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HOT TOPICS

Orexin modulation of stress reactivity as a novel targeted treatment for anxiety and alcohol use disorder

Stephanie M. Gorka[1,2]✉ and K. Luan Phan[1]

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Alcohol use disorder (AUD) and anxiety disorders (AD) commonly co-occur. Studies show up to 50% of individuals receiving treatment for AUD meet criteria for AD [1]. Available medications to treat these disorders are modestly effective and do not work for everyone. The development of new and more efficacious pharmacotherapies for AD+AUD is urgently needed. Related, a recent emphasis in medication development is the use of biologically plausible and valid human laboratory measures of AD+AUD pathophysiology to screen promising compounds and test target engagement to inform the go/no-go decision to move to a clinical trial. The ultimate goal is to more quickly identify compounds deserving of clinical testing and accelerate the pace of mechanistic drug discovery. To this end, assays of stress reactivity and the orexin system have emerged as promising targets for a next-generation treatment strategy.

Our lab has developed a reliable assay of stress reactivity that is robustly associated with AD and AUD. We have shown that 'fear-based' anxiety disorders and AUD are similarly characterized by exaggerated aversive reactivity during threats that are unpredictable (U-threat) [2, 3]. Using complimentary psychophysiological and neuroimaging measures, we find that greater behavioral (i.e., startle eyeblink) and brain (i.e., anterior insula and dorsal anterior cingulate cortex) reactivity to U-threat correlates with severity of AD and AUD symptoms, and stress-related coping motives for alcohol. These brain-behavioral markers are effectively and selectively reduced during alcohol intoxication. Our paradigm substantiates the negative reinforcement model of AD and AUD and the established role of anterior insula function in AD and AUD. The paradigm can therefore be leveraged for drug discovery.

The hypocretin/orexin (ORX) hypothalamic neuropeptide system is a potential means for disrupting the negative reinforcement cycle of AD+AUD. Preclinical studies show that orexin neurons are activated by stress, and ORX signaling blockade blunts responses to stress challenges that elicit high arousal. In parallel, studies have shown that antagonism of ORX receptors decreases alcohol consumption, blocks alcohol conditioned place preference, and prevents cue-induced reinstatement of alcohol seeking [4]. Interesting, the effects of ORX antagonism are most robust in animals with high motivation for alcohol, a characteristic feature of human AUD. Studies also show ORX antagonism is particularly effective at reducing stress-induced alcohol relapse [5], and that orexin transmission in the anterior insula is directly involved in substance relapse following prolonged abstinence [6]. The ORX system is therefore involved in the functional interactions between stress/anxiety and alcohol and can be targeted to reduce arousal and motivations for drinking.

Theoretically, ORX antagonism is a promising pharmacological treatment for individuals with AD+AUD who display increased U-threat reactivity and engage in stress-related alcohol use. There is growing enthusiasm for ORX treatments for various individual disorders; though we argue ORX antagonism may be particularly beneficial for the intersection of anxiety and alcohol use. Studies in our lab are underway to deploy the U-threat paradigm as a human laboratory assay and test if ORX antagonism modulates stress reactivity and thereby reduces alcohol consumption. Studies such as these promise to bring new therapeutic options for patients with persistent anxiety and problematic alcohol use.

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REFERENCES

1. Kushner MG, Abrams K, Thuras P, Hanson KL, BrekkeM, Sletten S. Follow-up study of anxiety disorder and alcohol dependence in comorbid alcoholism treatment patients. Alcohol Clin Exp Res. 2005;29:1432–43.
2. Gorka SM, Lieberman L, Shankman SA, Phan KL. Startle potentiation to uncertain threat as a psychophysiological indicator of fear-based psychopathology: An examination across multiple internalizing disorders. J Abnorm Psychol. 2017;126:8.
3. Gorka SM, Kreutzer KA, Petrey KM, Radoman M, Phan KL. Behavioral and neural sensitivity to uncertain threat in individuals with alcohol use disorder: associations with drinking behaviors and motives. Addiction Biol. 2020;25:e12774.
4. Hopf FW. Recent perspectives on orexin/hypocretin promotion of addiction-related behaviors. Neuropharmacology. 2020;168:108013.
5. Campbell EJ, Marchant NJ, Lawrence AJ. A sleeping giant: suvorexant for the treatment of alcohol use disorder? Brain Res. 2020;1731:145902.
6. Hollander JA, Lu Q, Cameron MD, Kamenecka TM, Kenny PJ. Insular hypocretin transmission regulates nicotine reward. Proc Natl Acad Sci USA. 2008;105:19480–5.

[1]Department of Psychiatry and Behavioral Health, The Ohio State University, Columbus, OH, USA. [2]Institute for Behavioral Medicine Research, The Ohio State University, Columbus, OH, USA. ✉email: Stephanie.Gorka@osumc.edu

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to S.M.G.