Signaling Aversive Events in the Midbrain: Worse than Expected

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Although we know a great deal about how the brain processes information about aversive and appetitive stimuli, it is not clear how these two systems interact to guide behavior. In this issue of *Neuron*, Jhou and colleagues identify a region in the midbrain tegmentum that signals aversive events and inhibits midbrain dopamine neurons.

Learning to predict negative outcomes, and responding appropriately, is a basic function of the nervous system. To accomplish this, neurons in the amygdala and other structures respond to aversive events such as shock, as well as conditioned stimuli that predict shock. This leads to defensive responses such as freezing and avoidance, via descending projections to midbrain areas such as the periaqueductal gray (PAG). While this system has been extensively studied, important questions remain. One such question is how do aversive signaling systems interact with reward systems? On an intuitive level, the omission of an expected reward can be as aversive as an expected shock. Accordingly, aversive-signaling neurons should increase their rates to both types of aversive events (presence of shock and absence of reward), as well as decrease their rates to both types of rewarding events (presence of reward or omission of shock). In this way, the negative valence of the event or stimulus would be signaled in both directions and would take into account the animal's expectations.

Such a response profile is the opposite of what is seen in midbrain dopamine neurons, the heart of the reward system. These neurons increase activity to unexpected rewards and reward cues and decrease activity when expected rewards are omitted (Schultz, 2006). In this way, midbrain dopamine neurons are thought to provide a positive reward prediction error ("better than expected") signal that drives associative learning to cues predictive of reward (Sutton and Barto, 1998). In contrast, the aversive signaling system described above would supply a negative reward prediction error signal ("worse than expected"). Such negative reward prediction error neurons were recently discovered in the primate lateral habenula (Matsumoto and Hikosaka, 2007, 2009). It was proposed that habenula neurons inhibit midbrain dopamine neurons, thereby modulating reward signals during aversive learning. It can be argued, however, that habenular neurons show few direct projections to midbrain dopamine neurons. Furthermore, lesions of the habenula do not impair fear conditioning or the expression of unconditioned anxiety responses. This suggests the existence of another region that signals aversive events, projects to midbrain dopamine neurons, and modulates the expression of fear and anxiety.

In this issue of *Neuron*, Jhou and colleagues describe such a region in the midbrain reticular formation, the rostromedial tegmental nucleus (RMTg) (Jhou et al., 2009a). This collaborative study combined the expertise of four laboratories, employing neuroanatomical, neurophysiological, and behavioral techniques to thoroughly investigate the RMTg in rats. The reticular formation is notorious for being a heterogeneous collection of poorly delineated networks and "centers." Nevertheless, by combining retrograde tracing techniques with cFos histochemistry, the authors found a discrete region of the midbrain tegmentum whose cells project to the ventral tegmental area (VTA) and are activated by shock, as well as an auditory cue that predicts shock. The RMTg neurons projecting to the VTA were further shown to be GABAergic (expressing GAD67) and to contact dopaminergic neurons (expressing tyrosine hydroxylase) in the VTA, substantia nigra, and retrorubral areas. RMTg neurons also receive a major afferent from the lateral habenula (Jhou et al., 2009b). Thus, these anatomical findings support the idea that RMTg signals aversive events and inhibits dopamine neurons.

cFos is an indirect method of assessing cell activity and gives little information about response timing or selectivity. To overcome this, Jhou and coworkers took the next step and recorded individual RMTg neurons in rats undergoing associative learning. RMTg neurons fired at high spontaneous rates (20 Hz), typical of inhibitory neurons. Consistent with an aversive signal, RMTg neurons responded to shocks and cues associated with shocks and were inhibited by sucrose reward and cues associated with sucrose. An impressive 55% of RMTg neurons responded to cues, with the majority preferring shock over sucrose. Finally, in a smaller dataset, the authors showed that RMTg neurons were activated by the omission of an expected sucrose reward, similar to primate lateral habenula neurons. The short latency of RMTg responses to cues (~100 ms) suggests that this signal could be used by target structures to modulate synaptic plasticity.

In order to determine the functional significance of this aversive signal, Jhou et al. performed chemical lesions of the RMTg and surrounding areas. Unlike lesions of lateral habenula, RMTg lesions severely attenuated the expression of fear and anxiety responses, particularly those involving behavioral inhibition. Lesioned rats showed reduced freezing to tone-shock pairings and to a predator

odor and increased entries into open arms in an elevated plus maze. Prior lesion studies have dissociated the roles of three structures in these behaviors: the central amygdala (freezing during conditioning), bed nucleus of the stria terminalis medial amygdala (freezing to cat odor), and the lateral septum (avoidance of open arms). All of these structures are upstream from RMTg, suggesting that RMTg may serve a central role in mediating fear responses (see Figure 1). Prior to this study, no single lesion had been shown to eliminate all three fear responses. Thus, in addition to regulating reward signals in midbrain dopamine neurons, the aversive signal of RMTg appears to directly influence the expression of multiple fear behaviors.

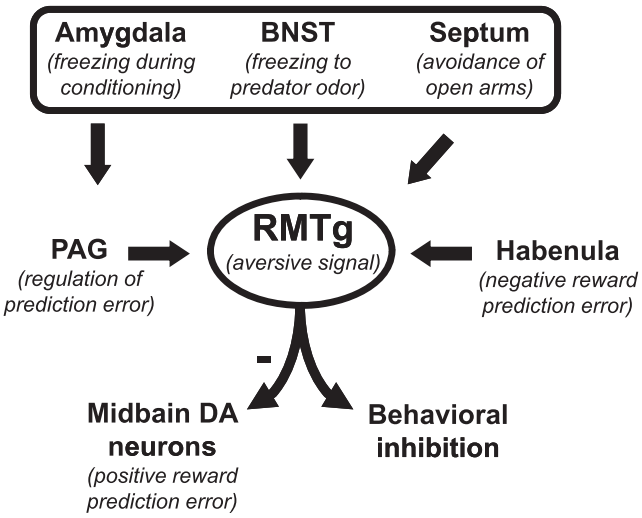

Figure 1. Connections of the Rostromedial Tegmental Nucleus
Multiple fear and anxiety areas converge onto the midbrain rostromedial tegmental nucleus (RMTg), which promotes behavioral inhibition and inhibits ascending reward signals from midbrain dopamine neurons. BNST, bed nucleus of the stria terminalis; PAG, periaqueductal grey matter; DA, dopamine.

While prior studies have described positive and negative valence signals (Paton et al., 2006; Saddoris et al., 2005), this is the first demonstration of an almost exclusively negative valence signal within the fear expression circuit. It has been hypothesized that the PAG regulates aversive prediction errors, in that blocking opiate receptors in PAG impairs extinction of fear and other forms of learning that depend on negative valence signals (McNally and Westbrook, 2006). Both the PAG and the lateral habenula project to the RMTg and could regulate aversive prediction errors via this projection. An open question, however, is the extent to which aversive signaling in RMTg is necessary for the actual learning of fear conditioning and active avoidance. Additional studies will be necessary to determine if temporary inactivation of RMTg prior to training prevents subsequent expression of fear memory. A role of RMTg error signaling in fear learning would suggest that reducing reward is necessary for learning to predict negative events.

REFERENCES

Jhou, T.C., Fields, H.L., Baxter, M.G., Saper, C.B., and Holland, P.C. (2009a). Neuron *61*, this issue, 786–800.

Jhou, T.C., Geisler, S., Marinelli, M., Degarmo, B.A., and Zahm, D.S. (2009b). J. Comp. Neurol. *513*, 566–596.

Matsumoto, M., and Hikosaka, O. (2007). Nature *447*, 1111–1115.

Matsumoto, M., and Hikosaka, O. (2009). Nat. Neurosci. *12*, 77–84.

McNally, G.P., and Westbrook, R.F. (2006). Learn. Mem. *13*, 245–253.

Paton, J.J., Belova, M.A., Morrison, S.E., and Salzman, C.D. (2006). Nature *439*, 865–870.

Saddoris, M.P., Gallagher, M., and Schoenbaum, G. (2005). Neuron *46*, 321–331.

Schultz, W. (2006). Annu. Rev. Psychol. *57*, 87–115.

Sutton, R.S., and Barto, A.G. (1998). Reinforcement Learning, an Introduction (Cambridge, MA: MIT Press).