a mouse model of Alzheimer's disease neuropathology. *Gene Expr*. 2002; 10:271–278. [PubMed: 12450219]
- Yan Q, et al. Anti-inflammatory drug therapy alters beta-amyloid processing and deposition in an animal model of Alzheimer's disease. *J. Neurosci*. 2003; 23:7504–7509. [PubMed: 12930788]
- Yao Y, et al. Elevation of 12/15 lipxygenase products in AD and mild cognitive impairment. *Ann. Neurol*. 2005; 58:623–626. [PubMed: 16037976]