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Analysis of Neurotoxic Beta Amyloid Peptides in Alzheimer's Disease

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Introduction

Alzheimer's disease is characterized by the presence of neurotoxic beta amyloid (Aß) deposits in the brain. This article briefly explains the production of Aß from amyloid precursor protein (APP).

Aβ peptides are produced by the proteolytic cleavage of the transmembrane protein amyloid precursor protein (APP) by enzyme complexes a, β and γ-secretases.

APP cleavage occurs through two distinct pathways – the amyloidogenic pathway generates neurotoxic Aβ peptides and the non-amyloidogenic pathway provides beneficial neurotrophic effects, as shown in figure 1. Formed through the amyloidogenic pathway, the Aβ peptides misfold and aggregate to create deposits that play a role in the pathology of Alzheimer’s disease.

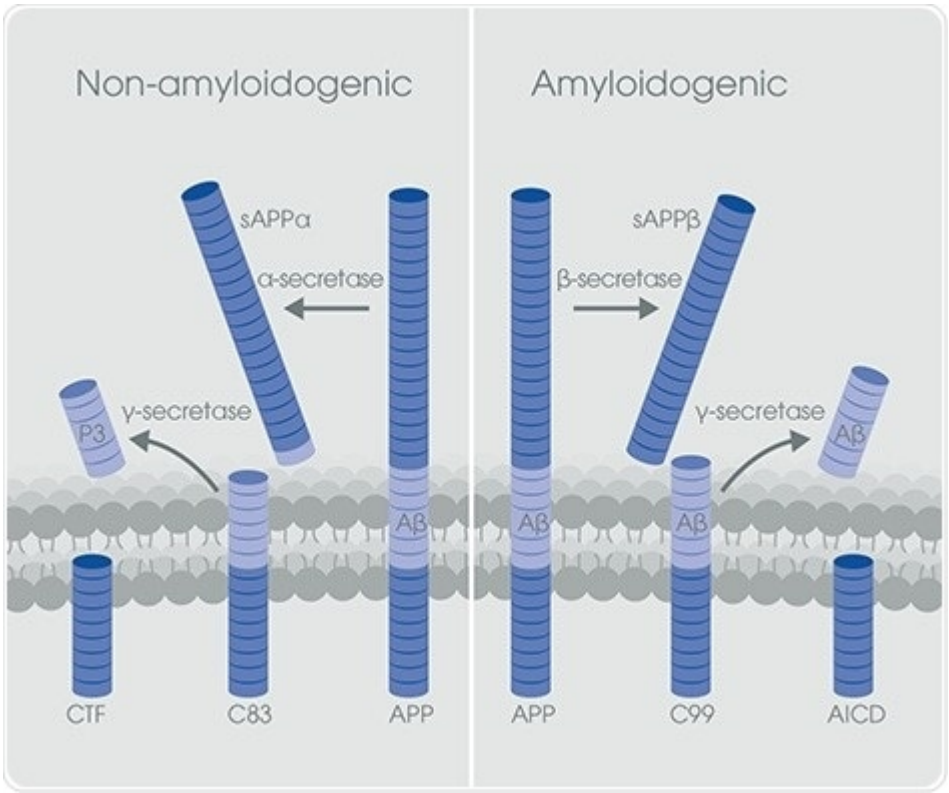

Figure 1. *The non-amyloidogenic and amyloidogenic pathways of APP processing.*

The non-amyloidogenic pathway

In the non-amyloidogenic pathway, APP is cleaved by α-secretase to produce two fragments – an N-terminal ectodomain (sAPPα) that is discharged into the extracellular medium and an 83-amino acid C-terminal fragment (C83) that continues to remain in the membrane.

Three enzymes ADAM9, ADAM10 and ADAM17[1] have been detected with α-secretase activity. Of note, the α-secretase promotes the cleavage of APP within the Aβ domain which thus prevents the production of Aβ peptides.

Importantly, the γ-secretase can later cleave the C83 membrane fragment to generate a C terminal fragment (CTF) and a short fragment known as P3 peptide. It is believed that this P3 peptide is pathologically irrelevant[2].

The amyloidogenic pathway

The amyloidogenic pathway promotes the generation of neurotoxic Aβ peptides. The first proteolysis step is mediated by β-secretase (BACE1), discharging a large N-terminal ectodomain (sAPPβ) into the extracellular medium. The membrane contains a 99-amino acid C terminal fragment (C99)[3–5].

The C99 N-terminus, which was newly exposed, matches with the first amino acid of Aβ. The Aβ peptide is released through consecutive cleavage of the C99 N-terminal fragment by γ-secretase (between residues 38 and 43). γ-secretase is a complex of enzymes that consist of nicastrin, presenilin 1 or 2 (PS1 and PS2), presenilin enhancer 2 (PEN2), and anterior pharynx defective (APH-1)[6–10].

A small percentage of Aβ peptides contain 42 residues (Aβ 1–42), while most of them contain 40 residues in length (Aβ 1–40). However, Aβ 1–42 is believed to be the more neurotoxic form of Aβ peptides because the two additional amino acids have a greater tendency to misfold and aggregate[11].

Alzheimer’s disease is linked to elevated plasma levels of Aβ 1–42[12].

BACE inhibitors

Slowing down the production of Aβ peptides to target its accumulation is gaining rapid importance in the effort to slowdown the progression of Alzheimer’s disease. Access to several β-secretase inhibitors has made it possible to block the APP cleavage. The following table lists of some of the commonly used inhibitors that target Aβ production and β-secretase.

Small molecule	Activity	AbID
β-Secretase Inhibitor II (Z-VLL-CHO)	Peptidyl β-secretase inhibitor (reversible). Corresponds to the VNL-DA cleavage site on APP[13].	ab146640
AZD3839	Potent and selective BACE-1 inhibitor (K_i = 26.1 nM), around 14-fold selectivity over BACE-2 (K_i = 372 nM)[14].	ab223887
Lanabecestat (AZD3293)	Highly potent BACE-1 inhibitor with 80 pM (SH-SY5Y cells over-expressing AβPP)[15], 310 pM (primary neuron cultures from guinea pigs), and IC_{50} = 610 pM (primary neuron cultures from mice).	ab223888
Loganin	Selective β-secretase inhibitor. Exhibits neuroprotective effects against Aβ(25-35)-induced cell death[16].	ab143653
LY2886721	Selective and potent BACE-1 inhibitor (IC_{50} = 20.3 nM for recombinant hBACE-1)[17].	ab223886
Nilvadipine	Potent Ca^{2+} channel blocker that promotes Aβ clearance from brain as well as reduced tau hyperphosphorylation[18].	ab141311

Verubecestat (MK-8931)	Potent and selective β-sectetase 1 inhibitor (IC_{50} = 13 nM)[19].	ab223883

Recommended Tools to Study Aβ in Alzheimer's Disease

Target	Tools
Beta amyloid	• Beta amyloid peptide (1–42, human) • Near-infrared fluorescent Aβ probes • Conformation-specific amyloid beta antibodies
β-secretase	• Anti-BACE1 antibody • β-secretase activity assay kit

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