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Feedforward Cycle Between Amphetamines, Microbes, and Host Psychomotor Responses

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The abuse potential and psychomotor stimulant properties of amphetamines (AMPHs) are associated with their ability to increase extracellular dopamine levels. This increase is mediated, at least in part, by reversal of dopamine transporter (DAT) function, causing non-vesicular dopamine release (efflux).

Recent studies suggest that imbalances in the host microbiome participate in the pathogenesis of substance use disorders. Microbial products, such as the short-chain fatty acid butyrate, are suspected to play a fundamental role in this process. Fusobacterium nucleatum (F.n.) is a bacterial species that secretes butyrate and whose abundance is increased by AMPHs in both rodents and humans.

We find that colonization of the intestinal tract of gnotobiotic Drosophila with F.n. significantly enhances AMPH-induced dopamine efflux and associated behaviors. Secretion of butyrate, inhibition of histone deacetylase 1, and elevated DAT expression, play a role in these effects. In parallel, we observed increases in Drosophila colonization by F.n. in the presence of AMPH. AMPH has no impact on bacterial growth, but instead, stabilizes bacterial biofilms, structures utilized by F.n. to promote survival. We found that AMPH enhances biofilm formation through upregulation of adhesion protein expression in F.n. Inhibition of adhesion proteins, and biofilm formation, blocks the enhancement of AMPH-induced efflux, and associated behaviors, that are typically observed upon exposure to F.n. These findings suggest a feed-forward, self-reinforcing, addictive cycle exists between AMPH, F.n., and host responses to AMPH; i.e. AMPH enhances the number of F.n. in the host and F.n. enhances the host response to AMPH by elevating levels of DAT.

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