5-HT_4 agonists: novel promising agents for AD prevention

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5-HT_4 agonists have been proved to exert procognitive effects in rodents and to induce the non-amyloidogenic processing of the amyloid precursor protein (APP), leading to an increase of soluble APPα (sAPPα). Therefore, 5-HT_4 receptors (5-HT_4R) could be of interest to delay AD progression. Following these observations, we decided to study the action mechanism of 5-HT_4R ligands and analyzed their effects on Aß production and amyloid plaque formation. COS-7 cells were stimulated with 5-HT_4R agonists and sAPPα release quantified through ELISA. Chronic administration of 5-HT_4 agonists was performed in an aggressive mouse model of AD, the 5xFAD, during the prodromal phase preceding the appearance of behavioural deficits. Following treatments, amyloid plaque load and Aß burden were measured through ELISA and thioflavin T staining. CSF was also collected and sAPPα and $Aß_{42}$ analyzed through ELISA. Besides, astroglial inflammation and microglia activation associated to plaques were revealed through GFAP and Iba-1 staining. Our results clearly show that 5-HT_4R agonists induced an increase of sAPPα release both in cell cultures and in the CSF of 5xFAD mice. Indeed, the chronic and prodromal administration of 5-HT_4R agonists to 5xFAD mice reduced the production of Aß peptides and slowed down the formation of plaques. These effects were prevented by a co-treatment with a specific 5-HT_4R antagonist that was ineffective by itself, demonstrating that the effects observed are specific to 5-HT_4 receptors. Finally, astroglial inflammation was also markedly reduced after 5-HT_4R agonist administration. In summary, chronic treatments promoting sAPPα release via the stimulation of 5-HT_4 receptors clearly hinder plaque formation and Aß load while jointly attenuating inflammation processes. We conclude that 5-HT_4 agonists administration could represent an interesting and promising strategy for AD prevention.