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RESEARCH HIGHLIGHT

Astrocytes and alcohol: cortical astrocytes regulate alcohol consumption and intoxication

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Drug addiction is a complex psychiatric disorder [1]. Most clinical and preclinical research to date focuses on neuronal adaptations following drug use that drive and sustain alcohol use [1, 2]. However, recent studies suggest that glia and glia–neuron interactions may contribute to the development of alcohol use disorder [3, 4]. For example, Erickson et al. reported that sustained alcohol exposure reduces the expression of genes related to G protein-coupled receptor (GPCR) signaling and calcium regulation in mouse prefrontal cortical (PFC) astrocytes [4]. In astrocytes, activation of G_q-coupled GPCRs (G_qGPCRs) leads to elevations in intracellular calcium and to the release of gliotransmitters, such as adenosine triphosphate (ATP), which in turn regulate synaptic transmission [5]. Astrocytic calcium modulation and downstream signaling are linked with multiple behaviors, including attention, cognition, emotional, and motor behaviors, sensory processing, circadian cycling, and drug seeking [3, 5, 6]. Since alcohol exposure produces molecular adaptations in astrocytes [3, 4], it is important to understand whether, and if so, how these changes contribute to alcohol-related behaviors.

In this issue of *Neuropsychopharmacology*, Erickson et al. examined the potential role of cortical astrocyte calcium signaling in alcohol consumption and intoxication [7]. By utilizing elegant approaches in mice to activate or inhibit calcium signaling in PFC astrocytes, the authors report that chemogenetically stimulating astrocyte-specific calcium signaling increases alcohol consumption and preference, while reducing calcium signaling in PFC astrocytes by overexpressing an exogenous calcium extruding transporter [8] suppresses alcohol consumption and alcohol-induced c-Fos expression.

As alcohol consumption patterns may result from differences in sensitivity to alcohol, Erickson et al. hypothesized that stimulation or inhibition of astrocytic calcium signaling in the PFC would differentially affect behavioral responses to an acute dose of alcohol. Indeed, the authors report that G_qGPCR activation in PFC astrocytes enhances the sensitivity to the acute hyperlocomotive effects of alcohol as well as to alcohol-induced sedation, while inhibition of astrocytic calcium signaling has an inverse effect.

Lastly, the authors set out to identify the potential mechanism through which G_qGPCR signaling in PFC astrocytes drives alcohol intoxication. Activation of astrocytic G_qGPCRs triggers the exocytosis of ATP, which is rapidly converted into adenosine in the extracellular space [6]. The authors hypothesized that alcohol increases extracellular adenosine, which then binds to inhibitory adenosine receptors (A1Rs) in the PFC, thus shaping alcohol-induced behavioral responses. To test this possibility, Erickson et al. administered an adenosine A1R antagonist and simultaneously activated the astrocytic G_qDREADD before delivering a hypnotic dose of alcohol. The authors found that blocking A1R attenuates G_qDREADD-dependent enhancement of alcohol intoxication and conclude that adenosine A1R signaling in PFC astrocytes is required to mediate the sedative effect of alcohol.

Although significant research has explored the effects of alcohol on neurons [1–3], the study by Erickson et al. represents an important step in deciphering the role that glial cells play in the behavioral effects of alcohol. Their elegant use of chemogenetics and restricted expression of a calcium extruder *in vivo* provides an exciting glimpse into the contribution of PFC astrocytes to alcohol drinking, locomotion, and intoxication.

Future studies are required to determine how PFC astrocytes contribute to the development of excessive alcohol use. While the possibility that PFC astrocytes contribute to the acute sensitivity to alcohol, which in turn promotes the initiation of heavy alcohol use, is tempting, the door remains open for alternate explanations. For example, astrocytes regulate cognitive function and behavior, usually via calcium signaling, by decoding afferent signals and coordinating downstream effects throughout the brain [5]. Therefore, it is plausible that alcohol is encoded as more rewarding when PFC astrocyte calcium signaling is activated, thus driving excessive consumption.

Furthermore, the authors focus on the PFC in this study, as their previous work showed changes in G_qGPCR-related gene expression in the PFC following chronic alcohol exposure [4]. More specifically, they target both the prelimbic (PL) and infralimbic (IL) cortices [7], and considering the neuronal and astrocytic heterogeneity in these brain regions, only a subset of astrocytes may be driving alcohol responses. It may also prove valuable to examine astrocyte G_qGPCR signaling in additional brain areas related to alcohol-induced acute hyperlocomotion and sedation, such as the dorsal striatum and cerebellum. Furthermore, other PFC-related behaviors related to drug use, such as motivated and compulsive seeking, may also be influenced by G_qGPCR/calcium signaling in PFC astrocytes.

Erickson et al. show that blocking the adenosine A1 receptor restores normal alcohol-induced sedation, even with G_qDREADD activation in PFC astrocytes. Dysregulation of astrocyte-mediated adenosine signaling has been previously linked with excessive alcohol consumption [6]. Specifically, acute alcohol exposure inhibits adenosine uptake and long-term alcohol drinking down-regulates the expression of an astrocytic adenosine transporter,

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equilibrative nucleoside transporter 1 (ENT1), in several other brain areas, including the nucleus accumbens [6].

In the study reviewed here, the authors also report that G_qGPCR signaling in PFC astrocytes has an effect on the development of alcohol drinking, but does not alter alcohol consumption once drinking has been established [7]. This may suggest that ENT1 expression dynamics play an integral role in alcohol drinking regulation by PFC astrocytes. In addition, ENT1 knockout mice display greater alcohol preference and are resistant to the locomotor and sedative effects of alcohol [6], further suggesting that adenosine signaling may be responsible for the different responses of mice to acute alcohol with and without G_qDREADD activation in PFC astrocytes.

Finally, one major remaining question following this study is which astrocytic G_qGPCRs are being activated by alcohol. Astrocytes express many of the same GPCRs that neurons do, including some related to addiction and reward [9]. In addition, a subset of G_qGPCRs expressed in cortical astrocytes [9] have been shown to drive or inhibit alcohol consumption, preference and/or seeking, such as metabotropic glutamate receptor 5, P2Y purinoceptor 1, and muscarinic acetylcholine receptors [10]. Determining which receptors in PFC astrocytes are specifically driving behavioral responses to alcohol and promoting alcohol consumption will prove a difficult, but rewarding, undertaking.

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AUTHOR CONTRIBUTIONS

JJM and DR prepared and wrote the manuscript.

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