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Sphingosine-1-phosphate receptor 1 (S1PR-1): A new target for the treatment of Tau-related pathologies

Guy Massicotte, Frédéric St-Cyr Giguère and **Michel Cyr**
University of Quebec, Canada

Tau proteins are known to help maintaining the structure of a neuron, including tiny tube-like structures called microtubules, which deliver nutrients throughout cells. However, when hyperphosphorylated, these proteins can become toxic for neurons by forming tangles in the hippocampus; one important region of the brain early affected by Alzheimer's disease. Researchers believe that therapies capable to limit Tau phosphorylation in the hippocampus may reduce tangle formation and ultimately intervene in the development of Alzheimer's disease and other Tau-related disorders. Global sphingosine-1-phosphate receptor (S1PR) agonists were recently found to exert neuroprotective effects in several model systems reproducing different brain disorders. Consequently, we assessed the influence of such compounds on Tau phosphorylation in the hippocampus. Transverse rat hippocampal slices were prepared with a McIlwain tissue chopper and placed on a nylon mesh in a liquid-gas interface chamber. They were treated for a period of 3 hours with S1PR-1 (SEW2871) and S1PR-3 (CYM5541) agonists. Tau phosphorylation was then estimated by Western blotting procedures. We noticed an important reduction in Tau-Ser262 phosphorylation after hippocampal slice treatments with the S1PR-1 agonist SEW2871. In terms of molecular mechanisms, SEW2871-induced Tau-Ser262 dephosphorylation seems to be dependent on AMPK (AMP-activated protein kinase) inactivation, a process involving the protein phosphatase PP2A. Comparable experiments indicate that neither Tau nor AMPK were influenced by the S1PR-3 agonist CYM5541. Our results suggest a new target for Tau dephosphorylation and provide an insight into the potential therapeutic effects of S1PR agonists in Alzheimer's disease and other Tau-related pathologies.

Biography

Guy Massicotte's work is mainly focusing on the role phospholipase enzymes and lipids in glutamate receptor regulation during both normal and neuropathological conditions. Full professor in human physiology at the University of Québec, He is actually investigating the role of ceramide derivatives in premature ageing of the brain. He is the author of 80 publications, some being published in top-quality journals such as Nature, Proceedings of the National Academy of Sciences, FASEB Journal, Diabetes, Neuroscience and Biobehavioral Reviews.

guy.massicotte@uqtr.ca

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