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RESEARCH HIGHLIGHT

Binge-like alcohol drinking remodels the inhibitory microcircuitry of the prelimbic cortex in male and female mice

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Alcohol use disorder (AUD) remains a major global public health concern. In the US, patterns of excessive drinking over short periods, termed binge drinking, are becoming increasingly common. Although binge drinking occurs in both men and women, there are gender-specific pathophysiological consequences that emerge as a consequence of this kind of problematic drinking. Much has been learned about the brain substrates of AUD but we still know surprisingly little about the neural circuitry governing binge drinking or the distinct neuronal adaptations that drive sex-dependent central nervous system changes associated with excessive alcohol consumption.

In this paper, Dao et al. [1] integrated "Drinking in the Dark" (DID), a well-validated mouse model of binge-like drinking, along with elegant optogenetic/chemogenetic approaches, to examine behavioral and neurophysiological adaptations in male and female mice. In the DID model, mice are given access to a 20% alcohol solution (roughly the concentration of fortified wine) for 2–4 h. drinking sessions initiated 3 h. into the dark cycle, corresponding to a period of high activity in mice. Following repeated cycles of 4 days of alcohol access and 3 days off, most mice attain blood alcohol levels that meet the NIAAA definition of a binge (80 mg%).

Dao et al. focused on the prelimbic (PL) region of the prefrontal cortex. The PL is a central node of the circuitry involved in AUD and affective disorders. As with other cortical regions, the PL can be subdivided into layers 1–6 which are all predominantly populated by glutamatergic pyramidal neurons (~80–90%) and a diverse array of heavily interconnected inhibitory cells [2]. In the AUD field, much more emphasis has been placed on neural adaptations in excitatory pyramidal neurons. Despite the powerful role that GABAergic interneurons play in modulating activity patterns throughout the cortex, considerably less research has focused on these cells. However, recent studies are beginning to identify unique synaptic adaptations during alcohol withdrawal across interneuron subtypes that, in some instances, exhibit profound sex-dependent adaptations [3]. Of note, Martinotti interneurons, which project to more superficial PL layers (L 1-3), show opposite sex-dependent adaptations, with a decrease in neuronal excitability in males but an increase in females, following chronic alcohol exposure [3].

In the present study, Dao et al. focused on layers 2 and 3 that are reciprocally connected with limbic structures, like the basolateral amygdala, that are known to play an integral role in alcohol dependence and comorbid neuropsychiatric disorders [2]. Notably, their investigation focused on both pyramidal neurons and interneurons, to obtain a more holistic PL circuit model of DID-associated neuronal adaptations. The authors first studied somatic excitability as well as the input strength of somatostatin positive (SST+) cells and pyramidal neurons using electrophysiological approaches. In a prior study, the authors identified neuronal adaptations in SST+ cells of the PFC following prolonged withdrawal from a two-bottle choice drinking procedure [4]. Here, they observed a significant reduction in the somatic excitability of PL SST+ cells as well as a decrease in excitatory input (sEPSC frequency) in both male and female mice. This decreased SST+ cell activity coincided with an increase in the excitability of PL pyramidal neurons that was also observed in both sexes.

Next, the authors used optogenetic approaches to further resolve the inhibitory microcircuit adaptations promoted by DID that may have contributed to the increase in PL pyramidal cell excitability. Based on prior work suggesting that SST+ neurons can also modulate PL pyramidal cells via an intermediary population of non-SST+ interneurons, they examined the effects of DID on optically evoked IPSCs (oIPSCs) onto both populations of cells. Somewhat surprisingly, oIPSCs recorded from PL pyramidal cells were not altered by DID but inhibitory responses onto non-SST+ GABAergic interneurons were significantly enhanced in both sexes, albeit via distinct mechanisms. Collectively, these findings reveal intricate inhibitory circuit adaptations, involving mono- and polysynaptic projections from SST+ GABAergic cells, through which binge drinking enhances PL pyramidal cell excitability.

In a final series of experiments, the authors employed chemogenetic methods to establish a causal connection between these PL circuit adaptations and binge-like alcohol drinking. In both male and female mice, chemogenetic activation of SST+ interneurons or inhibition of PL pyramidal cells both led to a decrease in alcohol intake in the DID procedure. Importantly, inhibiting SST+ neuronal activity had no effect on the consumption of a natural reinforcer (sucrose) in either sex. A minor wrinkle in this story was the finding that chemogenetic inhibition of SST+ interneurons had the same effects on drinking as did excitation of these cells, selectively decreasing alcohol, but not sucrose intake. However, the authors' careful electrophysiological characterization of chemogenetic modulation of SST+ neurons revealed that both excitation and inhibition of these cells strengthened elements of SST+ neuronal inhibition, likely via distinct interactions with elements of the complex PL inhibitory microcircuitry.

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Overall, these findings shed new light on the complexity of PL neuronal adaptations following binge-like alcohol drinking in mice. These data not only uncover an important role of the local PL inhibitory network but also identify some sex-specific adaptations that may prove relevant as more adaptations of this PL microcircuitry come to light. A few important future directions include defining the role of the interconnections between the layers of the PL. As noted above, Martinotti interneurons of layer 5 have been shown to undergo sex-specific adaptations in alcohol dependent rodents and this population projects to more superficial layers [3]. Thus, these cells represent an important population to consider in the overall PL network model being studied. Additionally, increasing evidence is emerging that some inhibitory cells (including SST+ neurons) also serve as projection neurons [5]. This opens up the possibility that the neuronal adaptations of PL GABAergic cells observed in the present study may have a long-range impact on downstream regions.

Together, the Dao et al. study significantly advances our understanding of PL circuit adaptations following binge drinking while also opening up many exciting future directions to explore. A more complete understanding of the circuitry impacted by excessive alcohol consumption may facilitate the development of more targeted treatment strategies for AUD.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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