Institutionen för Kvinnors och Barns Hälsa,
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Studies on Neuronal Signaling in the Hippocampus Related to Development, Pathogenesis and Treatment of Mood Disorders

AKADEMISK AVHANDLING
vilken, för avläggande av medicine doktorsexamen vid Karolinska Institutet
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Abstract:
The hippocampus is a central organ in the brain which is interconnected with different cortical regions and plays an important role in memory and learning processes. The anatomical position of the hippocampus together with the special sensitivity of its neurons renders it vulnerable to brain injury. This vulnerability is more pronounced during the developmental stages of the hippocampus and more specifically to hypoxic ischemic injuries. Such injuries affect the neuronal circuit formation and the synapses between neurons, which in turn affect the crucial functions of the hippocampus. MHC-I molecule has been found to play a role in the development and function of some neuronal systems in the visual cortex. It is also expressed in the hippocampus and plays a role in the functional plasticity of this organ. Dysregulation of this molecule, by different cytokines released during hypoxic ischemic brain injuries, speculated to be among the reason of hippocampal dysfunction. Recent findings point to the involvement of the hippocampus in the pathology and treatment of several mood disorders. This is more evident in depressive disorders, including major depression disorder and bipolar disorder, which are becoming more recognized among adolescents and children. Selective serotonin reuptake inhibitors and lithium are considered the most reliable in treating such disorders even among children and adolescents. However their use is still debatable due to severe side effects and increased suicidal ideations. Further research providing more information on the possible mechanisms of actions of these pharmacological therapies would lead to a better understanding of the cellular mechanisms behind depressive disorders. Such understanding would help in developing more target specific drug therapies for treating depressive disorders in young patients.
In this study, and first, we provide further evidence for the vulnerability of the hippocampus during the perinatal period. The expression of MHC-I and CD3ζ in the hippocampus is vulnerable during selective periods of development. TNF-α is a factor that would alter the MHC-I/CD3ζ signaling system. Taking into consideration the dual role of MHC-I and CD3ζ molecules as regulators of development and plasticity in the CNS, we hypothesize that alterations in the expression levels of these molecules may be involved in the pathogenesis of neuropsychiatric disorders.
Second, we highlight the fact that down-regulation of glutamate mediated calcium signaling is a potential target for lithium action. Together with previous reports on the hyperactivity of intracellular calcium ion mobilization in the peripheral cells of bipolar patients, one can speculate that calcium hyperactivity may play a role in the pathogenesis of bipolar disorder. Considering the importance of neuronal calcium homeostasis for the normal function of neuronal circuits and synapses, the use of lithium when treating children and youth can have advantages as where neuronal circuits and synapses are in the phase of maturation.
Third, we describe a unique distribution and vesicle trafficking of 5-HT1BRs in the dendrites of hippocampal neurons. This finding sets 5-HT1BRs apart from the majority of postsynaptic receptors and opens a new channel for a receptor-specific approach to 5-HT signal regulation. Using such channel could provide a more target specific anti-depressive therapy that would have more specific action with less side effects, when treating children and adolescents.

***Key words**: Hippocampus, MHC-I, CD3ζ, TNF-α, Lithium, Glutamate, Calcium, 5-HT1BR.*

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