

The contribution of CNS inflammation and Glycogen Synthase Kinase-3 (GSK-3)-cascades on adverse memory learning on mouse models of emotional stress

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VALORIZATION

Relevance for society

Depression is a heterogeneous group of mental disorders with high prevalence. At present, the exact pathophysiological mechanism of depression and associated processes of heightened negative memory acquisition still remains unclear, while researchers put forward various hypotheses to interpret the possible links to this disease, including excessive inflammation and deficient neuroplasticity.

As an outcome from my thesis work, my data will ultimately help to understand the molecular basis of depressive disorders of various etiologies to enable targeted treatment strategies of them. I pointed out isoforms of glycogen synthase kinase 3 (GSK-3), a molecular marker of distress and human depression in clinical studies, in two translational depression models of various etiologies. Importantly, modFST model replicates enhanced contextual conditioning of adversity that enables future studies of the mechanisms of certain neurobiological susceptibility mechanisms of depressive syndrome that is problematic to model in most of currently used rodent paradigms of the disease. As targeting of oxidative stress and neuroinflammation-related mechanisms of depression are regarded as a promising approach of efficient antidepressant therapy, main pro-

inflammatory cytokines including tumor necrosis factor (TNF), interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) were examined in my work with and without thiamine (vitamin B1), a compound with anti-oxidant and anti-stress properties, and classic antidepressant imipramine treatments. I demonstrated that thiamine was effective to counteract elevations of not only pro-inflammatory cytokines but also oxidative stress markers in the similar manner as imipramine that open new possibilities for thiamine-based treatment of some depression-related states, as thiamine is a nontoxic molecule that lacks side effects. Thus, this thesis is highly valuable as it aimed to investigate the contribution of ubiquitous environmental factors to the risk of having depressive syndrome, and to determine if thiamine can have beneficial impacts on depressive syndrome management.

Target groups

I consider my target groups to be individuals that are at higher risk of a diagnosis of depression, such as war veterans and survivors of car accidents and other traumatic experiences as these factors precipitate vulnerability to the disease.

Activity / Products

As potential outlook of presented work, I anticipate an interest of international research groups and pharmaceutical companies to use present animal paradigms in translational and academic research to study oxidative stress in depression models of various etiologies as well as study antidepressant and antioxidant activities of novel drugs in these paradigms. Using of thiamine-based compounds for targeted treatment of GSK-3 α mediated depression can be of additional importance.

Innovation

My work is innovative in various aspects: I broaden knowledge of two mouse depression paradigms that model various aspects of depressive syndrome. GSK-3 can be a universal marker of depressive syndrome in which the upregulation is accompanied by microglial activation, oxidative stress and neuroplasticity disruption. These changes were reversed by pre-treatments with antidepressants and a prominent anti-oxidant, thiamine, that highlights utility of thiamine-based anti-oxidants to prevent development of depressive-like traits through GSK-3 overlapping molecular mechanisms. Notably, while I have shown that GSK-3 can be a universal marker of depressive syndrome of various etiologies, the expression of its isoforms GSK-3 α and GSK-3 β is differentially regulated in both models.

Implementation

I anticipate publishing my results in peer-reviewed international journals, presenting them at national and international conferences and further widen current knowledge about overlapping molecular mechanisms underlying depressive syndrome induced by “emotional stress” and enhanced learning of adverse context.