NEW DRUG TARGET IN ALZHEIMER’S DISEASE

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HINTERGRUND

Alzheimer’s disease (AD) is characterized by large numbers of senile plaques consisting of amyloid beta protein (Aβ). Aβ results from amyloid precursor protein (APP), which is cleaved by β-secretase and γ-secretase. The APP processing pathway is therefore a prominent target of current therapeutic approaches like secretase blocker or inhibitors that prevent aggregation of amyloid plaques.

LÖSUNG

Here a new physiological APP processing is described, which generates proteolytic fragments capable of inhibiting neuronal activity in the hippocampus. This discovery offers new opportunities for therapeutic and diagnostic approaches, and should be considered in current therapy strategies.

Highlights

- CTF-η and Aη peptides are present in dystrophic neurites in brains derived from an AD mouse model (APPPS1-21 mice) as well as in human AD brains
- CTF-η and Aη-α fragments accumulate after β-secretase BACE1 inhibition and are enriched in dystrophic neurites
- η-secretase activity is highly increased in dystrophic neurites with close vicinity to Aβ-plaques
- Aη-α impairs hippocampal long term potentiation (LTP)
- Aη-α strongly suppresses the activity of hippocampal neurons in vivo, an effect not observed with Aη-β or the control peptide
- by using local application of synthetic Aη-α to hippocampal neurons, the inhibitory effect of Aη-α on neurons is readily reversible after washout
Figure: APP processing pathways The membrane bound APP is cleaved by both β-secretase (finally resulting in Aβ) and η-secretase. The latter generates the C-terminal fragment η (CTF-η) and the soluble sAPPη, which is further processed by α- and β-secretases to Aη-α and Aη-β.

VORTEILE

Aη-α as a new drug target and / or diagnostic marker for Alzheimer disease  
Presence of Aη-α fragments in AD brains should be taken into account for development/application of drugs targeting Aβ or inhibiting β-secretase, since these lead to accumulation of Aη-α  
Antibodies to detect η-secretase pathway peptides are available

PUBLIKATIONEN & VERWEISE

Willem et al., Nature 526, 443–447