Neuroprotective effect of SGLT2i: direct influence on amyloid-β related pathology

The rapid aging of the population that we are currently experiencing is leading to an increased incidence of cognitive impairment and related disability. Along with the ageing, amyloid-β deposits continue to accumulate, which precedes the symptoms of cognitive impairment for more than 20 years. WHO expects that by 2050 the number of people with cognitive impairment will have increased from 39 to 139 million. Alzheimer Disease (AD) is the most common type of dementia worldwide and the amyloid hypothesis is one of the best-known hallmark of AD. Amyloid-β is a promising target for the treatment of amyloid-related cognitive decline. Unfortunately, there is no causal treatment available, except for Aducanumab, which recent approval by FDA caused controversy due to serious side effects. The lack of safe and effective causal therapy in cognitive impairment is worrisome and invites to repurposing of commonly used drugs.

SGLT2i are safe and commonly used newer hypoglycemic drugs with numerous pleiotropic effects, which made the indications for their use go far beyond diabetes. The evidence for their neuroprotective effect and potential to improve Aβ-related neuropathology is promising. There is an emerging concept from murine studies that SGLT2i cross blood-brain barrier and may have various neuroprotective effect.

We believe that commonly used SGLT2i (empagliflozin, canagliflozin, dapagliflozin) exert protective effect on amyloid-β related neuropathology.

The study will investigate basic mechanisms of direct influence of SGLT2i on:

- human brain endothelial cells – crucial element of blood-brain barrier,
- trans-endothelial amyloid-β clearance,
- amyloid-β induced inflammation in microglia
- amyloid-β direct neurotoxic effect.