Chapter 5

The Non-Amyloidogenic Pathway: Structure and Function of α-Secretases

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Abstract: The amyloid cascade hypothesis is the most accepted explanation for the pathogenesis of Alzheimer's disease (AD). APP is the precursor of the amyloid β peptide (Aβ), the principal proteinaceous component of amyloid plaques in brains of Alzheimer's disease patients. Proteolytic cleavage of APP by the α-secretase within the Aβ sequence precludes formation of amyloidogenic peptides and leads to a release of soluble APPα which has neuroprotective properties. In several studies, a decreased amount of APPα in the cerebrospinal fluid of AD patients has been observed. Three members of the ADAM family (a disintegrin and metalloproteinase) ADAM-10, ADAM-17 (TACE) and ADAM-9 have been proposed as α-secretases. We review the evidence for each of these enzymes acting as a physiologically relevant α-secretase. In particular, we focus on ADAM-10, which recently was shown in a transgenic mouse model for AD, to act as an α-secretase in vivo. We also discuss the pharmacological up-regulation of α-secretases as a possible therapeutic treatment for AD.

Key words: α-secretase, non-amyloidogenic pathway, Alzheimer’s disease, ADAM-9, ADAM-10, ADAM-17, cholesterol, G-protein-coupled receptors, acetyl choline esterase inhibitors.

1. INTRODUCTION

The accumulation of the β-amyloid peptide (Aβ) in the brain is a central event leading to the development of Alzheimer’s disease (AD). Aβ is a 40/42-residue fragment of the brain transmembrane protein β-amyloid precursor protein (APP), released by two proteases known as β- and
γ-secretase. The Aβ-peptide sequence is located at the junction between the integral membrane domain and the extracellular domain of APP (Kang et al., 1987). In the alternative non-amyloidogenic pathway APP is cleaved within the Aβ domain by α-secretase between amino acids 16(Lys) and 17(Leu) of the Aβ region (Haass and Selkoe, 1993; Selkoe, 1996). The action of the α-secretase not only precludes the formation of Aβ peptides but also induces release of the large APP ectodomain from the cell surface. Soluble N-terminal APP fragments of 105-125 kDa (APPα) are released constitutively into vesicle lumens and from the cell surface; similar species are identified in human plasma and in the cerebrospinal fluid (Weidemann et al. 1989). Secreted APPα appears to have beneficial effects, evoking coordinated responses in neuronal and some peripheral target cells. APPα exerts proliferative effects in a variety of cell types as well as neurotrophic effects (Mucke et al., 1996; Mattson et al., 1993). The C-terminal 591-612 region of APPα contains a heparin-binding domain that is lacking in APPβ and that appears to play a key role in the neurotrophic and calcium regulation effects (Furukawa et al., 1996). APPα has potent memory-enhancing effects and blocks learning deficits induced by scopolamine in mice (Meziane et al., 1998). It is also interesting to note that a reduction of APPα is evident in the cerebrospinal fluid of AD patients (Lannfelt et al., 1995; Sennvik et al., 2000).

Stimulation of the α-secretase may have beneficial effects for two reasons: i) by preventing the formation of the neurotoxic Aβ; ii) by increasing the amount of the neuroprotective APPα. Therefore, pharmacological up-regulation of the α-secretase could be a possible therapeutic treatment for AD.

In this article we review: 1) enzymes of ADAM family as α-secretase candidates, and 2) the pharmacological up-regulation of α-secretases as a possible therapeutic treatment for AD.

2. BIOCHEMICAL AND PHYSIOLOGICAL PROPERTIES OF α-SECRETASES

Processing of APP by α-secretases was the first proteolytic pathway of APP to be characterized in detail. The amyloid precursor protein belongs to a family of type I membrane-spanning glycoproteins and is constitutively expressed in many types of mammalian cells. The major proteolytic pathway of APP is the constitutive secretory pathway that involves cleavage by a putative α-secretase within the Aβ sequence at the cell surface (Sisodia, 1992; Haass et al., 1992; Ikezu et al., 1998), and in the trans-Golgi network (Kuentzel et al., 1993; De Strooper et al., 1993; Sambamurti et al., 1992;