Title

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Neuroplasticity of the hypothalamic–pituitary–adrenal (HPA) axis early in life requires recurrent recruitment of stress-regulating brain regions

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Handling of rat pups repeatedly evokes neuroplasticity that may be termed: ''Experience-induced neuroplasticity'' (Fenoglio et al., 2006) and involves enduring changes in the expression of genes regulating hormonal and behavioral responses to stress (Plotsky and Meaney, 1993; Levine, 2000; Avishai-Eliner et al., 2001; Fenoglio et al., 2004). Handling evokes augmentation of maternal care of the pups (Fenoglio et al., 2006) which, in turn, induces a long-lasting reduction of hypothalamic corticotropin releasing hormone (CRH) expression and upregulates hippocampal glucocorticoid receptor levels (Plotsky and Meaney, 1993; Avishai-Eliner et al., 2001). These changes result in a persistent reduction of the hormonal stress responses. We have previously described that handling-evoked downregulation of CRH expression occurs already by postnatal day 9, suggesting that it was an early step in this experience-induced neuroplasticity (Avishai-Eliner et al., 2001; Fenoglio et al., 2004). Here, we studied the pathways within the central nervous system that are involved in this process (Eghbal-Ahmadi et al., 1999), as well as the cellular mechanisms that may contribute to it. CRH mRNA expression in hypothalamic paraventricular nucleus (PVN) declined after daily handling but not after handling once only, indicating that recurrent handling was necessary for this effect. The return of handled pups to their cage led to a burst of nurturing behavior in the mothers that, in turn, induced transient, coordinate Fos expression in several, specific regions of the pups' brains. These included the central nucleus of the amygdala (ACe) and the bed nucleus of the stria terminalis (BnST). These two areas are both afferent to PVN and influence CRH expression there (Herman et al., 1994; Prewitt and Herman, 1994). Whereas handling once was sufficient to evoke Fos expression within ACe and BnST, induction of this immediate early gene in the thalamic paraventricular nucleus, a region involved in storing and processing stress-related experience (Bhatnagar and Dallman, 1998; Bhatnagar et al., 2002), happened only after recurrent handling. After recurrent handling, reduced transcription factor phosphorylation and attenuated activation of CRH gene transcription were found in the PVN. These studies provide the network and mechanisms for the profound neuroplasticity of stress-related genes that result from early-life experience, and specifically maternal care (Fenoglio et al., 2006). (Supported by NS39307/MH73136, NS28912, and NS07444.)

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