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MOLECULAR MECHANISMS OF ALZHEIMER'S DISEASE AND ITS COMPLICATIONS

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ABSTRACT

Alzheimer's disease is the most common cause of dementia in elderly people. Research into Alzheimer's disease therapy has been at least partly successful in terms of developing symptomatic treatments, but has also had several failures in terms of developing disease-modifying therapies. These successes and failures have led to debate about the potential deficiencies in our understanding of the pathogenesis of Alzheimer's disease and potential pitfalls in diagnosis, choice of therapeutic targets, development of drug candidates, and design of clinical trials. Many clinical and experimental studies are ongoing, but we need to acknowledge that a single cure for Alzheimer's disease is unlikely to be found and that the approach to drug development for this disorder needs to be reconsidered. Preclinical research is constantly providing us with new information on pieces of the complex Alzheimer's disease puzzle, and an analysis of this information might reveal patterns of pharmacological interactions instead of single potential drug targets. Several promising randomized controlled trials are ongoing, and the increased collaboration between pharmaceutical companies, basic researchers, and clinical researchers has the potential to bring us closer to developing an optimum pharmaceutical approach for the treatment of Alzheimer's disease.

Keywords: Alzheimer's disease, astrocytes, NSAIDs, X-Rays.

INTRODUCTION

There is compelling evidence that Alzheimer's disease (AD) amyloid-b (Ab) deposition is associated with a local inflammatory response, which is initiated by the activation of microglia and the recruitment of astrocytes [1]. These cells secrete a number of cytokines and neurotoxic products that may contribute to neuronal degeneration and cell death. It has been documented that long-term intake of non-steroidal anti-inflammatory drugs (NSAIDs) decrease the risk for developing AD and delay the onset of the disease [2]. The mechanism behind these NSAIDs is still controversial and several hypotheses have been raised, including changes in the amyloid precursor protein (APP) metabolism, in Ab aggregation and a decrease in inflammatory mediators. Recently, it was proposed that some NSAIDs might activate the peroxisome proliferator-activated receptor-gamma (PPAR-g). PPAR-g belongs to a family of nuclearreceptors that are able to regulate the transcription of pro-inflammatory molecules, such as iNOS [3-5]. The activation ofPPAR-g has been recently reported to reduce Ab levels in cell culture and AD animal models. The implication of PPAR gamma in the control of Ab-induced inflammation suggests a new target for AD therapy and emphasizes the contribution of neuroinflammatory mechanisms to the pathogenesis of AD [6-9].

The deposition of aggregated amyloid β-protein (Aβ) in the human brain is a major lesion in Alzheimer's disease (AD). The process of Aβ fibril formation is associated with a cascade of neuropathogenic events that induces brain neurodegeneration leading to the cognitive and behavioral decline characteristic of AD. Although a detailed knowledge of Aβ assembly is crucial for the development of new therapeutic approaches, our understanding of the molecular mechanisms underlying the

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initiation of Aβ fibril formation remains very incomplete. The genetic defects responsible for familial AD influence fibrillogenesis. In a majority of familial cases determined by amyloid precursor protein (APP) and presenilin (PS) mutations, a significant overproduction of Aβ and an increase in the Aβ42/Aβ40 ratio are observed. Recently, it was shown that the two main alloforms of Aβ have distinct biological activity and behavior at the earliest stage of assembly [10-13].

In vitro studies demonstrated that Aβ42 monomers, but not Aβ40, form initial and minimal structures (pentamer/hexamer units called paranuclei) that can oligomerize to larger forms. It is now apparent that Aβ oligomers and protofibrils are more neurotoxic than mature Aβ fibrils or amyloid plaques. The neurotoxicity of the prefibrillar aggregates appears to result from their ability to impair fundamental cellular processes by interacting with the cellular membrane, causing oxidative stress and increasing free Ca2+ that eventually lead to apoptotic cell death [14-17].

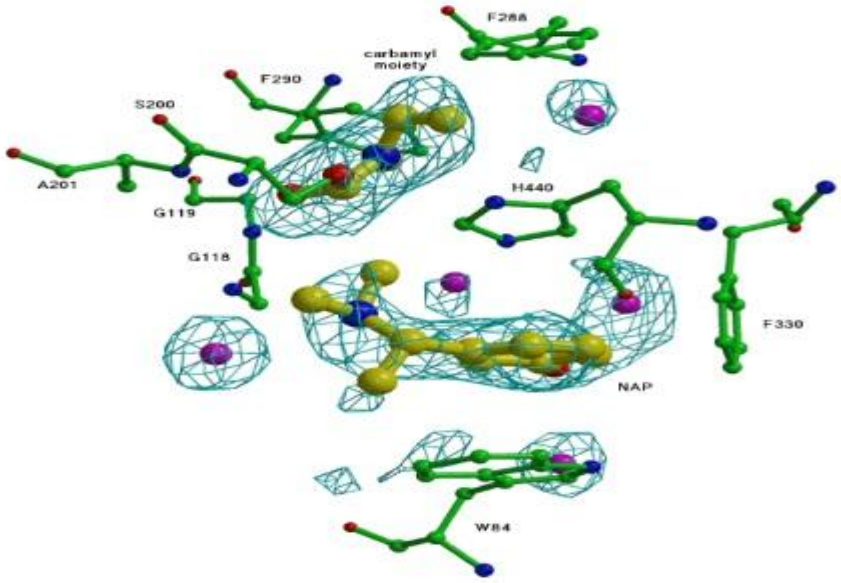
NSAIDs as preventive treatment for AD

Epidemiological studies have documented a beneficial effect of non-steroideal anti-inflammatory drugs (NSAIDs) in AD patients receiving long-term NSAIDs therapymanifested delayed onset and progression of the disease,reduced symptomatic severity, and significantly slowed the rateof cognitive impairment. The diverseness ofthe results between different epidemiological studies can beexplained by the duration of the treatment. In an editorial from independent of COX activity, corroborating the recent failure of a clinical trial with a selective COX-2 inhibitor and suggesting another mechanism behind the protective effect of NSAIDs. Furthermore, recent data revealed that the effects of COX-2 inhibitors could be even adverse, since many COX-2-selective NSAIDs are able to raise Ab42 levels [18-20].

Inflammation and AD

Alzheimer's disease (AD) is a neurological disorder that presently affects 20–30 million individuals around the world. In AD, degeneration of cholinergic basal forebrain neurons within the medial septum and the nucleus basalis of Meynert leads to cholinergic hippocampal/cortical hypofunction and therefore to cognitive decline and profound dementia. Brains of individuals with AD manifest two characteristic lesions: extracellular amyloid (or senile plaques) and intracellular neurofibrillary tangles of hyperphosphorylated tau protein. The amyloid hypothesis states that formation of amyloid peptides (Ab) by neurons is the prime trigger of the pathogenesis of AD, and during years Ab deposition was considered to be the cause of the disease. Evidence supporting the amyloid hypothesis has been recently reviewed. However, it is still unclear how Ab causes cell damage. Several mechanisms have been proposed. One view suggests that Abprotofibrils activate microglia, inciting an inflammatory response and release of neurotoxins or neurotoxic cytokines. It has been speculated that this inflammatory response associated with the presence of neuritic plaques is secondary to Ab accumulation and could be involved in neuronal damage and with the progression of the disease. Activated microglia and reactive astrocytes surrounding extracellular deposits of amyloid b-protein initiate an inflammatory response characterised by a local cytokine-mediated acute phase response, activation of the complement cascade and subsequent further cell damage [21-23].

Fig 1. Close-up view of how the drug rivastigmine binds to the active site of the acetylcholinesterase (AChE)



Anti-Alzheimers and X-Rays

Using x-rays produced by the NSLS, a team of scientists has gained new insight into the effects of a newly approved drug, called rivastigmine, in the treatment of Alzheimer.s disease. Debilitating brain disease causing memory loss and other cognitive deficits in about 10 percent of the elderly. The x-ray molecular maps allow us to see how every atom of rivastigmine interacts with the atoms of AChE.s active site. Silman says. .This information will be important in designing new chemicals that will target specific atomic sites in AChE, possibly leading to better drugs that last longer and have less undesirable effects on Alzheimer's patients [24-26].

After binding to the active site of AChE, the drug is broken into two parts, called carbamyl moiety and NAP. Rivastigmine is rendered as a ball-and-stick model, with carbon atoms colored yellow, oxygen atoms colored red, and nitrogen atoms colored blue. Selected key molecules in the vicinity of rivastigmine are also rendered in ball-and-stick format, with carbon atoms colored green.

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