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Modeling 'Addiction' in Drosophila melanogaster from the Perspective of Neuronal Homeostasis

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Although genetics and heritability play a major role in its etiology, the molecular and neuronal mechanisms underlying drug addiction remain largely unknown. While current dogmas stipulate that addiction is specifically associated with the dopaminergic reward system, emerging data suggest that this model cannot explain all physiological aspects of the phenotype. Here we propose to test an alternative, non-mutually exclusive model, which looks at addiction as a direct product of neurodevelopmental processes associated with the homeostatic response to chronic drug exposure. Specifically, we hypothesize that drug exposure during critical periods of nervous system development leads to modulation of the molecular and physiological processes that maintain physiological neuronal homeostasis in the presence of the drug. Subsequently, once these pathways mature, the affected cells and circuit depend on the presence of the drug for their normal functions. To test our hypothesis, we are investigating the effects of chronic exposure of *Drosophila melanogaster* to nicotine, a highly addictive acetylcholine receptor agonist, on the neuronal homeostatic response to stress. By using behavioral and genetic approaches, my thesis work suggests that withdrawal from long-term nicotine exposure leads to impaired homeostatic responses to acute heat stress, which is associated with alterations in the expression levels of genes involved in nicotinic neuronal signaling. We conclude that chronic developmental exposure to nicotine leads to molecular and physiological changes, which affect the homeostatic neuronal response, and therefore, might provide a novel mechanism for drug addiction.