HIPPOCAMPAL M1 MUSCARINIC RECEPTOR ACTIVITY MODULATES ABETA RELEASE IN AWAKE AND FREELY MOVING ANIMALS - AN IN VIVO MICRODIALYSIS STUDY

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Background: Understanding the mechanisms regulating Aβ production is critical to our understanding of AD, as well as for the development of better diagnostic and treatment methods. Levels of Aβ can be mediated by the activity of certain receptor subtypes, and in particular, activation of muscarinic receptor subtypes can influence APP processing.

Aims: We adapted the technique of intracerebral in vivo microdialysis (MD) to characterize the relationship between cholinergic neurotransmission and hippocampal ISF Aβ release in awake and freely moving animals.

Methods: ISF levels of Aβ were measured over a time period of 24 hours, simultaneously, a muscarinic receptor agonist or antagonist respectively was via retrodialysis directly infused into the hippocampus.

Results: We found that hippocampal infusion with a muscarinic M1 receptor antagonist (Dicyclomine) resulted in an increase of Aβ ISF levels. This shift was associated with a reduction in phosphorylated PKCα and phosphorylated ERK1/2, as well as higher levels of BACE1 in hippocampal protein extracts. Conversely, hippocampal infusion with the muscarinic M1 receptor agonist (AF102B) by retrodialysis shifted APP metabolism towards the non-amyloidogenic pathway and decreased ISF Aβ40 and Aβ42 levels in the hippocampus. This was associated with an increase in ERK1/2 phosphorylation.

Conclusion: These results provide evidence that cholinergic function regulates APP metabolism in vivo, and support pharmacological modulation of muscarinic neurotransmission for APP metabolism in those suffering cognitive decline and progression to AD. Further, direct assessment of the ISF pool of Aβ in living animals provides unique insight into the regulation of Aβ metabolism, aggregation and plaque formation in vivo.