STEP (Striatal-enriched protein tyrosine phosphatase) is a critical component of the CRF system signaling in the extended amygdala of the rat brain.

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STEP (Striatal-enriched protein tyrosine phosphatase), a recently discovered neuron-specific tyrosine phosphatase, is widely distributed in the rodent brain. STEP has been reported to be critically involved in the glutamate (NMDA receptor)-mediated regulation of the ERK (extracellular signal-regulated kinase) signaling cascade in rat neurons. Activation of the ERK cascade is thought to be an important signal transduction factor that regulates synaptic function, long-term potentiation (LTP), and consequently learning and memory. STEP has been shown to downregulate the activity of ERK by dephosphorylation of ERK tyrosine residue. We have found robust somatodendritic expression of STEP in the extended amygdala: primarily in the anterolateral BNST (aBNST) and central amygdala (CeA). Because STEP distribution was highest in those regions of the extended amygdala that also show high corticotrophin releasing factor (CRF) expression, we performed dual immunofluorescence experiments to determine the relative co-localization of CRF and STEP. Dual labeling experiments revealed almost complete co-localization of CRF and STEP in aBNST and CeA. In contrast to CRF neurons of the extended amygdala, the population of CRF-positive neurons in paraventricular nucleus of the hypothalamus (PVN) did not express STEP. These data suggest that CRF neurons in the extended amygdala can utilize distinct second messenger pathways from CRF neurons of the PVN. CRF-expressing neurons in the extended amygdala are believed to be associated with the chronic affective (emotional) component of the stress response, in contrast to CRF neurons in the PVN, which are associated with acute mobilization of the hypothalamic-pituitary-adrenal (HPA) axis. Here, we used repeated stress paradigm to examine the effects of chronic stress on STEP expression in the aBNST. Rats were subjected to one-hour restraint stress for four consecutive days. Six days after the final stress manipulation (day 10), BNST samples from control and stressed animals were collected for protein assay (Western Blot), mRNA expression (RT-PCR) and immunohistochemistry. We have observed decreased levels of STEP in the BNST of stressed rats at the level of protein expression (STEP total protein content and STEP-positive neurons’ expression) as well as significantly decreased mRNA expression. We conclude that STEP might be directly involved in stress-induced regulation of CRF signaling in the BNST, and deficits in STEP may therefore modulate the long-lasting effects of stress that are associated with states of fear and anxiety as well as etiology of PTSD, panic attacks and depression.