ACETYLCOLINESTERASE REGULATES PRESENILIN-1 LEVELS AND METABOLISM OF THE ALZHEIMER'S AMYLOID PRECURSOR PROTEIN

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Introduction: Several investigations have argued for a strict interrelation between amyloid precursor protein (APP) processing and levels of acetylcholinesterase (AChE), an enzyme associated with amyloid plaques. The physiopathologic implications of this interrelationship have remained elusive. We have previously reported the identification of presenilin 1 (PS1), the active proteolytic component of the γ-secretase protease complex, as an AChE interacting protein in the Alzheimer's brain.

Aims: Here, we have explored the physiopathologic consequences of AChE-PS1 interaction, especially relevant due to the use of AChE inhibitors (AChE-I) in Alzheimer's disease therapy.

Methods: We tested whether the genetic modulation of AChE expression may influences PS1 levels in SH-SY5Y neuroblastoma cells. We also evaluated PS1 levels in amyloid Aβ42-treated SH-SY5Y cells with and without AChE knock-down. The AChE-I tacrine was finally employed to asses PS1 expression and amyloid metabolism in SH-SY5Y cells.

Results: AChE knock-down with siRNA in SH-SY5Y cells decreased PS1 levels, while AChE overexpression exerted opposing effect. We exposed neuroblastoma cells to Aβ42 which triggered elevation of both AChE and PS1 levels. The Aβ42-induced PS1 increase was abolished by pre-treatment of SH-SY5Y with siRNA AChE, suggesting that AChE may participate in the pathological feed-back loop between PS1 and Aβ. Treatment of SH-SY5Y cells with tacrine also decreased PS1 levels, in parallel with increase in the secretion of APPα. However, sustained AChE inhibition failed to exert long-term effect on PS1.

Conclusions: Our results provide insight into cholinergic-amyloid interrelationships and identify a new molecular interaction that may contribute to AD pathology and have therapeutic implications.