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Authors

Macedo, GC
Okhuarobo, A
Sidhu, H
et al.

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CAPTURING NEGATIVE AFFECT IN THE CIE-2BC MOUSE MODEL OF ALCOHOL DEPENDENCE

G.C. Macedo, A. Okhuarobo, H. Sidhu, M. Kreifeldt, J.L. Bolton, E.P. Zorrilla, T.Z. Baram, C. Contet
The Scripps Research Institute, Department of Molecular Medicine, La Jolla, CA 92037, USA University of California Irvine, School of Medicine, Department of Anatomy & Neurobiology, Irvine, CA 92697, USA

Exposing C57BL/6J mice to chronic intermittent ethanol (CIE) vapor inhalation elicits a gradual escalation of their voluntary alcohol consumption during two-bottle choice (2BC) sessions, which makes this procedure valuable for studying the neurobiological mechanisms driving the transition to alcohol dependence. Alcohol intake escalation in CIE-exposed mice is thought to be driven by negative reinforcement. Accordingly, we sought to characterize affective disturbances associated with a history of excessive alcohol drinking in C57BL/6J males withdrawn from CIE-2BC. We used conventional assays of anxiety-like and depressive-like behaviors, as well as measures of innate behaviors, at different withdrawal time-points. During early withdrawal (first week), we observed increases in digging activity and active coping strategy in the tail suspension test, which may result from psychomotor agitation; the latter dissipated after 3 weeks of withdrawal. During protracted abstinence (4-10 weeks), aggression against an intruder and urinary marking in response to a novel environment or female odor were dramatically reduced, which may reflect apathy. Open arm exploration in the elevated plus-maze was not affected in early or late abstinence. Furthermore, mechanical nociception was increased up to 3 days after CIE but normalized by day 6. Next, we examined how a history of early life adversity, which is a strong risk factor for alcohol use disorders in humans, influences ethanol intake and negative affect in mice subjected to CIE-2BC. Mice were reared under limited bedding and nesting conditions from postnatal days 2 to 9 to produce early life adversity via fragmented maternal care. C57BL/6J males exposed to early life adversity escalated their voluntary ethanol intake at an earlier stage of CIE exposure than control-reared counterparts. They also exhibited reduced open arm exploration in the elevated plus-maze and increased immobility in the tail suspension test during withdrawal from CIE-2BC, suggesting that early life adversity and chronic alcohol exert synergistic effects on negative affect. These results highlight the dynamic nature of emotional regulation during abstinence from alcohol and validate the relevance of the CIE-2BC mouse model for the study of neurobiological mechanisms driving the hyperkatifeia associated with excessive alcohol drinking and potentiated by early life adversity.