Noradrenergic Innervation of the mPFCd Modulates HPA Responses to Acute Emotional Stress

(continued from page 1)

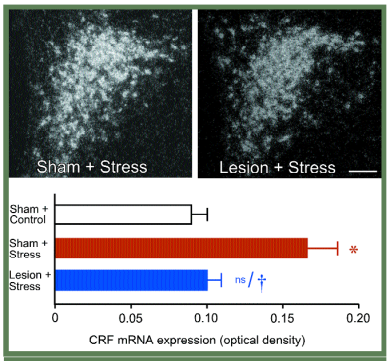

Figure 2. Effects of noradrenergic denervation of mPFCd on restraint-induced upregulation of CRF mRNA in PVH.

involved dopaminergic fibers and terminals in dual immunofluorescence preparations for tyrosine hydroxylase (TH) and DBH (Fig. 1). TH converts tyrosine to dihydroxyphenylalanine, a precursor of both dopamine (DA) and norepinephrine (NE). Immunolabeling of this enzyme represents both DA and NE fibers and terminals, whereas staining for DBH in cortex is specific to NE. Thus, the overlay of TH and DBH stained fibers and varicosities represents the subpopulation of inputs into mPFCd that are noradrenergic, whereas fibers singly-labeled for TH are dopaminergic (Fig. 1, top). Following anti-DBH-SAP injections into PL, the density of dopaminergic fibers and varicosities was comparable to controls in density and distribution, while there was a near complete elimination of DBH staining in mPFCd, as well as of elements doubly-labeled for both enzymes (Fig. 1, bottom). Ancillary analyses revealed that IT injection in mPFCd resulted in a 23% decrease in the number of LC neurons and a corresponding decrease in stress-induced LC activational responses, compared to sham-lesioned controls.[9] Anti-DBH-SAP is an effective tool for achieving focal noradrenergic denervation by ablating the neurons from LC that project to targeted terminal fields in mPFCd.

We initially surveyed the effects of lesions in mPFCd on stress-induced expression of Fos protein, a generic marker of neuronal activation, in the PVH. Acute stress resulted in a marked increase in Fos expression in the sham-lesioned animals, focused in the CRF-rich hypophysiotropic zone of PVH. This effect was reduced by 28% in anti-DBH-SAP lesioned animals. Ancillary analyses from sham- and IT-lesioned groups failed to reveal any effect of lesion status on the number of Fos immunoreactive neurons in the PVH of unstressed rats. We examined relative levels of CRF mRNA in PVH using densitometry (Fig. 2, top). Consistent with the Fos expression data, restraint stress resulted in a two-fold increase in CRF mRNA expression in the hypophysiotropic zone of PVH in sham-lesioned animals compared to unstressed controls (Fig. 2, bottom). In contrast, IT lesions diminished this effect to levels that did not differ significantly from those of unstressed controls.

HPA secretory responses before and after the 30-min restraint stress were examined in separate groups of sham- and IT-lesioned animals (Fig. 3). Blood samples were obtained from indwelling jugular catheters that were implanted 2 days prior to stress exposure. Stress exposure significantly increased plasma levels of ACTH in both sham- and IT-lesioned animals. While these data suggest a difference between peak plasma levels of ACTH in IT- as compared to sham-lesioned animals, they did not differ significantly. Nonetheless, there was a significant reduction in total integrated plasma ACTH levels in lesioned compared to sham groups, assessed by calculating areas under the curve. Stress exposure also significantly increased plasma levels of corticosterone in sham- and IT-lesioned animals. While there were no significant differences at any individual time point between sham and lesioned groups, there was an overall main effect for treatment, and a decrease in integrated corticosterone levels in lesioned as compared to unlesioned groups. Sham-lesioned animals also showed a prolonged increase in stress-induced plasma corticosterone levels, whereas lesioned animals show a more rapid recovery.

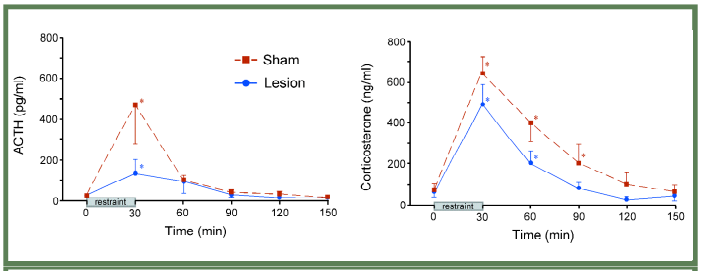

Figure 3. Noradrenergic denervation of mPFCd attenuates pituitary-adrenal secretory responses to acute restraint.

The present findings localize previously documented HPA-facilitatory influences of LC, at least in part, to its projections to mPFCd and help to clarify the extended circuitry underlying mPFC modulation of HPA responses to acute emotional stress. In addition to participating in the regulation of stress responses, the mPFC is also a target of them. Repeated exposure to emotional stress gives rise to dendritic atrophy and synapse loss in this region,[10,11] findings that have clinical parallels in reports of mPFC shrinkage and functional impairment in posttraumatic stress disorder (PTSD).[12,13] NE has been linked to the mediation of maladaptive, as well as adaptive, consequences of stress exposure, being implicated in various psychiatric conditions, including PTSD.[14] Drugs that modulate noradrenergic transmission have demonstrated efficacy in treating such mood disorders via actions that may be exerted, at least in part, on the mPFC.[15] Further progress in unraveling the broader circuitry governing HPA responses to emotional stress, and the places of the LC and mPFC within it, should foster more informed management of stress-related psychiatric conditions.

Article References are on page 5.

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