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RESEARCH HIGHLIGHT

Sound of silent synapses from the addicted hippocampus

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Enriched in the developing brain, most silent synapses are immature glutamatergic synapses that contain stable NMDA receptors (NMDARs) with AMPA receptors (AMPARs) that are either absent or highly labile, and thus are AMPAR-silent [1]. They serve as initial connections between neurons to form new neural circuits. During development, some silent synapses undergo experience-dependent maturation by recruiting or stabilizing AMPARs to consolidate synaptic connections.

Prior studies have revealed in adult rodents that non-contingent cocaine injections generate silent synapses in the nucleus accumbens (NAc) [2, 3], a brain region implicated in motivational learning and memory relevant to addiction [4]. Subsequent studies demonstrated that cocaine self-administration generates silent synapses in the amygdalar and prefrontal cortical projections to the NAc, followed by AMPAR insertion-mediated maturation after cocaine withdrawal. This silent synapse-mediated circuit remodeling contributes to incubation of cue-induced cocaine craving [5, 6], a time-dependent enhancement of cue-induced cocaine seeking after withdrawal [7]. These results suggest that cocaine re-activates silent synapse-mediated developmental mechanisms in the adult brain to remodel critical brain circuits and promote addiction-related behaviors [4]. As such, several questions arise: (1) Is silent synapse-based circuit remodeling a mechanism only employed by cocaine or also by other abused drugs to redefine circuit properties?; (2) Does drug experience induce silent synapse-mediated circuit remodeling in other brain regions apart from the NAc?; and (3) in addition to behaviors controlled by cue-drug associations, is silent synapse-mediated circuit remodeling involved in other hallmark features of addiction?

In this issue of Neuropsychopharmacology, Beroun et al. [8] heroically addressed these questions. They employed an extended alcohol intake procedure involving training mice for alcohol self-administration over 90 days. They then categorized the alcohol-exposed mice into "addicted" vs. "non-addicted" using five DSM-IV criteria for alcohol dependence (American Psychiatric Association 2000): (1) high drinking levels during free access; (2) high motivation to drink; (3) persistent alcohol seeking despite alcohol unavailability; (4) alcohol cue exposure induced alcohol seeking; (5) excessive alcohol consumption during relapse after withdrawal. Mice that scored in the upper 35% were defined to be 'positive' for a criterion, and mice that exhibited two or more positive criteria were considered 'addicted'.

Using this clinically relevant animal model, they performed electrophysiological and morphological investigations on granule cells in the dentate gyrus (DG), a reward-relevant region whose role in addiction remains underexplored. By chemogenetic manipulations via inhibitory (hM4Di) DREADDs, they demonstrated that after extended access to alcohol, inhibition of DG granule neurons increased both alcohol drinking and seeking in an enduring (7 days) manner, indicating that a decreased excitation of DG granule neurons promotes alcohol abuse.

The authors then examined the dynamic changes of silent synapses within the perforant path to DG granule cells. Silent synapse levels increased in both addicted and non-addicted mice during alcohol self-administration, but declined to basal levels after alcohol withdrawal. Strikingly, 90 min following cue-induced alcohol seeking after withdrawal, addicted mice exhibited higher levels of silent synapses compared to non-addicted mice, suggesting an enhanced capability of excitatory synapses at DG granule cells in addicted mice to rapidly undergo synaptic remodeling.

In the adult brain, drug-induced generation of silent synapses in the NAc can occur via a synaptogenesis process involving delivery of new NMDARs to new synaptic locations or a synapse weakening process involving internalization of AMPARs from pre-existing synapses, depending on the administered drug per se and likely drug procedures [9]. Furthermore, the number of synaptic AMPARs is typically correlated with the head size of dendritic spines, the postsynaptic structures of excitatory synapses [10]. Thus, the authors examined the density and morphology of dendritic spines in the upper blade, where the DG is preferentially innervated by the perforant path. The density of thin spines in addicted mice was preferentially decreased during alcohol self-administration compared to non-addicts, then reversed following withdrawal and remained unchanged 90 min after cue-induced relapse. Moreover, within addicted mice, spine size decreased during alcohol withdrawal and then increased following cue-induced relapse, but no size differences were detected between addicted and non-addicted mice during withdrawal and relapse. Thus, the differential changes in silent synapses between addicted and non-addicted mice following cue-induced relapse were not strictly correlated to changes in spine density and area. Finally, when they repeatedly administered addicted mice with acamprosate, a drug used to treat alcohol abuse, at a dose that prevented cue-induced generation of silent synapses, these mice reduced alcohol consumption during free access and alcohol seeking during withdrawal. Despite some interpretational caveats, these results suggest that cue re-exposure-induced generation of silent synapses reflects synapse weakening, and the resulting decreased excitation of DG granule neurons promotes alcohol consumption and seeking.

Collectively, the authors reveal unique synaptic dynamics in the DG over the development and expression of alcohol addiction-like behaviors, and provide significant insights into addiction circuit mechanisms. First, the potential silent synapse-mediated synaptic weakening upon cue-induced relapse may function as an acute homeostatic response to relieve the excitation pressure presumably accumulated during alcohol withdrawal. Second, the

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differential synaptic responses to cue-induced relapse in addicted vs. non-addicted mice present a possibility that the cellular machineries governing synaptic trafficking of AMPARs are redefined in addicted individuals. Finally, given that acamprosate prevented cue-induced generation of silent synapses but not cue-induced alcohol relapse, the mechanistic link between silent synapse formation and alcohol cue reactivity may need to be further refined. Indeed, acamprosate may also target other arousal-related forms of cue reactivity to dampen the emotional impact of alcohol-contingent cues. Hence, future investigations are warranted to examine other conditioned responses to obtain a complete picture behind alcohol cue reactivity and silent synapses. Taken together, results from Beroun et al. suggest that silent synapse-based circuit remodeling is likely a common mechanism through which abused drugs of different classes redefine neural circuits in different brain regions during the development and expression of the addictive state. As such, drug-induced silent synapses may serve as potential therapeutic targets to reduce drug taking and relapse.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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