

Silent Synapse-based Circuitry Remodeling in Cocaine Craving
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A transient but prominent increase in the level of “silent synapses” – a signature of immature glutamatergic synapses that contain only NMDA receptors without stably expressed AMPA receptors – has been identified in the nucleus accumbens (NAc) following exposure to cocaine. As the NAc is a critical forebrain region implicated in forming addiction-associated behaviors, the initial discoveries have raised speculations about whether and how these drug-induced synapses mature and potentially contribute to addiction-related behaviors. Here, we summarize recent progress in recognizing the pathway-specific regulations of silent synapse maturation, and its diverse impacts on behavior. We provide an update of the guiding hypothesis – the Neural Rejuvenation Hypothesis – with recently emerged evidence of silent synapses in cocaine craving and relapse.

Methods: Electrophysiological recordings combined with rat model of incubation of cue-induced cocaine craving were used to determine cocaine-induced generation of silent synapses and subsequent maturation of silent synapses.

Results: AMPA receptor-silent synapses were detected in the nucleus accumbens after exposure to cocaine. These synapses share several core features of immature excitatory synapses during development. After withdrawal from cocaine self-administration, these immature synapses matured into fully functional synapses to remodel several afferents to the nucleus accumbens. Reversing maturation of silent synapses within these accumbens afferents reversed the development of incubation of cocaine craving.

Discussion: A series of studies from our lab demonstrate that exposure to cocaine and other drugs of abuse may wake up some dormant developmental mechanisms in the adult nucleus accumbens to redevelop or remodel its afferents, resulting in persistent behavioral alterations.

Reference: Dong Y, Nestler EJ. 2014. The Neural Rejuvenation Hypothesis of Drug Addiction. *Trends in Pharmacological Sciences* **35**(8): 374-383; Huang YH, Schlüter OM, Dong Y. 2015. Silent Synapses Speak Up: Updates of the Neural Rejuvenation Hypothesis of Drug Addiction. *Neuroscientist*. In Press. PMID: 25829364.

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