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Editorial

Alzheimer's disease prevention & acetyl salicylic acid: a believable story

Age-related synapse loss: a major risk for AD

It has been suggested that cognitive decline in ageing is the result of a growing vulnerability to an asymptomatic state of neuroinflammation. A prominent astrogliosis, mostly observed in the cells surrounding amyloid plaques, is present in Alzheimer's brains[1] and Alzheimer himself originally suggested the pathological potential of glial cells in progression of dementia[2]. We have an incomplete knowledge of the events triggered by Alzheimer's disease (AD) and causing memory loss. However, synaptic dysfunction lies at the heart of age- and dementia-induced defects of the brain. For these reasons, the formation and repair of synaptic connections is a major issue of AD and ageing. Establishing and maintaining connections is crucial throughout life and neurons require support from glial cells, astrocytes in particular. Degradation of beta-amyloid (Aβ) protein by astrocytes has been documented in Alzheimer's disease, but the accumulation of Aβ in astrocytes causes gliosis[1]. The importance of this inflammatory reaction is clear considering the central, structural and physiological functions that astrocytes carry out in the normal brain.

The AD prevention remains a high priority for the scientific community

Several studies[3] have shown that use of various non steroidal anti-inflammatory drugs (NSAIDs) is associated with reduced risk of developing AD. Recently the Cochrane Dementia and Cognitive Improvement Group has analyzed a series (n=14) of randomized clinical trials; the conclusion was that the use of these drugs cannot be recommended for the treatment of AD[4]. According to this study, aspirin (acetyl salicylic acid, ASA), steroid and NSAIDs [traditional and the selective cyclooxygenase-2 (COX-2) inhibitors] showed no significant benefit in the treatment of AD. By contrast, AD is less common in ASA (or NSAIDs) users than non-users. Hence, prevention is easier than cure.

Could aspirin protect cognition in the elderly? Exploring new approaches

Although attention must be paid to the adverse effects of ASA - specifically the risk for bleeding complications - there are biochemical reasons whereby ASA (or selected NSAIDs) might slow the progression of Alzheimer-type pathology; moreover, the protective action of these drugs may be more complex than for long believed.

ASA exerts its anti-inflammatory action by inhibiting the enzyme COX and, thus, preventing the formation of prostanoids, including prostaglandins and thromboxane (TX). There are two major isoforms of COX: COX-1 is constitutive and expressed in most tissues. COX-2 is largely absent from normal tissues, but its expression can be induced rapidly in response to inflammatory and mitogenic stimuli; however, in the brain, COX-2 is constitutively expressed. Low-dose ASA inhibits COX-1 on platelets, suppresses arachidonic acid (AA) metabolism, and prevents the synthesis of thromboxane A2 (TXA2), a compound that causes platelet aggregation. ASA acts on internal COX-1 via a hydrophobic channel and irreversibly acetylates Ser529, which is located close to the active site (tyrosine 385 of COX-1), and that acetylation of this serine residue hinders the access of AA to the active site. Access to the COX-1 active site is then impeded for the lifetime of the platelet. After COX-1 on platelets is acetylated by ASA, the antiplatelet effects are thought to depend on platelet turnover (approx. 7 to 10 days), and to be maintained until new platelets, not acetylated by ASA, are produced. The therapeutic efficacy of ASA in myocardial infarction

and ischaemic stroke has been clearly attributed to its inhibition of platelet COX-1 activity. ASA inhibits COX-2 through a similar mechanism, but is less potent because the substrate channel of COX-2 is larger and more flexible than that of COX-1[5]. Low-dose ASA is expected to determine in platelet COX-2, the typical shift from COX to lipooxygenase activity.

A very peculiar enzymatic mechanism is operating during the concurrent presence of ASA and omega-3 (n-3) polyunsaturated fatty acids (FAs). For example, ASA in presence of docosahexaenoic acid (DHA) triggers the biosynthesis of a new group of mediators that may exert neuroprotection[6,7] DHA metabolites reduced AA metabolites, and increased trophic factors or downstream trophic signal transduction. The novel bioactive compounds are generated by enzymatic pathways and display potent anti-inflammatory and immunoregulatory properties. The main enzymes responsible for the production of these oxygenated products include COX-2, aspirin-induced acetylated COX-2, 5-lipoxygenase (5-LO), 12-LO and 15-LO and cytochrome p450. In particular, the acetylation of COX-2 leads to bioactive anti-inflammatory and protective mediators, namely resolvins and protectins (for example, neuroprotectin D1, NPD1).

During inflammation, the spontaneous generation of these compounds which potently inhibit microglial cell cytokine expression, is markedly increased in the presence of ASA[8]. Endothelial cells grown under hypoxic conditions and treated with ASA convert DHA into two sets of novel di- and trihydroxy products, thus the protection of brain cells and synapses is immediately programmed and activated. Particularly, vascular, leukocytes and neural cells treated with ASA (ASA acetylates COX-2, enabling the mono-oxygenation of DHA) convert DHA to 17R-hydroxy-DHA series. The 17-hydroxy derivatives are further transformed in 17R series of resolvins and protectins[8].

Resolvins D and protectins D are also generated when macrophages are treated with ASA[9]. Intriguingly, while enzymatic oxidation dramatically reduces the bioactivity of the new mediators, enzymatic conversion of ASA-generated resolvins and protectins resists rapid inactivation. Hence, these new pathways - especially in presence of acetylated COX-2 - might provide new means to mark the impact of essential n-3 FAs in ageing, as well as supply new preventive dietary interventions for dementia (and for the protection of synaptic loss?). At this point our question is if these pathways are actually recent in the metabolism of humans. Is there an endogenous ASA, which is able to promote an allosteric activation of an unknown lipoxygenase activity with following extra benefits?

Conclusions and perspectives

There is a trend towards delayed onset of dementia in vegetarians[10], despite the fact that vegetarian diets may be generally marginal in DHA. For this reason vegetarians may need a constant and high intake (> 1.6 g per day) of alpha-linolenic acid, the dietary precursor of DHA. Obviously, salicylic acid is a component of our diet, and in particular of the vegetarian diets. Most fruits, mainly berry fruits and dried fruits, contain salicylate, as well as vegetables, and some herbs and spices, which contain very high amounts per 100 g, (*e.g.* curry powder, paprika, thyme, and rosemary). Among all beverages, tea provides substantial amounts of salicylate. Cereals, meat, fish, and dairy products contain no or minimal amounts.

Although there are no reports suggesting that the molecular pharmacology of ASA differs between sexes, the pharmacodynamics do differ: concentrations of salycilate are higher in women than in men after identical doses of ASA, and platelets from women and men who have ingested ASA show different responses when tested *in vitro*[11]. Blacklock *et al*[12] showed that although median serum concentration of salicylic acid in patients taking ASA (75 mg daily) was significantly higher than that reported in non-vegetarians and vegetarians, higher serum concentrations of salicylate were detected in ASA-free vegetarians than in ASA-free non-vegetarians. The main findings of Blacklock *et al*[12] were that salicylate was present in every serum sample analyzed. Do humans produce an endogenous ASA? Does any human acetylase exist which can convert salicylate to ASA? Can endogenous ASA and dietary salicylate be molecules which protect against dementia? Can the association between DHA-oxygenation and acetyl-COX-2 protect our synapses?

This reasoning is supported by literature data. In fact, high fish intake - or dietary supplementation with n-3 FAs was linked to reductions in the risk of developing AD and in delaying cognitive decline in patients with very mild AD[13]. The Framingham Study[14], monitoring about 900 men and women for a mean of more than 9 years, reported that those with the highest quartile of plasma DHA (mean intake of 0.18 g) and a mean fish intake of 3.0 servings per week, had a sharp reduction of the risk of dementia. This observational

study was the first research to link blood levels of DHA to protection against AD. Although the association was specific to DHA as none of the other n-3 FAs was associated with AD risk, unfortunately the ASA use was not monitored in these studies.

An additional question is: why should DHA-oxygenation COX-2-dependent function be better at low ASA concentration? The answer is salicylate, which can inhibit lipoxygenase activity at therapeutic concentrations of ASA.

In conclusion, ASA may generate messengers that are counter-proinflammatory signals and may shed new light on how the brain modulates its response to Alzheimer's injury.

The Alzheimer's prevention remains an imperative need for the scientific community.

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