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Inhibitory Effects of Cypermethrin on Hippocampal Neurogenesis are Dependent on Transcriptional co-activator PGC-1 alpha

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Abstract

The distinctive ability of NSCs to self-renew and proliferate is indispensable to maintain the stem cell pool and regenerative potential of the neurogenic regions in the brain. The maintenance of stem cell pool relies on a balance between self-renewal, proliferation, cell fate decisions and cell death, whereby any imbalance can lead to depletion of stem cell pool. In recent years, several studies have highlighted that environmental toxicants disrupt this balance, resulting in degenerative changes and cognitive disabilities. Cypermethrin is a type II synthetic pyrethroid insecticide widely used to control a broad range of insect pests in agriculture, public health, veterinary medicine and residential settings. Despite beneficial roles of cypermethrin, its uncontrolled and repetitive use has lead to unintended effects in non-target organisms. In the current study, we observed that cypermethrin exposure alters the expression of key neurogenesis and mitochondrial biogenesis proteins resulting in impaired neurogenesis and mitochondrial dynamics in the neurogenic regions of the brain. But we were unsure of the co-dependency of these two processes in the neurogenic regions of brain. Hence, to gain a clear picture of the involvement of mitochondria in regulating NSC proliferation and differentiation we carried out genetic/pharmacological inhibition and activation of PGC-1α (a key protein that regulates mitochondrial biogenesis) in both hippocampal derived primary NSC cultures and rat hippocampus. Interestingly we found that siRNA mediated knockdown of PGC-1α in primary NSC cultures decreased NSC proliferation and neuronal differentiation. Inhibition of PGC-1α in conjunction with cypermethrin treatment aggravated cypermethrin mediated toxicity. On the contrary genetic and pharmacological activation of PGC-1α with AdPGC-1α and nicotinamide in the rat brain rescued the inhibitory effects of cypermethrin on neurogenesis by replenishing the NSC pool, and improving cognitive functions in cypermethrin exposed rats. Collectively, these results demonstrate that PGC-1α plays an instructive role in controlling the self-renewal, proliferation and switch of stem cell fate, and a potential target to ameliorate cypermethrin induced neurogenesis deficits in the rat brain.

Biography

Anuradha yadav is a senior researcher at Developmental Toxicology Laboratory, Systems Toxicology and Health Risk Assessment Group, CSIR-Indian Institute of Toxicology Research (CSIR-IITR).

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