Neuropsychopharmacology www.nature.com/npp

RESEARCH HIGHLIGHT

From head to tail (of the VTA): role of projections from prelimbic cortex to rostromedial tegmental nucleus in cocaine reinstatement

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Neuropsychopharmacology (2021) 46:1395–1396; https://doi.org/10.1038/s41386-020-00933-z

Research into the neurobiological mechanisms of drug seeking has expanded recently, in part because of the development of neuroscience techniques that target and manipulate neuronal activity. Studies using these techniques, together with studies using more classical pharmacological approaches, have demonstrated similarities and differences of brain mechanisms of reinstatement of drug seeking induced by drug priming, cues, or context [1]. However, understanding how these brain regions communicate with each other to control drug seeking provides further mechanistic insight into reinstatement of drug seeking and may result in the development of improved treatment strategies.

Previous studies have shown a critical role of the prelimbic cortex (PL) in cue-, cocaine priming-, and stress-induced reinstatement of cocaine seeking after extinction in rats [2]. These studies suggest that PL neuronal activity promotes cocaine-seeking behavior. However, other studies show that PL activity inhibits cocaine seeking-behavior in the presence of discriminative stimuli that signal cocaine unavailability or cocaine-taking behavior under conditions of high frequency cocaine intake [3, 4]. Together, these studies suggest a more complex and nuanced role of PL in cocaine seeking that may depend on the downstream brain regions and circuits engaged by PL.

In this issue of *Neuropsychopharmacology*, Cruz et al. [5] hypothesized that inhibition of PL projections to the rostromedial tegmental nucleus (RMTg), a predominately GABAergic region that also plays a role in extinction learning of cocaine seeking [6], would enhance cocaine seeking during reinstatement. The authors first injected the retrograde tracer Cholera Toxin B (CTb) into RMTg and observed retrogradely-labeled cell bodies in PL, ~75% of which were ipsilateral and 25% were contralateral projections. They then used an asymmetrical anatomical disconnection procedure to examine the role of projections between PL and RMTg in cue- and cocaine priming-induced reinstatement. In a classical disconnection procedure [7], the role of a neuronal pathway in a behavioral procedure can be inferred when behavior is disrupted by contralateral but not ipsilateral inactivation of two anatomically connected brain regions. If projections between two regions are both ipsilateral and contralateral, data interpretation is less straightforward. In the present study, Cruz et al. addressed this interpretation issue by including groups that received unilateral inactivation of either PL or RMTg.

The authors performed the anatomical disconnection by injecting GABA receptor agonists (muscimol + baclofen) into PL and the AMPA receptor antagonist NBQX into either the contralateral or ipsilateral RMTg before the reinstatement sessions. Importantly, the authors included two separate groups of rats that received a unilateral injection of muscimol + baclofen in PL or NBQX in RMTg as controls. The authors reported that both the contralateral and ipsilateral disconnection increase cue-induced reinstatement of cocaine seeking. In contrast, the unilateral manipulations have no effect on cue-induced reinstatement. Additionally, the authors showed that contralateral disconnection of PL and RMTg has no effect on extinction responding or cocaine priming-induced reinstatement. These data indicate that both ipsilateral and contralateral projections from PL to RMTg are involved in cue-induced reinstatement of cocaine seeking. However, one limitation of this study is that the authors only used male rats and therefore the generality of the findings to females is unknown.

The authors investigated how a given brain region (e.g., PL) can both increase or decrease cocaine seeking during reinstatement, and if this dual function could be influenced by the downstream projections engaged. The authors' data suggest that PL neurons projecting to RMTg are involved in cue- but not cocaine priming-induced reinstatement of cocaine seeking. This may be due to different mechanisms of cue-induced vs. cocaine-priming induced reinstatement, in terms of either how distinct PL neuronal subtypes or their downstream projections are recruited. Further understanding of how PL neuronal subtypes are engaged during exposure to different reinstating stimuli will allow for a more precise ability to probe how PL downstream projections are recruited to promote or inhibit cocaine seeking. Combining retrograde tracing with immunohistochemistry for the neuronal activity marker Fos is one approach to understand how these circuits may be differentially recruited by cue- or cocaine priming-induced reinstatement.

Although technological advancements have led to development of modern neuroscience techniques such as designer receptors exclusively activated by designer drugs (DREADDs) and optogenetics to study neurocircuitry of behavior, the use of the anatomical disconnection procedure can still provide important and interpretable data, as demonstrated in Cruz et al. Indeed, though it may be possible to perform this study with DREADDs and optogenetics, the use of these modern technologies runs into the possible issue of viral spread that may also affect other circuits given the PL's extensive

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Received: 23 November 2020 Accepted: 27 November 2020
Published online: 15 January 2021

connectivity [8]. Thus, the use of the anatomical disconnection procedure, in combination with appropriate controls, allowed for the identification the role of PL projections to RMTg in cocaine seeking during reinstatement.

Altogether, Cruz et al. used a classical anatomical disconnection procedure to show that the projections from PL to RMTg are critical for cue-induced cocaine seeking and provided an elegant example of how certain downstream projections can influence behavior during reinstatement. These data demonstrate that use of classical neuroscience techniques with proper experimental controls still have a place in modern neuroscience and can provide meaningful insight into circuit mechanisms of behavior.

FUNDING AND DISCLOSURE

The research was supported by a National Institute of General Medical Sciences Postdoctoral Research Associate Grant 1FI2GM128603 (DJR) and Intramural Research Program of NIDA. The authors declare that they do not have any conflicts of interest (financial or otherwise) related to the text of the paper.

ACKNOWLEDGEMENTS

We thank Yavin Shaham for comments on an earlier version of this commentary.

AUTHOR CONTRIBUTIONS

JJC and DJR drafted and edited the commentary and approved of the final version.

ADDITIONAL INFORMATION

REFERENCES

1. Bossert JM, Marchant NJ, Calu DJ, Shaham Y. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. Psychopharmacol (Berl). 2013;229:453–76.
2. Kalivas PW, McFarland K. Brain circuitry and the reinstatement of cocaine-seeking behavior. Psychopharmacology. 2003;168:44–56.
3. Mihindou C, Guillem K, Navailles S, Vouilac C, Ahmed SH. Discriminative inhibitory control of cocaine seeking involves the prelimbic prefrontal cortex. Biol Psychiatry. 2013;73:271–9.
4. Martin-Garcia E, Courtin J, Renault P, Fiancette JF, Wurtz H, Simonnet A, et al. Frequency of cocaine self-administration influences drug seeking in the rat: optogenetic evidence for a role of the prelimbic cortex. Neuropsychopharmacology. 2014;39:2317–30.
5. Cruz AM, Spencer HF, Kim TH, Jhou TC, Smith RJ. Prelimbic cortical projections to rostromedial tegmental nucleus play a suppressive role in cue-induced reinstatement of cocaine seeking. 2020. https://doi.org/10.1038/s41386-020-00909-z. [Online ahead of print].
6. Huff ML, LaLumiere RT. The rostromedial tegmental nucleus modulates behavioral inhibition following cocaine self-administration in rats. Neuropsychopharmacology. 2015;40:861–73.
7. Setlow B, Holland PC, Gallagher M. Disconnection of the basolateral amygdala complex and nucleus accumbens impairs appetitive pavlovian second-order conditioned responses. Behav Neurosci. 2002;116:267–75.
8. Vertes RP. Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse. 2004;51:32–58.