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Anti-homeostatic Excessive Alcohol Consumption Exacerbated by Vitamin B6 deficiency in Drosophila

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Chronic alcohol consumption has a host of deleterious effects on nutrition and vitamin content, including the active form of vitamin B6, pyridoxal-5'-phosphate (PLP). PLP is a cofactor for GAD that is required for GABA synthesis, suggesting a potential link between alcohol and GABA neurotransmission which has never been systematically studied. Dietary vitamin B6 (pyridoxine or pyridoxamine) is inactive and is metabolized into PLP by the highly conserved pyridox(am)ine-5'-phosphate oxidase (PNPO) enzyme. We previously generated and characterized knock-in fly models in which we replaced the fly PNPO gene with several mutant human PNPO genes across a range of severity from epilepsy patients. Combining these genetic models of PNPO defects with dietary PLP supplementation offers a unique approach to investigate how PLP deficiency and GABAergic signaling may contribute and respond to alcohol use. The present study demonstrates that PNPO and PLP play a highly significant role in both acute and chronic alcohol use. We show that 1) both alcohol consumption and PNPO mutations lead to PLP reduction; 2) PNPO defects increase alcohol preference and consumption; 3) PNPO defects increase lethality which is worsened by alcohol consumption and rescued with PLP supplementation; 4) PNPO defects result in increased tissue alcohol content following acute alcohol exposure; and 5) PNPO mutant flies exhibit altered neurotransmitter levels and altered behavioral responses to alcohol. In summary, our data suggest that either genetic disposition or excessive alcohol use could lead to PLP deficiency and potentially initiate vicious cycles of anti-homeostatic alcohol consumption.