Review

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The 12/15-lipoxygenase as an emerging therapeutic target for Alzheimer's disease

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Alzheimer's disease (AD) is a chronic neurodegenerative condition characterized by progressive memory loss. Mutations in genes involved in the production of amyloid-β (Aβ) are linked to the early-onset variant of AD. However, the most common form, sporadic AD, is considered to be the result of an interaction between environmental risk factors and various genes. Among them, recent work has highlighted the potential role that the 12/15-lipoxygenase (12/15LO) pathway may play in AD pathogenesis. 12/15LO is widely distributed in the central nervous system, and its levels are upregulated in patients with AD or mild cognitive impairments. Studies using animal models have implicated 12/15LO in the molecular pathology of AD, including the metabolism of Aβ and tau, synaptic integrity, and cognitive functions. We provide an overview of this pathway and its relevance to AD pathogenesis, discuss the mechanism(s) involved, and provide an assessment of how targeting 12/15LO could lead to novel AD therapeutics.

Introduction

Lipoxygenases (LOs) are not only key enzymes in the biosynthesis of a variety of biologically active lipids but also, by directly oxidizing lipid components in cell membranes, generate inducers of structural changes that play a role in the maturation and differentiation of various cell types [1]. While the mouse has seven different lipoxygenase genes, only five have been found in humans. Nomenclature for the different LOs is based on the positional specificity of their substrate oxygenation. For example, the 12LO oxygenates the arachidonate substrate at carbon in position 12, whereas the 5LO modifies carbon 5. When more than one LO is present in the same species, they are named after the prototypical tissue of occurrence. The five human LOs include 5LO, 12LO with platelet-type and leukocyte-type isoforms, and 15LO which is further separated into the reticulocyte- or leukocyte-type, 15LO-1, and the epidermis-type, 15LO-2 [2,3]. While some LOs exclusively form one compound from their substrate, others possess dual specificity [4]. For example, leukocyte-type 12LO and reticulocyte-type 15LO-1 catalyze both carbon 12 and carbon 15 oxygenation to form two products: 12- and 15-hydroxyeicosatetraenoic acid (12-HETE and 15-HETE), and for this reason they are also referred to as 12/15LO [5,6]. Among the dual-specificity LOs is arachidonate 12LO, the brain isoform originally isolated from rat brain, which generates both 12-HETE and 15-HETE [7,8]. LOs are widely expressed throughout many tissues and have been implicated in several different diseases including diabetes (both types 1 and 2), atherosclerosis, renal disease, and obesity [9,10]. Recently, LOs have been also implicated in some disorders of the central nervous system (CNS), including AD. In this article we provide an overview of this enzymatic pathway in the context of AD pathogenesis by exploring its contribution to the molecular and behavioral insults seen in the disease. In addition, we present a rationale for why targeting 12/15LO could lead to viable therapeutics relevant not only for AD but also for other diseases of the CNS.

AD

Characterized by profound and irreversible memory impairment and cognitive deficits, AD is the most common neurodegenerative dementia. The disease is a global dilemma, with over 30 million patients worldwide and an economic burden exceeding half a trillion USD. Epidemiological studies suggest that 11% of those aged 65 years and older, and almost one third of those 85 and older, have some form of the disease [11]. Because population demographics predict a worldwide increase in those aged 65 and older in the next 15 years, AD is a serious public health challenge. However, current therapeutic strategies are very limited for AD patients and do not modify disease course [12,13]. Therefore, investigation of new therapeutic targets that address multiple different facets of the AD phenotype and related pathophysiology must be actively sought to help to address this problem.

Aβ and tau in Alzheimer's disease

The two classical histopathological hallmarks of AD are extracellular insoluble Aβ deposits, known as Aβ plaques, and intracellular accumulations of insoluble microtubule-associated tau protein, known as neurofibrillary tangles

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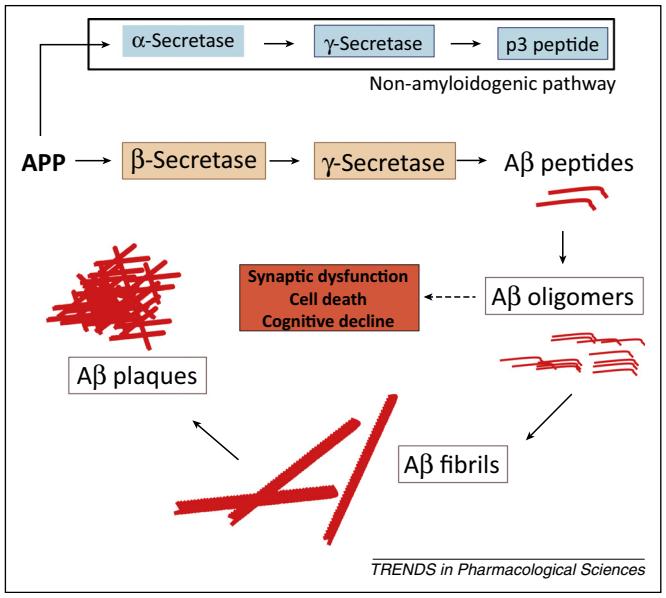

Figure 1. Aβ metabolic pathway. The Aβ precursor protein (APP) is processed in one of two main pathways that yield either Aβ peptides or non-amyloidogenic products. If APP is sequentially cleaved by α-secretase and then γ-secretase, non-amyloidogenic products form. However, if APP is cleaved by β-secretase and then γ-secretase, Aβ is produced. As Aβ peptides continue to be produced, they form low-*n* oligomers, fibrils, and eventually plaques. It is believed that soluble low-*n* oligomers produce the neuronal and cytotoxic injury in Alzheimer's disease.

[14]. Aβ peptides are produced as a result of the sequential cleavage of the Aβ precursor protein (APP) by the β-secretase (β APP cleavage enzyme – BACE-1) and the γ-secretase complex [composed of the nicastrin, presenilin-1 (PS1), anterior-pharynx defective-1 protein (APH-1), and presenilin enhancer protein-2 (Pen-2)] (Figure 1). APP may be also cleaved by α-secretase (ADAM – a disintegrin and metalloproteinase domain-containing protein) family of proteins and then γ-secretase to produce non-amyloidogenic products, but the Aβ producing pathway is thought to predominate in AD. As Aβ levels rise, soluble Aβ oligomers form, which are precursors to Aβ fibrils, eventually creating insoluble Aβ plaques. Although it was once assumed insoluble plaques cause cellular damage in AD, it is now thought that low-*n* Aβ oligomers cause neuronal damage and synaptic insult (Figure 1) [15].

In addition to Aβ, the hyperphosphorylation of tau protein is also a crucial event in AD pathogenesis. Tau is thought to serve as a physiological stabilizer of neuronal microtubules, and contributes to axon stability and overall neuronal function [12]. In AD, tau becomes hyperphosphorylated and, by losing its affinity for microtubules, tends to aggregate – eventually forming neurofibrillary tangles (Figure 2). Although tau protein phosphorylation is typically regulated by the balanced action of both tau-associated kinases and phosphatases, in AD two tau-associated kinases are thought to be abnormally functional: cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3β (GSK3B) [16–18].

The 12/15LO

12/15LO catalyzes the oxidation of free and esterified fatty acids in phospholipids, generating bioactive lipid mediators such as 12-HETE and 15HETE from arachidonic acid, and 13-hydroxyoctadecadienoic acid (13-HODE) from linoleic acid, which have a multitude of functions in human tissue (Figure 3) [19]. 12/15LO lipid products are involved in protein kinase C (PKC)-mediated monocyte binding in vasculature, and in cell growth, acting through various mitogen-activated protein kinases [20,21]. In addition to cell signaling, 12/15LO can initiate oxidation of

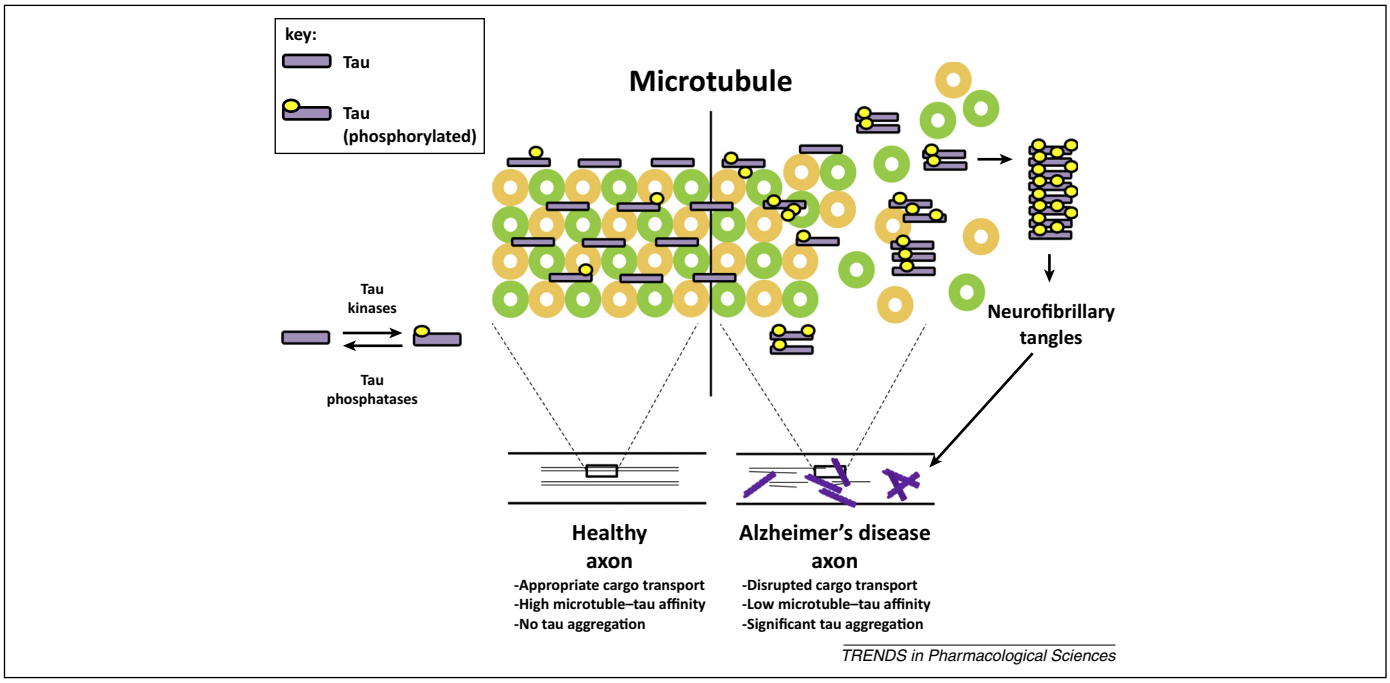

Figure 2. Tau metabolic pathway. The microtubule-associated tau protein maintains phosphorylation status through the combined actions of tau-associated kinases and tau-associated phosphatases. When appropriate physiological tau phosphorylation is in place, tau affinity to microtubules is maintained and microtubule structure, axon integrity, and cellular function are preserved. When tau is hyperphosphorylated (as found in Alzheimer's disease), tau is thought to lose affinity for microtubules and form insoluble aggregates, which eventually lead to impaired axonal transport, neuronal ultrastructure damage, and cell death.