work package 3: Cell Biology and model organisms

Activation of cholesterol turnover as a pharmacological approach to increase neuronal activity in Alzheimer's disease.

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Alzheimer disease (AD) is characterized by the presence in the brain of intraneuronal neurofibrillary tangles and extracellular senile plaques containing an amyloid core of Aβ peptide produced from the amyloid precursor protein (APP). Although processing of APP has been extensively studied, its neuronal function remains unclear. Recently, cholesterol was shown to be increased in brains of patients with AD, and genome wide association studies identified genes encoding proteins involved in cholesterol metabolism as risk factors for sporadic AD. Altogether, these data strongly argue for alteration of cholesterol homeostasis in AD.

The biosynthesis of cholesterol is regulated by sterol regulatory element binding proteins (SREBP). In cultured neurons, we have demonstrated that interaction between APP and SREBP controls production the mature SREBP transcription factor and consequently expression of its target genes, including the gene encoding HMG-CoA reductase, the limiting enzyme in biosynthesis of cholesterol. Therefore, over expression of APP inhibits biosynthesis of cholesterol while down regulation of endogenous APP has the opposite effect, but without affecting neuronal membrane cholesterol content. This results from the APP-mediated control of expression of cholesterol 24-hydroxylase, a neuronal specific enzyme involved in hydroxylation of cholesterol. Consequently, an essential function of APP, which could be altered in AD, is to control cholesterol turnover which is needed for neuronal activity (*Pierrot et al. EMBO Mol Med Apr 2013*).

These findings offer therapeutical alternatives for AD treatment based on the function of APP. Cholesterol turnover can be stimulated by activation of nuclear receptors of the liver X receptor (LXR) family, which are activated by oxysterols, and in particular by 24-S-hydroxycholesterol in neurons. Our data indicate that activation of LXRs by the pharmacological agonist GW3965 is able to increase cholesterol turnover and neuronal activity in rodent cultured neurons, in organotypic cultures of rat hippocampus and in transgenic mouse models of AD.