5-HT4 RECEPTORS PROMOTE NON-AMYLOIDOCGENIC PROCESSING OF APP BY ENHANCING TRAFFICKING OF ADAM-10 AND APP

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Introduction: Non-amyloidogenic α-secretase cleavage of amyloid precursor protein (APP) promotes the release of soluble APPα (sAPPα), which has neuroprotective effects and prevents from β-amyloid (Aβ) peptide formation and accumulation in senile plaques of patients suffering from Alzheimer's disease (AD).

Aims: 5-HT₄ receptor (5-HT₄R) has been reported to favour sAPPα release. We wish to explain how this G protein-coupled receptor (GPCR) can promote non-amyloidogenic processing of APP in order to identify new therapeutical issues in AD.

Methods: 5-HT₄R and APP were co-expressed in HEK-293 cells and in neuronal primary cultures. The amount of secreted APP N-terminal fragments was quantified in the presence of increasing amount of 5-HT₄R. Secreted fragments and proteins interacting with the receptor were identified by Western blotting and co-immunoprecipitations.

Results: A direct and constitutive interaction of a desintegrin and metalloprotease (ADAM10) with the 5-HT₄R induced a constitutive release of sAPPα, only slightly enhanced by 5-HT₄R agonist stimulation. 5-HT₄R-induced cleavage of APP was independent of classical G proteins, as opposed to other GPCR-mediated release of sAPPα. Increasing 5-HT₄R expression promoted trafficking of mature ADAM-10 to the plasma membrane, where the α-secretase activity preferentially takes place, and prevented APP processing by the β- and γ-secretases. The APP transport to the plasma membrane is specific to 5-HT₄R, as none of the GPCR tested in our study increased APP trafficking.

Conclusions: This study provides evidence that 5-HT₄R expression promotes complex assembly of the α-secretase ADAM-10 and APP to the plasma membrane, leading to the release of the sAPPα neuroprotective fragment.