Jul-Aug-Sep 2008
Volume 9, Issue 3

Targeting Trends

Reporting the latest news in Molecular Surgery

Noradrenergic Innervation of the Dorsal Medial Prefrontal Cortex Modulates Hypothalamo-Pituitary-Adrenal Responses to Acute Emotional Stress

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The medial prefrontal cortex (mPFC) has been proposed to play a role in the inhibition of hypothalamo-pituitary-adrenal (HPA) responses to emotional stress via influences on neuroendocrine effector mechanisms housed in the paraventricular hypothalamic nucleus (PVH).[1,2] The locus coeruleus (LC) is the principal noradrenergic cell group in the brain, and plays established roles in promoting behavioral adaptations to a variety of alerting stimuli, including stressful ones.[3,4] While the PVH receives a substantial catecholaminergic innervation, the bulk of this arises not from the LC, but from medullary cell groups,[5] which are implicated in mediating HPA responses to physiologic, but not emotional, stressors.[6] This raises the possibility that LC's influence on stress-induced HPA activation might be mediated indirectly, through its projections to limbic and forebrain regions implicated in HPA control. The mPFC is involved in the processing of convergent cognitive and emotionally relevant information, and the LC noradrenergic projections to this region have been proposed to play a critical role in the modulation of working memory and attention.[7] These operations are likely to be involved in the mPFC's capacity to evaluate the contextual relevance and emotional valence of potentially threatening stimuli in order to effect adaptive responses. Nonetheless, the involvement of the LC-to-mPFC pathway in HPA regulation has not been tested, and is problematic, since dorsal mPFC (mPFCd) lesions have been shown to enhance,[1,2] while LC lesions attenuate,[8] HPA activation in response to acute emotional stressors.

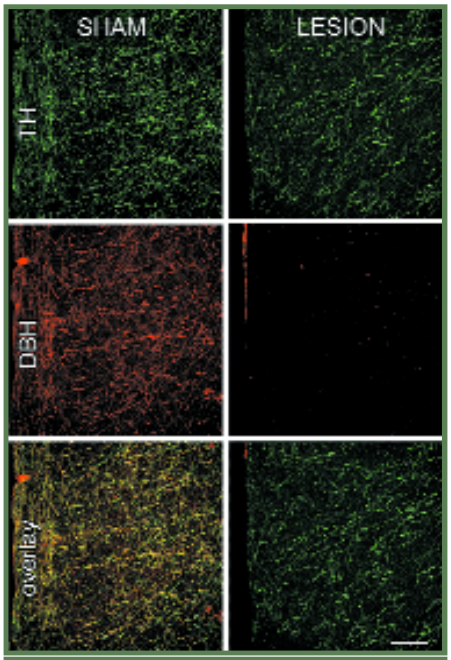

Figure 1. Specificity of anti-DBH-SAP-mediated denervation of mPFCd.

We assessed the effects of selectively ablating noradrenergic inputs into the mPFC, employing the axonally-transported catecholamine immunotoxin (IT), saporin-conjugated anti-dopamine-beta-hydroxylase (anti-DBH-SAP, Cat. #IT-03), on acute restraint stress-induced activation of HPA output.[9] Rats received dorsal mPFC injections of IT or sham injections of IgG-saporin (mouse IgG-SAP, Cat. #IT-18) or saline. Fourteen days later, rats were subjected to 30 min of restraint stress and perfused 2 h later.

Anti-DBH-SAP injections virtually eliminated noradrenergic fibers and varicosities from the mPFCd, whereas control injections of the untargeted toxin (IgG-saporin) or CSF left these inputs intact (Fig. 1, middle). The specificity of the noradrenergic denervation of the mPFCd was assessed by examining the extent to which damage from the IT injection

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Denise Higgins, Editor

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