This Week in The Journal

Links between Endocrine and Autonomic Systems in Hypothalamus

Khalid Elsaafien, Matthew K. Kirchner, Mazher Mohammed, Sophia A. Eikenberry, Chloe West, et al.

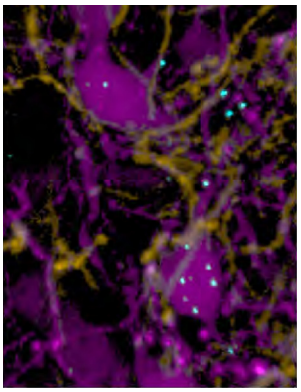
(see pages 4641–4657)

The paraventricular nucleus (PVN) of the hypothalamus regulates neuroendocrine and autonomic responses to stress. One group of PVN neurons elicits neuroendocrine responses by releasing corticotropin releasing hormone (CRH), which stimulates the release of adrenocorticotrophic hormone from the anterior pituitary; this leads to release of corticosteroids from the adrenal glands. Other PVN neurons govern autonomic responses via projections to brainstem nuclei, such as the sympathetic rostral ventrolateral medulla (RVLM), which regulates cardiovascular function. Elsaafien, Kirchner, et al. have discovered how these two signaling pathways might be coordinated.

The authors expressed channelrhodopsin in PVN neurons that express angiotensin type 1a receptors (Agtr1a), which were previously implicated in neuroendocrine and autonomic stress responses. Optical stimulation of these neurons caused elevation in blood pressure without affecting heart rate. The effect was prevented by systemic blockade of nicotinic acetylcholine receptors, indicating it was mediated by vasoconstriction induced by the sympathetic nervous system.

Agtr1a-expressing neurons were located predominantly in the medial PVN, where CRH-expressing neurons reside. Indeed, most CRH-expressing neurons expressed Agtr1a. Surprisingly, however, Agtr1a-expressing PVN neurons did not project to the RVLM. Instead, they projected caudally within PVN, terminating near the somata of RVLM-projecting neurons. Notably, the latter neurons expressed CRH receptors. Moreover, optical stimulation of Agtr1a-expressing neurons evoked spiking in RVLM-projecting neurons, and this effect was blocked by blocking CRH receptors. Bath application of angiotensin also activated RVLM-projecting neurons, and this effect was likewise blocked by a CRH receptor antagonist. Finally, blocking CRH receptors reduced baseline blood pressure and prevented increases in blood pressure evoked by optical stimulation of Agtr1a-expressing neurons.

These results suggest that CRH-releasing neurons in the PVN tonically excite nearby RVLM-projecting neurons to maintain blood pressure. Activation of these neurons by local release of angiotensin not only potentiates this response, but may also activate the hypothalamo-pituitary-adrenal axis. Thus, these neurons may coordinate neuroendocrine and autonomic responses to stress. Given that these pathways are implicated in cardiovascular diseases brought on by chronic stress, CRH neurons may be a good target for lowering the risk of these diseases, particularly those stemming from high blood pressure.



PVN neurons that express Agtr1a (yellow) release CRH, which activates CRH receptors (cyan) on PVN neurons that project to the RVLM (magenta). See Elsaafien, Kirchner, et al. for details.

Changes in Insular Responses to Reward Cues after Cocaine

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(see pages 4667–4677)

Repeated drug use induces plasticity in brain circuits involved in reward processing, associative learning, and motivation, as well as in cortical regions that exert executive control over these circuits. Notably, such circuit modification continues even after the cessation of drug use, and this may contribute to drug craving and relapse. Functional imaging in people addicted to drugs has suggested that elevated activation of the insular cortex contributes to relapse, but little is known about how activity in this area is affected by drug use and withdrawal. Therefore Pribut et al. recorded from insular neurons as rats with previous cocaine experience performed a cued choice task.

Before cocaine exposure, rats learned to discriminate three odors that instructed them to go left, right, or either direction to receive a sucrose reward. In some trial blocks, one port consistently delivered an immediate reward while the other delivered a delayed reward. In other blocks, one port provided a large reward and the other provided a small reward. After rats learned these associations, when instructed to go to either reward port, they generally chose the one that delivered the immediate or the large reward in the current block. This pattern persisted in rats tested after 12 d of cocaine self-administration followed by 1 month of abstinence. Consistent with previous results, however, cocaine-experienced rats showed a greater-than-normal preference for larger/earlier rewards, and they made their choices more quickly than controls.

These behavioral changes were associated with altered activity patterns in the insula. Significantly fewer insula neurons responded to odor cues in cocaine-exposed rats than in controls, whereas more neurons in cocaine-experienced rats showed elevated firing during reward anticipation and delivery. Furthermore, whereas neurons in control rats usually remained active throughout long delays, firing tapered off in cocaine-experienced rats. Finally, insula activity in control rats was influenced by the type of block, that is, whether reward size or delay differed between ports. This type of encoding was absent in cocaine-exposed rats.

These results suggest that cocaine use followed by abstinence alters neural encoding in the insula, leading to less overall encoding of reward-associated cues and stronger encoding of reward itself. Future work should determine how these changes contribute to changes in behavior, particularly drug-seeking behavior.

This Week in The Journal was written by Teresa Esch, Ph.D.
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