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RESEARCH HIGHLIGHT

A little night(PA)CAP: pituitary adenylate cyclase-activating polypeptide mediates behavioral effects of alcohol withdrawal

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Alcohol use disorder is a chronic, relapsing disorder characterized by compulsive seeking and intake of alcohol, feelings of loss of control over its consumption, and the emergence of negative affective states during abstinence [1]. With dependence, alcohol drinking is thought to be driven by negative rather than positive reinforcement, whereby the intake of alcohol removes aversive abstinence-related states. The emergence of dependence is thought to occur through a loss of function in the reward systems of the brain and a recruitment of the stress systems in the extended amygdala, which is comprised of the bed nucleus of the stria terminalis (BNST), central nucleus of the amygdala, and nucleus accumbens shell [1]. Importantly, few medications effectively treat alcohol use disorder. Thus, identifying new pharmacotherapeutic targets is a top priority.

The neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP), and its cognate receptor (PAC1R), are involved in both ethanol intake and the stress response, and they are heavily expressed in the BNST [2, 3]. In rats, chronic intermittent access ethanol drinking increases peptide levels of PACAP in cells of the paraventricular nucleus of the thalamus [4]. Chronic variable stress upregulates gene expression of PACAP and PAC1R in the BNST [5], and injection of PACAP or a PAC1R agonist into the BNST stimulates anxiety-like behaviors, as measured in elevated plus maze and open field tests [6]. While this connects PACAP with ethanol drinking and the stress response, a specific role for PACAP in ethanol dependence, and whether or not this occurs through actions in the extended amygdala, remained unknown.

In this issue of *Neuropsychopharmacology*, Ferragud et al. [7] tested the hypothesis that the PACAP/PAC1R system of the BNST represents a major component of the brain stress system that promotes the increased ethanol drinking and anxiety-like behavior that occur in ethanol dependence. Using 8 weeks of intermittent ethanol vapor or air exposure in adult, male Wistar rats, a procedure that induces ethanol dependence, the authors first use immunohistochemistry to identify changes in the PACAP system in the extended amygdala during acute withdrawal (8–10 h after vapor offset). Next, to determine the effects of their observed increase in endogenous PACAP levels in the BNST on ethanol intake and anxiety-like behavior, they train a second group of rats to self-administer ethanol and water prior to and then throughout the period of ethanol vapor or air exposure, during acute withdrawal. They then test these rats for ethanol and water self-administration and, one week later, for anxiety-like behavior in a light-dark conflict test, following bilateral injection into the BNST of the PAC1R antagonist, PACAP(6-38), during acute withdrawal.

The authors first find that, during acute withdrawal, rats exposed to chronic intermittent ethanol vapor exhibit increased levels of PACAP in the dorsal part of the lateral subdivision or oval nucleus of the BNST, primarily in incoming fibers. In contrast, there is no difference in the central nucleus of the amygdala, where PACAP immunoreactivity is again suggestive of fibers. There is also no difference in the number of PAC1R positive cells in the dorsal BNST. Next, they find that ethanol-dependent rats self-administer ethanol at higher levels than non-dependent rats, and that this elevated drinking in the dependent rats is selectively and dose-dependently blocked by BNST PACAP(6-38) injections. Finally, Ferragud et al. show that ethanol-dependent rats display enhanced ethanol withdrawal-induced anxiety-like behavior, as evidenced by reduced time spent in the aversive light compartment in a light-dark conflict test, and that this behavior is similarly blocked, in the ethanol-dependent but not non-dependent rats, by BNST PACAP(6-38) injections.

The data from Ferragud et al. show that ethanol dependence involves the neuropeptide PACAP and its specific actions in the BNST. The finding that ethanol dependence increases levels of PACAP in this nucleus agrees with previous work, which found that PACAP gene expression is elevated following exposure to chronic variable stress [5] and by repeated exposure to cocaine [8]. Importantly, the present data also show that this increase in BNST PACAP occurs specifically within incoming fibers in this nucleus, suggesting that there could be enhanced release of PACAP into the BNST in the drug-dependent state. In agreement with this notion, the authors demonstrate that blockade of endogenous PACAP activity, through site-specific injection of a PAC1R antagonist, blocks the dependence-induced enhancement of ethanol self-administration and anxiety-like behavior during acute withdrawal.

The present behavioral results are also consistent with prior research, which found that injection of a PAC1R agonist into the BNST of ethanol-naïve rats stimulates anxiety-like behavior [6] and that injection of the PAC1R antagonist into the BNST prevents stress-induced reinstatement of extinguished cocaine seeking [8]. However, the data in the present study appear to contrast with results from a recent study showing that, in ethanol non-dependent rats, PACAP injections into the nucleus accumbens shell or core reduce intermittent access ethanol drinking and that a PACAP receptor antagonist stimulates drinking [9]. We propose that the potential opposite role of PACAP in the BNST and nucleus accumbens in dependent and non-dependent rats supports the idea that under normal conditions PACAP functions to tightly regulate ethanol intake, inhibiting it through negative feedback in the nucleus accumbens, but that this relationship changes with

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the development of dependence, so that PACAP in the BNST instead acts through positive feedback to promote drug intake [2].

In conclusion, the present data demonstrate that BNST PACAP is recruited with ethanol dependence to induce elevated ethanol drinking and negative affective states during abstinence. As such, the findings suggest that PACAP-based medications could be effective in the treatment of alcohol use disorder.

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AUTHOR CONTRIBUTIONS

BEP and JRB wrote and edited the manuscript.

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