Journal Club

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The Neural Substrate of Disappointment Revealed?

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Review of Ji and Shepard (http://www.jneurosci.org/cgi/content/full/27/26/6923)

Dopamine (DA) neurons in the substantia nigra (SN) and ventral tegmental area (VTA) transiently increase their firing rates after presentation of an unexpected reward (Schultz et al., 1997). Reward-predicting cues produce a temporal shift in the dopaminergic response such that phasic DA cell firing coincides with the first predictor of reward, rather than the primary reinforcer (Schultz et al., 1997). Furthermore, dopaminergic activity transiently decreases after the failure of a predicted reward to occur (Schultz et al., 1997). These findings engendered the reward prediction-error theory, which suggests that DA cell activity encodes the adherence of ongoing environmental events to previously established predictions (Schultz et al., 1997). Although reward-associated increases in DA cell firing have predominantly been attributed to glutamatergic afferents from brain regions including the pedunculopontine nucleus and prefrontal cortex (Sesack et al., 2003), the neural substrates that transiently inhibit dopaminergic action potentials have yet to be identified. A recent publication by Ji and Shepard (2007) in *The Journal of Neuroscience* reports that stimulation of the lateral habenula (LHb) transiently suppresses DA cell firing, implicating the LHb as a candidate mediator of negative reward-prediction error.

The authors recorded extracellular, single-unit activity in the ventral midbrain of anesthetized rats and characterized the electrophysiological responses in the SN and VTA to single-pulse (0.5 mA, 100 μs) electrical stimulation of the ipsilateral LHb. DA neurons responded to LHb stimulation with either transient (~80 ms) cessation of spontaneous activity or cessation of activity followed by transient (~150 ms) excitation [Ji and Shepard (2007), their Fig. 1 (http://www.jneurosci.org/cgi/content/full/27/26/6923/F1)]. To verify that these findings were mediated by the LHb, and not by inadvertent excitation of the surrounding neural tissue, the authors lesioned the fasciculus retroflexus (the constitutive fibers of the habenulomesencephalic pathway) 1 h before recording. LHb stimulation in lesioned animals failed to evoke DA cell responses. Although this result substantiates that attenuation of DA neuron firing was indeed LHb mediated, recordings in the terminal field of acutely lesioned fibers can be difficult to interpret. Given that LHb projections are predominantly glutamatergic (Brinschwitz et al., 2005), the applied lesion could result in massive excitatory neurotransmitter release in the SN/VTA. Such a nonphysiological surge in extracellular glutamate could induce excitotoxicity. It is therefore possible that dopaminergic responses were absent because of nonspecific cytotoxic effects such as depolarization block, rather than lesion-induced deafferentation.

Despite this concern, baseline dopaminergic firing rates were indistinguishable in lesioned and nonlesioned animals, suggesting that potential cytotoxic effects in the SN/VTA were negligible; thus, the reported findings remain compelling. The brief latency to onset of DA cell inhibition (~5.8 ms) suggests that LHb-driven dopaminergic suppression is monosynaptic and presumably mediated by a fast-acting amino acid transmitter such as GABA. However, the glutamatergic nature of LHb efferents is inconsistent with such a notion. Furthermore, the complete cessation of firing in 97% of recorded DA neurons seems incongruent with the relatively sparse LHb innervation of the SN/VTA. Ji and Shepard (2007) therefore suggest a disynaptic mechanism by which LHb efferents excite GABAergic projection neuron collaterals in the VTA, which in turn attenuate DA cell firing.

To investigate this idea, the authors characterized responses of nondopaminergic cells in the ventral midbrain to LHb stimulation. These cells, presumed to be GABAergic based on their electrophysiological profile, responded heterogeneously to LHb stimulation [Ji and Shepard (2007), their Fig. 3 (http://www.jneurosci.org/cgi/content/full/27/26/6923/F3) and Table 2 (http://www.jneurosci.org/cgi/content/full/27/26/6923/T2)]. Fast responding cells (~3.2 ms latency to response onset) displayed biphasic excitatory/inhibitory responses, whereas both intermediate responding cells (~10–14 ms latency to onset) and slow responding cells

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(~16–23 ms latency to onset) expressed a mixture of monophasic and biphasic responses. Interpreting such complex physiological effects can be problematic. Perhaps most pertinent is which responses (if any) constitute the GABAergic component of the proposed disynaptic LHb–SN/VTA circuit. Intermediate and slow GABAergic responses occurred subsequent to the transient cessation of DA cell firing (~5.8 ms after stimulation). Thus, only the excitatory phase of fast cell responses (~3.2 ms after stimulation) was brief enough to contribute to the LHb-induced suppression in dopaminergic neurons.

The authors then sought to pharmacologically confirm that the proposed inhibitory mechanism is indeed GABA dependent. Local application of the $GABA_A$ antagonist bicuculline, but not the SK Ca^{2+}-activated K^+ channel blocker apamin, occluded LHb-induced suppression of DA cell firing. Although this observation is consistent with the disynaptic circuit model, other questions remain to be answered. Does sufficient temporal correlation exist between the fast excitation of GABAergic neurons and the phasic dopaminergic responses to presume a casual relationship? How might slower GABA-induced responses affect reward-related DA neural activity?

The questions answered by Ji and Shepard (2007), as well as those left unanswered, become all the more pressing in light of a recent paper by Matsumoto and Hikosaka (2007), which reports LHb excitation in rhesus monkeys in response to a cue predicting the absence of reward. The increase in LHb cell firing directly preceded an inhibition in DA cell activity typically associated with reward absence. Thus, a highly conserved, GABA-dependent LHb–SN/VTA interaction could constitute a neural substrate of negative reward-prediction error in both rodents and primates.

References

Brinschwitz K, Lommel R, Penkalla A, Goertzen A, Geisler S, Veh RW (2005) Glutamatergic fibers from the lateral habenula do not terminate on dopaminergic neurons in the ventral tegmental area. Soc Neurosci Abstr 31:891.823.

Ji H, Shepard PD (2007) Lateral habenula stimulation inhibits rat midbrain dopamine neurons through a $GABA_A$ receptor-mediated mechanism. J Neurosci 27:6923–6930.

Matsumoto M, Hikosaka O (2007) Lateral habenula as a source of negative reward signals in dopamine neurons. Nature 447:1111–1115.

Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275:1593–1599.

Sesack SR, Carr DB, Omelchenko N, Pinto A (2003) Anatomical substrates for glutamate-dopamine interactions: evidence for specificity of connections and extrasynaptic actions. Ann NY Acad Sci 1003:36–52.