Tangui Maurice, J Alzheimers Dis Parkinsonism 2015, 5:3
http://dx.doi.org/10.4172/2161-0460.C1.015

OMICS International
conferenceseries.com

3rd International Conference on
Alzheimer's Disease & Dementia
August 31 - September 02, 2015 Toronto, Canada

Development of sigma-1 receptor agonists as neuroprotectants in Alzheimer's disease and related Dementia

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The sigma-1 receptor (S1R) is a ligand-operated molecular chaperone localized on endoplasmic reticulum (ER), mitochondria and plasma membranes. Its activation modulates IP3 receptor-dependent Ca2+ mobilizations, facilitates the activation of ER stress sensor proteins and kinase pathways. Under chronic activation, it also recomposes lipid domains in membranes which are highly functionalized domains. Interestingly the chaperone can be directly activated (or inactivated) by several classes of ligands. These S1R agonists are potent neuromodulatory and neuro protective drugs in different neurodegenerative insults and pathologies (stroke, Alzheimer's disease (AD), Parkinson's disease, ALS). We examine the involvement of the S1R in AD pathology and validate selective or non-selective S1R agonists as neuro protective agents. First, we analyzed the impact of S1R invalidation (using S1R KO mice) on the vulnerability to AD pathology. Two main AD models were used, a non-transgenic model by direct ICV injection of oligomeric amyloid-β (Aβ) protein fragments (Aβ25-35) in mice and transgenic lines over expressing hAPPSwe or hAPPSwe Ind. We observed that AD toxicity and behavioral deficits are significantly amplified in S1R KO mice injected with Aβ25-35 and in S1R KO×hAPPm lines. Second, we showed the protective potency of S1R agonists and mixed muscarinic / S1R ligands in AD models. The pathology was analyzed in terms of ER and oxidative stress, inflammation, mitochondrial damage, cell loss, memory deficits, increased APP processing and TAU hyper phosphorylation. We therefore confirmed the role of endogenous neuro protection system in neurodegenerative processes and identified S1R agonists as potent neuro protective and putatively disease-modifying agents.

Biography

Tangui Maurice after graduating Chemical Engineer from ENSCM (Montpellier, France) in 1987, he got his PhD in neuropharmacology in 1990. He made 2 Postdoctoral fellowships at the Jouveinal Research Institute (Paris) and Nagoya University Hospital and Meijo University (Nagoya, Japan). He joined CNRS in 1992 starting to work on sigma-1 receptors. He is now Team Leader at INSERM U. 710 (U. 1198 since 01/01, 2015). He got 120+ publications and 4 patents. He also created a CRO company, Amylgen, co-founded with 3 scientists from University and Industry, where he is currently acting as CSO.

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