IV. Abstract

Alzheimer's disease (AD) is a highly complex neurological disorder and the mechanisms behind its origin are yet to be understood. Synaptic function is believed to be one of the first mechanisms that are affected by AD. Treatment with soluble amyloid beta (Aβ) has shown to impair a form of hippocampal synaptic plasticity known as long-term potentiation (LTP), both in vitro and in vivo. In vivo, this effect is persistent over weeks—this suggests that one acute application of soluble Aβ can trigger cascades and accordingly create severe AD pathology. This doctoral thesis tested the properties of soluble Aβ oligomer toxicity by means of this AD model. Moreover, treatment strategies to ameliorate AD were explored.

Experiments were conducted via recordings of evoked potentials, elicited by stimulating the perforant path and field excitatory postsynaptic potentials recorded from the dentate gyrus granule cell layer. LTP was triggered by high-frequency stimulation of afferent fibres to the dentate gyrus. Aβ oligomers were administered via the intracerebral ventricle. The experiments were conducted in freely behaving adult rats.

As the toxicity of Aβ may be mediated by specific sequences of the Aβ(1–42) peptide chain, the effects of Aβ(1–42) were compared with Aβ(1–10) and Aβ(12–28). Acute treatment with Aβ(1–42) led to a distinct impairment of LTP. Aβ(12–28) administration induced similar deficits in LTP ability. Interestingly, Aβ(1–10)-treated animals showed a normal LTP profile. These results suggest that in contrast to the transmembrane element of the peptide, the N-terminal part of the Aβ(1–42) peptide probably does not contribute to the toxicity.

A separate study examined different therapeutic strategies. Environmental Enrichment (EE) is known to diminish AD symptoms at the level of learning and memory. LTP stability significantly improved in rats acutely treated with Aβ(1–42) which underwent EE, in comparison with other animals that had received Aβ but not undergone EE. It can be assumed that an active, stimulating lifestyle can at least decelerate the progress of AD at the level of synaptic plasticity.

To test for a therapeutic target at a more mechanistic level, the peptide P85 was used. This agent hinders the binding of Aβ oligomers with lipid bilayers. Administration of P85 two hours before Aβ(1–42)-treatment resulted in a stable LTP. This effect was persistent
for about one month. Controls that were treated with Aβ(1–42) alone showed permanently impaired synaptic plasticity. It suggests that a ‘vaccination’ strategy could comprise a successful treatment strategy in the battle against AD.

Dysregulations similar to those seen in Type 2 diabetes mellitus (T2DM) can be observed in AD. Successful therapeutic strategies for T2DM treatment may prove helpful in case of AD treatment. Here, we explored the effect of leptin treatment. Leptin could rescue the Aβ(1–42)-induced damage of LTP, without interfering with basal synaptic transmission or synaptic plasticity in controls. This effect was not persistent and could not be replicated in a later stage of the disease. Furthermore, antagonism of amylin receptors led to similar promising results. It is worth noting that the ameliorating effect of the antagonist on impaired LTP could be replicated in a more progressed stage of the disease.