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RESEARCH HIGHLIGHT

GSK3β in the prefrontal cortex: a molecular handle specific to addiction pathology?

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The past two decades have seen an explosion of research into the molecular and cellular underpinnings of addiction, with preclinical studies providing evidence that disordered reward processing and decision-making due to altered function of myriad pathways in the medial prefrontal cortex (mPFC) plays a key role in addiction-related behaviors, including alcohol use disorder [1]. However, it is also clear that the neural substrates of various addictions, from drugs to food to sex, are overlapping, and that the pathways that underlie these pathologies are not exclusive to addictive disorders but rather resemble the intersection of circuits that process reward, emotion, memory, and other essential functions [2]. Directly targeting molecular pathways central to the ability of the mPFC to process reward, or to seek rewarding stimuli, in order to treat addiction is thus likely to adversely affect non-pathological behaviors, such as appropriate eating for the drug addict or the normal sex life of the gambling addict. It is therefore critical to uncover the molecular mechanisms unique to the behavioral antecedents of addiction, potentially allowing targeted treatment of alcohol use disorder with reduced untoward effects on the unrelated behaviors of the patient.

In the current issue of Neuropsychopharmacology, van der Vaart and colleagues [3] characterize a novel role for mPFC activity of glycogen synthase kinase 3-beta (*Gsk3b*) in the reinstatement of ethanol seeking—an established model of drug seeking behavior that mirrors drug seeking observed in clinical addiction. Critically, they demonstrate that this role is specific to ethanol relapse, with no effect on relapse to sucrose seeking. The study finds that mPFC GSK3β phosphorylation is increased by acute ethanol exposure, and that AAV-mediated overexpression of GSK3β in mPFC of mice increases ethanol consumption and preference. The authors go on to demonstrate that in rats, operant intake of both ethanol and sucrose is reduced by systemic inhibition of GSK3β, but that subsequent relapse to ethanol seeking after prolonged withdrawal is reduced by systemic GSK3β inhibition while relapse to sucrose seeking is unaffected.

Parsing the differential roles of GSK3B in seeking of ethanol vs seeking of a "natural" reward like sucrose can be challenging. The authors found that overexpression of GSK3β in mPFC had an anxiogenic effect during abstinence from ethanol self-administration, suggesting that mPFC GSK3β may play a role in the adverse effects of withdrawal from ethanol. As abstinence from sucrose self-administration does not induce the same negative emotional state found in abstinence from ethanol consumption, it is possible that the specific effects of GSK3β inhibition of relapse to ethanol seeking after prolonged withdrawal are driven by a targeted reduction in the aversive effects of abstinence. It is also possible that these ethanol-specific effects are mediated by the role of GSK3β in ethanol neurotoxicity: GSK3β inhibition provides protection against ethanol neurotoxicity, whereas high GSK3β activity/expression sensitizes neuronal cells to ethanol-induced damage [4]. As ethanol neurotoxicity can contribute to cognitive decline and decreased behavioral inhibition leading to poor decision making, it is possible that reducing this cell loss via GSK3β inhibition could prevent binge drinking and relapse.

It is notable that systemic GSK3β inhibition affects the behavioral antecedents of exposure to several drugs of abuse. For instance, GSK3β inhibition increases cocaine self-administration [5] and interferes with reconsolidation of cocaine-associated reward memories [6]. Although it will be critical to determine whether systemic GSK3β inhibition is effective in preventing relapse to other drugs in a preclinical setting, it is tempting to imagine that targeting this pathway in patients could prevent relapse to several addictive drugs. This could be potentially useful, as most addicts report polysubstance abuse [7].

Finally, the authors suggest that the downstream mediator of mPFC GSK3β effects on ethanol seeking is brain-derived neurotrophic factor (BDNF), as they demonstrate that GSK3β overexpression reduces BDNF message and protein in mPFC. mPFC afferents supply BDNF to the dorsal and ventral striatum, and multiple studies suggest that alcohol increases striatal BDNF as a negative feedback mechanism to suppress alcohol intake [8]. These and other studies have shown that alcohol consumption escalates when this corticostriatal BDNF supply is dysregulated, and thus the work by van der Vaart et al. may provide a novel mechanism whereby ethanol consumption can drive GSK3β-mediated reduction in corticostriatal BDNF secretion to drive relapse to ethanol seeking. As the ubiquitous nature of BDNF in brain function and health makes it a poor therapeutic target, the identification of GSK3β as an upstream mediator of ethanol effects on BDNF and the finding that its systemic inhibition could be used to potentially prevent drug seeking without altering the drive for "natural rewards" (i.e., sucrose) represents a key advance in our understanding and prospective treatment of substance use disorders.

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