Prolyl hydroxylase (PHD) inhibitor FG-4592 exerts antidepressant effect in the rat CUMS model via HIF-1-mediated neural plasticity

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FG-4592, an inhibitor of prolyl hydroxylase (PHD), stabilizes HIF-1α and has been used in Phase III trials for the treatment of anemia patients with chronic kidney disease (CKD). Chronic Unpredictable Mild Stress (CUMS), an animal model recapitulating the core symptoms of human depression, showed an atrophy of dendritic spines and a decrease in neurogenesis on hippocampus. In the current study, we investigated whether FG-4592 exhibits anti-depressant effect in rat CUMS model and its possible molecular mechanisms. We found that FG-4592 not only reversed the depressive behaviors, but also reversed impaired learning and spatial memory in the rat CUMS model. Moreover, FG-4592 increased hippocampal neurogenesis and synaptic plasticity including the density and the length of dendritic spines. At the molecular level, FG-4592 increased HIF-1α expression and activation, hence increase its target genes expression of EPO and BDNF (and other HIF target genes). Taken together, our findings demonstrated that FG-4592 has a therapeutic potential similar to an antidepressant in animal models of depression and could be developed as a treatment therapeutic option against this pathophysiological state.

Biography

Lingling Zhu has completed her PhD at Jichi Medical University, Japan and Postdoctoral studies from Academy of Military Medical Sciences, Beijing, China. She is the Director of Department of Cognitive Sciences of the Institute of Military Cognition and Brain Science. As the first author or corresponding author, she has published more than 25 papers in reputed journals and was invited to write English chapters.

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