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Authors: Kristine Marceau, Emily Abel



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Running Head: CORTISOL AND SUBSTANCE USE

Mechanisms of cortisol – substance use development associations: Hypothesis generation through gene enrichment analysis

Kristine Marceau*, Emily Abel

Purdue University

***Address correspondence** to Kristine Marceau, email: KristineMarceau@purdue.edu, tel: 765-494-9410, 225 Hanley Hall, Purdue University, 1202 West State St., West Lafayette, IN 47907.

Highlights

- Cortisol is associated with substance use (SU) phenotypes across the SU progression
- Associations observed at multiple levels, from intra-cellular action to psychological
- Associations of cortisol and SU across the SU progression are often bi-directional
- There is potential for some genetic confounding in cortisol-SU associations
- Genetically informed designs are critically needed to test cortisol-SU associations

Abstract

There are many theories about the mechanisms of associations between hypothalamic-pituitary-adrenal (HPA) function (indexed by cortisol) and substance use. However, the potential for genes that contribute to both HPA function and substance use to confound the association (e.g., genetic confounding) has largely been ignored. We explore the potential role of genetics in cortisol-substance use associations, build a conceptual framework placing theories and mechanisms for how cortisol and substance use are related into a developmental progression, and develop new hypotheses based on our findings. We conclude that the relationship between cortisol function and substance use is complex, occurs at multiple levels of analysis, and is bidirectional at multiple phases of the

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