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HOT TOPICS

Recent findings on the role of sensory and interoceptive-related circuits in relapse to drug seeking

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One main challenge in treating drug addiction is high rates of relapse during abstinence. Preclinical models of drug relapse, which allow for mechanistic causal studies, have recently shown critical roles of sensory- and interoceptive-related systems, including agranular insular cortex (AI), vagus nerve, and the piriform cortex (Pir), in drug relapse. Interoception refers to "*sensitivity to stimuli inside the body, resulting from the response of specialized sensory cells called interoceptors, to occurrences within the body*" (https://dictionary.apa.org/interoception). Here, we briefly summarize the main findings from these studies and propose that research aimed at understanding interoceptive mechanisms driving drug relapse may lead to a new understanding of mechanisms of relapse and new treatment strategies for drug addiction.

AI is hypothesized to play a major role in interoception and is activated by cues and internal states to drive motivated behavior. Pharmacological inactivation of AI with muscimol +baclofen decreases context-induced reinstatement of cocaine seeking after extinction, context-induced reinstatement of alcohol seeking after punishment, and methamphetamine and fentanyl relapse after food choice-induced voluntary abstinence [1–4]. In addition, chemogenetic inhibition of projections from AI to the central amygdala decreases methamphetamine relapse after food choice-induced abstinence [4]. Together, these studies suggest that the AI plays a role in drug relapse across drug classes and relapse/reinstatement models. AI is anatomically connected to thalamic and amygdala regions, as well as sensory and visceral-related regions. Thus, determining the causal role of upstream and downstream circuitry underlying AI's role in relapse will also allow for a broader understanding of interoceptive and sensory systems in drug-related motivated behaviors.

Recent studies have identified roles of the vagus nerve and the olfaction-related Pir in relapse to drug seeking. The vagus nerve provides visceral information from the body to the brain via the nucleus tractus solitarius (NTS), and paradoxically, stimulation of or severing the vagus nerve-NTS pathway decreases relapse in rat models. Stimulation of the vagus nerve decreases cue and context-induced reinstatement of cocaine seeking [5]. On the other hand, vagotomy decreases the inhibitory effect of systemically administered oxytocin on cue- and drug priming-induced reinstatement of methamphetamine seeking in male but not female rats [6].

Pir provides olfactory information to the brain through inputs from the olfactory bulb but is also anatomically connected to the thalamic, amygdala, and cortical regions (including AI). We recently showed that Pir and projections between Pir and orbitofrontal cortex play a role in fentanyl relapse after food choice-induced abstinence [3]. This study suggests that Pir plays a causal role in drug relapse through projections with cortical regions like the orbitofrontal cortex and potentially AI.

Together, these recent findings support the notion that interoceptive and sensory systems contribute to relapse across drug classes, relapse/reinstatement models, and relapse-provoking stimuli. We propose that future studies using mechanistic approaches at the cellular, circuit, and systems levels will improve our understanding of the role of sensory and interoceptive signaling in drug relapse and motivated behaviors. We hope that such studies will lead to new strategies to treat drug addiction.

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AUTHOR CONTRIBUTIONS

Both DJR and YS drafted and edited the hot topic commentary and approved the final version.

ADDITIONAL INFORMATION

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