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Mechanisms of diet modulating experience-dependent amphetamine preference

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Psychostimulants accounted for about a third of drug overdose deaths last year, however, as of today, there are no approved pharmacotherapies for treatment of psychostimulant use disorders. Therefore, new approaches and insights are needed. Recent studies point towards a role for diet and the gut-brain axis in mental health, including substance use disorders (SUD). Despite this knowledge, studies examining the molecular mechanisms by which diet affects the response to addictive substances remain scarce. We want to identify the molecules and mechanisms of gut-brain communication modulating dopaminergic neurons and SUD-related behavior. To do this, we take advantage of the genetic tools, fast generation time and high-throughput economy of scale of Drosophila. While Drosophila has been used for decades to isolate conserved genes mediating behavioral responses to alcohol, the study of psychostimulants has historically been hampered by the lack of a longitudinal assay that allows to monitor preference. We have recently established an assay monitoring the development of Experience-Dependent Amphetamine Preference. Amphetamine preference requires the canonical Drosophila 'reward system'. With this novel assay, our results show that supplementing flies' regular food with protein prior the behavioral assay, blunts the development of amphetamine preference. Our overarching hypothesis is that the effect of diet on amphetamine preference is mediated by gut signals that directly regulate brain dopaminergic neurons. Obtaining mechanistic insight into the regulation of drug preference over time can inform our understanding of SUD. Furthermore, diet is an accessible, and translatable intervention that could assist both in SUD prevention and recovery.