Adaptor Protein APPL2 Could Be a Therapeutic Target for Improving Hippocampal Neurogenesis and Attenuating Depressant Behaviors and Olfactory Dysfunctions in Chronic Corticosterone-induced Depression

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Abstract : Olfactory dysfunction is a common symptom companied by anxiety- and depressive-like behaviors in depressive patients. Chronic stress triggers hormone responses and inhibits the proliferation and differentiation of neural stem cells (NSCs) in the hippocampus and subventricular zone (SVZ)-olfactory bulb (OB), contributing to depressive behaviors and olfactory dysfunction. However, the cellular signaling molecules to regulate chronic stress mediated olfactory dysfunction are largely unclear. Adaptor proteins containing the pleckstrin homology domain, phosphotyrosine binding domain, and leucine zipper motif (APPLs) are multifunctional adaptor proteins. Herein, we tested the hypothesis that APPL2 could inhibit hippocampal neurogenesis by affecting glucocorticoid receptor (GR) signaling, subsequently contributing to depressive and anxiety behaviors as well as olfactory dysfunctions. The major discoveries are included: (1) APPL2 Tg mice had enhanced GR phosphorylation under basic conditions but had no different plasma corticosterone (CORT) level and GR phosphorylation under stress stimulation. (2) APPL2 Tg mice had impaired hippocampal neurogenesis and revealed depressive and anxiety behaviors. (3) GR antagonist RU486 reversed the impaired hippocampal neurogenesis in the APPL2 Tg mice. (4) APPL2 Tg mice displayed higher GR activity and less capacity for neurogenesis at the olfactory system with lesser olfactory sensitivity than WT mice. (5) APPL2 negatively regulates olfactory functions by switching fate commitments of NSCs in adult olfactory bulbs via interaction with Notch1 signaling. Furthermore, baicalin, a natural medicinal compound, was found to be a promising agent targeting APPL2/GR signaling and promoting adult neurogenesis in APPL2 Tg mice and chronic corticosterone-induced depression mouse models. Behavioral tests revealed that baicalin had antidepressant and olfactory-improving effects. Taken together, APPL2 is a critical therapeutic target for antidepressant treatment.

Keywords : APPL2, hippocampal neurogenesis, depressive behaviors and olfactory dysfunction, stress
Conference Title : ICAPN 2023 : International Conference on Ageing, Psychology and Neuroscience
Conference Location : London, United Kingdom
Conference Dates : December 11-12, 2023