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Differential effects of NSAIDs on amyloid β_{1-42} peptide aggregation

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SUMMARY

Alzheimer's disease (AD) is the most common cause of dementia and one of the great health-care challenges of the 21st century. The disease is characterised by extracellular aggregation of the amyloid beta ($A\beta_{1-42}$) peptide within the brain, with subsequent formation of plaques leading to dementia. Currently, there is no cure for AD with only symptomatic therapies available which have demonstrated no, or limited, efficacy. Current pharmacologic studies into AD have focused principally on the development of disease-modifying therapies that can slow the progression of AD. Targets of these investigational agents include $A\beta_{1-42}$ production, aggregation, and clearance. The ability of non-steroidal anti-inflammatory drugs (NSAIDs) to influence $A\beta_{1-42}$ aggregation was assessed using the thioflavin-T spectrofluorimetric assay. Mefenamic acid and flufenamic acid both significantly reduced $A\beta_{1-42}$ aggregation *in vitro*; however ibuprofen and naproxen had no significant effect on aggregation. These studies highlight that NSAIDs may have potential for helping manage or treat AD.

INTRODUCTION

Alzheimer's disease (AD), an irreversible, progressive brain disease that destroys memory and cognitive functions, is the most common cause of dementia. AD is characterised by extracellular accumulation of amyloid beta$_{1-42}$ ($A\beta_{1-42}$) peptide with subsequent formation of plaques (Möller et al., 1998). A reduced prevalence of AD in individuals receiving long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has been reported in epidemiological studies (Eriksen et al., 2003) and it has been suggested NSAIDs decrease neurotoxic inflammatory responses in the brain (Weggen et al., 2001). The fenamate class of NSAIDs are cyclooxygenase inhibitors (Warner et al., 1999) which selectively and potently inhibit the Nod-like receptor protein 3 (NLRP3) inflammasome (Khansari et al., 2009). In a transgenic mouse model of AD fenamates have been shown to have beneficial effects on memory loss and it has been suggested fenamate NSAIDs could be repurposed as NLRP3 inflammasome inhibitors in inflammatory diseases such as AD (Daniels et al., 2016).

MATERIALS AND METHODS

$A\beta_{1-42}$ was purchased from Cellmano Biotech Limited, China. Mefenamic acid, flufenamic acid, ibuprofen, naproxen and Thioflavin T were purchased from Sigma-Aldrich, UK. Aggregation of $A\beta_{1-42}$ was measured spectrofluorimetrically using the thioflavin-T assay. The effects of mefenamic acid, flufenamic acid, ibuprofen and naproxen on $A\beta_{1-42}$ aggregation were analysed over 72 h.

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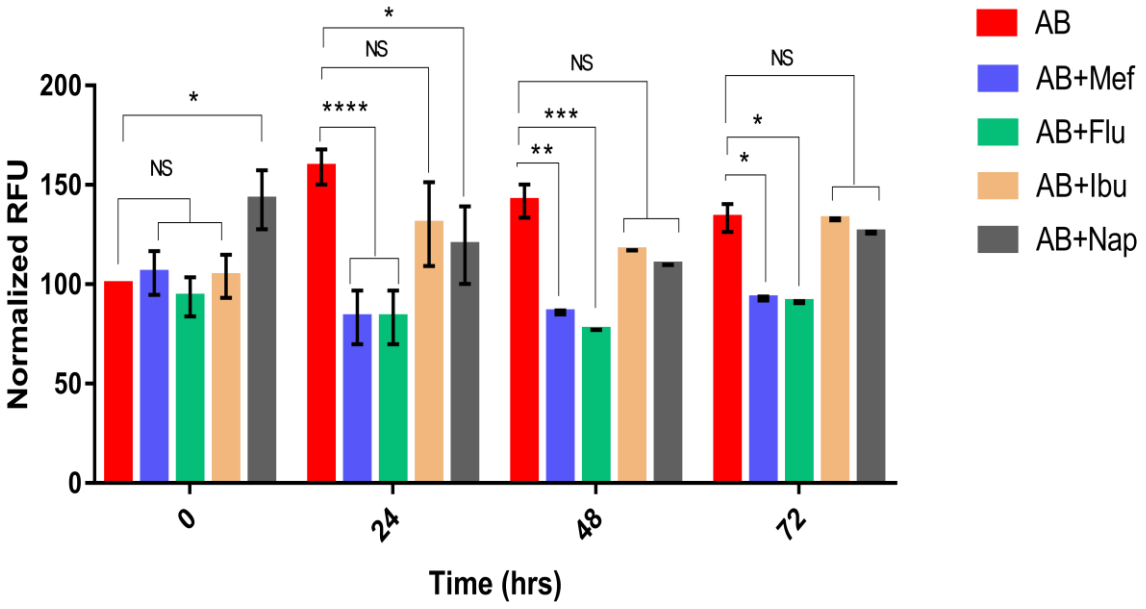

Fig. 1. *$A\beta_{1-42}$ monomers (100 µM) were incubated with compounds (2 mM) in ThT assay buffer (50 µM glycine pH 8.5 and 2 µM ThT) in a sealed black 96-well plate at 37 ℃. Fluorescence was measured over 72 h (excitation at 440 nm and emission at 495 nm). Data were analysed using ANOVA and are presented as the mean ± SEM of 3 independent experiments with 3 replicates in each experiment. *p< 0.05; **p< 0.01; ***p< 0.001; ****p< 0.0001.*

RESULTS AND DISCUSSION

Both mefenamic acid and flufenamic acid significantly inhibited $A\beta_{1-42}$ aggregation whilst naproxen and ibuprofen had no significant effect (Figure 1). These findings are consistent with those that demonstrate mefenamic acid reduced neurotoxicity and improved learning and memory in a rat model of AD (Joo et al., 2006).

CONCLUSIONS

The current study suggests that mefenamic acid and flufenamic acid have the potential to reduce $A\beta_{1-42}$ aggregation, a key hallmark of AD, and may have potential for helping manage or treat AD.

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REFERENCES

Daniels, M.J.D. et al., 2016. Fenamate NSAIDs inhibit the NLRP3 inflammasome and protect against Alzheimer's disease in rodent models. *Nature Communications*, 7, p. 12504.

Eriksen, J. L., Sagi, S. A., Smith, T. E., Weggen, S., Das, P., McLendon, D. C., Ozols, V. V., Jessing, K. W., Zavitz, K. H., Koo, E. H. & Golde, T. E., 2003. NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 in vivo. *J Clin Invest,* 112(3), 440-9.

Joo, Y. et al., 2006. Mefenamic acid shows neuroprotective effects and improves cognitive impairment in in vitro and in vivo Alzheimer's disease models. *Molecular Pharmacology*, 69(1), pp.76–84.

Khansari, P.S. & Halliwell, R.F., 2009. Evidence for neuroprotection by the fenamate NSAID, mefenamic acid. *Neurochemistry International*, 55(7), pp.683–8.

Möller, H.-J. & Graeber, M. B., 1998. The case described by Alois Alzheimer in 1911. *European Archives of Psychiatry and Clinical Neuroscience,* 248(3), 111-122.

Warner, T. D., Giuliano, F., Vojnovic, I., Bukasa, A., Mitchell, J. A. & Vane, J. R., 1999. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A,* 96(13), 7563-8.

Weggen, S. et al., 2001. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. *Nature*, 414(6860), pp.212–6.