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Baicalin modulates APPL2/glucocorticoid receptor signaling cascades, promotes neurogenesis, and attenuates emotional and olfactory dysfunctions in chronic corticosterone-induced depression

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Olfactory dysfunction is accompanied by anxiety- and depressive-like behaviors. Impaired neurogenesis in hippocampus and subventricular zone (SVZ)-olfactory bulb (OB) contribute to anxiety- and depressive behaviors and olfactory dysfunctions. However, the underlying mechanisms remain unclear. Adaptor proteins containing the pleckstrin homology domain, phosphotyrosine binding domain, and leucine zipper motif (APPLs) are involved in regulating many biological activities. APPL2 showed the potentials to modulate cell growth, but whether APPL2 could affect adult neurogenesis and animal mood behaviors remains unknown. Herein, we tested the hypothesis that APPL2 could affect glucocorticoid receptor (GR) signaling and modulate hippocampal neurogenesis, contributing to depressive and anxiety behaviors. APPL2 Tg mice had enhanced GR phosphorylation under basic condition but had no different plasma corticosterone (CORT) level and GR phosphorylation under stress stimulation. APPL2 Tg mice had decreased hippocampal neurogenesis that was reversed by GR antagonist RU486. APPL2 Tg mice had impaired hippocampal neurogenesis and depressive and anxiety behaviors. We further identified the roles of APPL2 in olfactory functions. APPL2 Tg mice displayed higher GR activity and less neurogenesis at an olfactory system with less olfactory sensitivity than WT mice, indicating that APPL2 could be a potential therapeutic target for depression and olfactory deficits. We then studied the effects of baicalin, a natural antioxidant, on modulating APPL2/GR signaling pathway and promoting neurogenesis for antidepressant and improving olfactory functions. Baicalin inhibited APPL2/GR signaling pathway and improved neurogenesis at SVZ, OB, and hippocampus in APPL2 Tg mice and chronic corticosterone-induced depression mouse model. Baicalin attenuated depressive- and anxiety-like behaviors and improved olfactory functions in a chronic depression mouse model and APPL2 Tg mice. In conclusion, APPL2 could be a novel therapeutic target for improving depressant related olfactory dysfunctions. Antioxidant therapy with baicalin could inhibit APPL2-mediated GR hyperactivity and promote neurogenesis, releasing depressive and anxiety symptoms and improving olfactory functions.

Biography

Shen Jiangang is Professor and Associate Director (Research) in the School of Chinese Medicine, University of Hong Kong. His major research interests: (1) Oxidative stress and redox signaling in brain damage and brain repair in post-stroke and neurodegenerative diseases; (2) Experimental and clinical studies of Chinese herbal medicine for cerebral and cardiovascular diseases. His studies have been supported by many highly competitive research funds. He has published more than 170 peer-reviewed papers in prestigious academic journals and 16 book chapters. He received many academic and research awards and appointed as honor professorship at 15 universities from China and USA. He is the editorial board member and reviewer of many international academic journals.

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