Neuropsychopharmacology (2018) 43, 675–676

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Commentary

Intrinsic Excitability of Cocaine-Associated Memories

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Neuropsychopharmacology (2018) **43,** 675–676; doi:10.1038/npp.2017.127; published online 26 July 2017

The neuroadaptation theory postulates that drugs of abuse harness cellular mechanisms that underlie general learning and memory processes to form addiction-related memories (Hyman *et al*, 2006). Recently, it has been shown that after withdrawal from repeated cocaine exposure, a small population of medium spiny neurons (MSNs) in the nucleus accumbens (NAc) are strongly activated by re-exposure to cocaine-associated stimuli, exhibiting distinct synaptic properties compared to the vast majority of NAc MSNs (Koya *et al*, 2012). These unique adaptations may serve to allocate specific MSNs into functional ensembles encoding cocaine-associated memories. In addition to synaptic adaptations, exposure to cocaine also alters the intrinsic membrane excitability, a parameter determining whether MSNs fire action potentials and how many to fire upon activation of excitatory synaptic inputs (Huang *et al*, 2011). Experience-dependent regulation of intrinsic membrane excitability is thought to be critical in allocating neurons into memory encoding ensembles (Rogerson *et al*, 2014).

In this issue of *Neuropsychopharmacology*, Ziminski *et al* (this issue) assessed the intrinsic membrane excitability of a population of MSNs that were strongly activated by cocaine-associated contextual cues throughout the striatum. To target MSNs that were involved in encoding cocaine-context associations, Ziminski *et al* (this issue) used a Fos-GFP mouse line, in which c-fos expression resulting from strong cellular activation labels the cells with GFP (Koya *et al*, 2012). After repeated cocaine exposure, reactivation of cocaine-context memories by re-exposing mice to a context associated with cocaine administration increased the number of Fos-positive cells in the NAc shell compared to mice exposed to a novel context (control). Thus, the cocaine-context associations require more neurons to be strongly activated. It should be noted that the percentage of Fos-positive neurons after memory reactivation is much less than the functionally active neurons defined through *in vivo* electrophysiology ($<5\%$ *vs* $>20\%$) (Ghitza *et al*, 2003). As such, the Fos-positive neurons likely do not represent the entire cocaine-memory engram, but possibly distinct nodes of the engram requiring gene transcription. Ziminski *et al* (this issue) also observed an increase in Fos-positive neurons in the dorsal striatum (DS) after cocaine-memory reactivation. In contrast to the NAc shell and DS, there was no change in the number of Fos-positive neurons in the NAc core after cocaine-memory reactivation.

Ziminski *et al* (this issue) then took a leap to compare the intrinsic membrane excitability between Fos-positive *vs* Fos-negative MSNs following cocaine-memory reactivation. While most previous studies either randomly sampled striatal MSNs or distinguished neurons using genetic markers, separating Fos-positive *vs* Fos-negative MSNs allows Ziminski *et al* (this issue) to trace down the cellular differences between the functionally 'active' *vs* 'inert' MSNs after cocaine-memory reactivation. Their results revealed that Fos-positive MSNs in the NAc core, but not in the NAc shell or DS, exhibited functional alterations. Specifically, Fos-positive MSNs in the NAc core displayed a relatively greater membrane excitability compared to Fos-negative neurons, and this difference was due to a general decrease in the membrane excitability of Fos-negative MSNs, opposed to an increase in Fos-positive MSNs compared to the novel context group. These results suggest that memory reactivation-induced expression of Fos may not serve as a causal mechanism underlying the observed cellular changes. Alternatively, expression of Fos produces different cellular consequences, depending on neuronal types and anatomical locations of the neurons.

While these findings implicate the altered intrinsic membrane excitability in the encoding of cocaine-associated memories, there are several significant questions arising. First, are the altered membrane excitability in Fos-positive neurons due to the initial cocaine exposure and represent the encoding of the cocaine-context memory, or is it transiently induced only during the memory reactivation? After reactivation, memories undergo reconsolidation, during which the memory is destabilized to allow for modification (Bonin and De Koninck, 2015). This process is often associated with transient functional alterations, such as synaptic modifications. Indeed, reactivation of cocaine cue-associated memories results in a number of transient structural and functional synaptic adaptations in the NAc core (Mulholland *et al*, 2016). While adaptations in the

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Received 31 May 2017; accepted 5 June 2017; accepted article preview online 20 June 2017

membrane excitability have not been assessed during reconsolidation to our knowledge, it remains possible that transient increases (eg, in Fos-positive neurons) or decreases (eg, in Fos-negative neurons) in excitability are triggered during the memory reactivation.

Second, what is the neural identity of the cocaine-context encoding neurons? Two prominent populations of MSNs in the NAc and DS are dopamine receptor D1 (D1R)- and D2 (D2R)-expressing MSNs. While recorded neurons were verified as MSNs based on their electrophysiological properties, Ziminski *et al* (this issue) did not differentiate between D1R- and D2R-expressing MSNs. This is an important consideration as they often mediate different aspects of behavior. Furthermore, D2 MSNs have greater basal excitability (Grueter *et al*, 2010). Thus, the different membrane properties between Fos-positive and Fos-negative MSNs may stem from the relative percentage of D1 *vs* D2 MSNs composing each experimental group.

Third, what are the behavioral consequences of altered excitability of this select population of MSNs? If Fos-positive MSNs in the NAc core are critical for the encoding of the cocaine-associated memory, their potentiated membrane excitability would be expected to strengthen the memory, enhancing cocaine-associated psychomotor sensitization or drug seeking. However, a recent study using a similar transgenic rat line demonstrated the activity of these Fos-positive MSNs in the NAc core is not required for contextual cocaine seeking (Cruz *et al*, 2014).

Collectively, Ziminski *et al* (this issue) reported relative changes in the intrinsic membrane excitability of a small population of neurons strongly activated by cocaine-associated memories within distinct striatal sub-compartments. This is one of the first studies linking the cocaine-induced adaptations in neuronal excitability and the encoding of cocaine-associated memories. Future related studies may expand our mechanistic understanding of how drug-associated memories are encoded by changes in membrane properties in addition to synaptic alterations.

FUNDING AND DISCLOSURE

Research of the authors is supported by NIH NIDA grants R01DA23206 (YD), R01DA34856 (YD), R01DA40620 (YD), and NINDS grant T32NS007433 (WJW), and Mellon Fellowship (WJW). The authors declare no conflict of interest.

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