ZonMw – Sphingolipids: A new target in the treatment of Alzheimer’s disease

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Research Abstract
Key features of Alzheimer’s disease (AD) pathology are aggregates of amyloid-ß peptides, neurofibrillary tangles, blood-brain barrier (BBB) damage and neuroinflammation. To date, the cause of AD remains largely unknown. Elucidation of the deregulated biological mechanisms that lead to the onset and progression of AD is critical to identify new treatment strategies. We hypothesize that early in the disease process, an altered balance between the different classes of sphingolipids (SL), including ceramides and sphingomyelins, plays a key role in disease onset and progression. Using a translational approach, we therefore aim to identify the role of SL metabolism in AD and models thereof and reveal if pharmacological modulation of this

pathway using already approved drugs is beneficial in slowing down the disease process.

SL are ubiquitous structural lipids in cellular membranes and also potent regulators of critical biological processes. In the brain, SL are abundantly present in different cell types, including neurons and glial, and in the vascular compartment. To guarantee optimal neuronal function, levels and the proper balance of SL and associated metabolites are tightly regulated. As a consequence, alterations of the delicate balance in SL metabolism may contribute to the development of age-related neurological and neuroinflammatory diseases. It is now generally thought that ceramide, a pro-inflammatory and pro-apoptotic lipid, has detrimental effects in the brain thereby contributing to disease pathogenesis. In contrast, a metabolite of ceramide, sphingosine-1-phosphate (S1P), exerts (neuro)protective and anti-inflammatory functions. Recent data indicate that impaired SL metabolism is involved in disease pathogenesis of AD. For instance, high serum ceramide levels in patients have been associated with a markedly increased risk of developing cognitive impairment and AD. In experimental models, ceramide-enriched vesicles secreted by astrocytes cause glial apoptosis and neurodegeneration. In contrast, S1P is typically anti-inflammatory and anti-apoptotic, promotes proper neuronal, glial and brain endothelial functions.

Based on the implication that impaired SL balance may be causative for AD pathogenesis, we hypothesize that these lipids and their metabolites are of fundamental importance for the treatment or even prevention of AD. Members of this research group have shown that modulating this pathway is beneficial in models of neuro-inflammation and neurodegeneration. Moreover, initial data indicate that in post-mortem material of patients with AD, levels of the lipid ceramide and the enzymes involved in its production are increasingly expressed. Together this indicates that the delicate balance of SL is deregulated, further supporting our hypothesis that targeting this pathway may be beneficial to slow down or even stop disease progression. To address this hypothesis we will:

1. Quantify SL and involved enzymes in different forms and subtypes of dementia and correlate the SL levels and enzymatic activity to associated neuropathology, as determined by the level of neuroinflammation, changes at the BBB and neurodegeneration in selected brain regions.

2. Correlate the SL profiles identified in body fluids (plasma and CSF) to clinical features, including cognitive decline in humans and in AD mouse models at different disease stages and during normal brain aging, to identify specific SL patterns that can be used as biomarkers of early disease progression.

3. Explore whether modulation of the SL pathway via existing compounds (FTY-720P, a S1P analogue) reduces inflammatory events and promotes neuronal survival using human in vitro models.

4. Provide the first proof-of-concept that pharmacological modulation of SL metabolism using existing drugs in animal models of AD prevents and/or retards disease progression.

The proposed preclinical studies are essential to:

(i) Identify which asymptomatic elderly individuals might benefit from SL modulation for the prevention or delay of AD.

(ii) Provide the first proof-of-concept data to establish that an approved drug approved for other indications is effective for AD.

(iii) Develop targeted therapies for select patient subgroups by stratifying patients according to their levels of SL metabolites.

(iv) Design targeted clinical trials which can dramatically reduce the number of patients required for the study and the associated costs.

(v) Proceed directly to phase I/II clinical trials in AD with a Food and Drug Administration (FDA) approved drug, with a novel application in AD.

Ultimately, this research will be the first proof-of-concept study to test the feasibility and relevance of the personalized medicine approach in the area of SL.

Further information available at:

https://www.zonmw.nl/nl/over-zonmw/ehealth-en-ict-in-de-zorg/programmas/project-detail/memorabel/sphingolipids-a-novel-target-in-the-treatment-of-alzheimer-disease/verslagen/

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