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Research Report

Effects of intracerebroventricular corticotropin releasing factor on sensory-evoked responses in the rat visual thalamus

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ABSTRACT

Corticotropin releasing factor (CRF) coordinates the brain's responses to stress. Recent evidence suggests that CRF-mediated activation of the locus coeruleus-norepinephrine (LC-NE) system contributes to alterations in sensory signal processing during stress. However, it remains unclear whether these actions are dependent upon the degree of CRF release. Using intracerebroventricular (ICV) infusions, we examine the dose-dependent actions of CRF on sensory-evoked discharges of neurons in the dorsal lateral geniculate nucleus of the thalamus (dLGN). The LGN is the primary relay for visual signals from retina to cortex, receiving noradrenergic modulation from the LC. In vivo extracellular recording in anesthetized rats was used to monitor single dLGN neuron responses to light flashes at three different stimulus intensities before and after administration of CRF (0.1, 0.3, 1.0, 3.0 or 10.0 μg). CRF produced three main effects on dLGN stimulus evoked activity: (1) increased magnitude of sensory evoked discharges at moderate doses, (2) decreased response latency, and (3) dose-dependent increases in the number of cells responding to a previously sub-threshold (low intensity) stimulus. These modulatory actions were blocked or attenuated by intra-LC infusion of a CRF antagonist prior to ICV CRF administration. Moreover, intra-LC administration of CRF (10 ng) mimicked the facilitating effects of moderate doses of ICV CRF on dLGN neuron responsiveness to light stimuli. These findings suggest that stressor-induced changes in sensory signal processing cannot be defined in terms of a singular modulatory effect, but rather are multi-dimensional and dictated by variable degrees of activation of the CRF-LC-NE system.

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Abbreviations: LC, locus coeruleus; dLGN, dorsal lateral geniculate nucleus; CRF, corticotropin releasing factor; NE, norepinephrine; ICV, intracerebroventricular

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1. Introduction

An integral component of the stress response is activation of the hypothalamic–pituitary–adrenal (HPA) axis. This system is coordinated by the release of the neuropeptide corticotropin releasing factor (CRF), which initiates pituitary adrenocorticotropin release and subsequent adrenal corticosteroid release (Vale et al., 1981). In addition, extra-hypophyseal CRF functions as a neuromodulator with several targets throughout the brain that coordinate the cognitive and behavioral attributes of stress (Bale and Vale, 2004; Valentino and Van Bockstaele, 2001).

One target of CRF transmission is the noradrenergic brainstem nucleus locus coeruleus (LC) (Valentino and Van Bockstaele, 2001; Van Bockstaele et al., 1996). Exposure to various stressors elicits CRF release and activation of LC neurons, which can be blocked by administration of a CRF antagonist (Curtis et al., 2001; Valentino and Wehby, 1988; Valentino et al., 1991). Stressor-induced activation of the LC-NE system is associated with increased arousal and scanning attention, both of which serve as adaptive responses to stressors, facilitating executive function and sensorimotor responses (Valentino and Van Bockstaele, 2008). Activation of the LC prompts a range of modulatory effects on single neuron and neural circuit responses to afferent synaptic inputs (Berridge and Waterhouse, 2003; Devilbiss and Waterhouse, 2004; Devilbiss et al., 2006). Because of the extensive projection of the LC-NE system (Grzanna and Molliver, 1980; Swanson and Hartman, 1976), stressor exposure and subsequent CRF release can simultaneously influence the function of diverse populations of neurons across the brain.

Acute stress has been shown to impair sensory information processing (Clark et al., 1986; Ermutlu et al., 2005; Grillon and Davis, 1997; Liu et al., 2011; Miyazato et al., 2000; Sutherland and Conti, 2011). Recent findings suggest that CRF-mediated activation of the LC-NE system is a contributing factor. Acute exposure to a physiological stressor alters single neuron responsiveness to sensory stimuli by a LC-CRF-dependent mechanism (Zitnik et al., 2013). Additionally, local application of CRF onto the LC was shown to modulate thalamic and cortical sensory evoked responses (Devilbiss et al., 2012). Although these studies reveal how stress may alter sensory signal processing, the specific relationship between modulation of sensory signals and the degree of CRF activation of LC is unclear.

Although stressor-induced activation of the LC-NE system has been linked to distractibility and labile attention (Aston-Jones and Bloom, 1981; Berridge and Foote, 1991), other evidence suggests that the stress response can enhance cognitive performance according to an inverted-U relationship (Beylin and Shors, 1998; de Kloet et al., 1999; Luine et al., 1996). CRF has been implicated in this effect (Snyder et al., 2012). Similarly, activation of the LC has been shown to augment single neuron or neural circuit responses to sensory stimuli according to the same inverted-U dose–response relationship (Devilbiss and Waterhouse, 2004; Devilbiss et al., 2006). The link between CRF and LC activation provides a means through which stressors can impact behavior and sensory signal processing across a dynamic range of environmental and physiological challenges.

Several stressors generate CRF-mediated increases in LC output, but the degree of activation varies according to the stressor (Curtis et al., 2012; Lechner et al., 1997; Page et al., 1992; Valentino, 1989). One way to mimic stressor-induced activation of the LC-NE system is by direct infusion of CRF into the ventricular system of the brain. Intracerebroventricular (ICV) infusions of CRF cause dose-dependent increases in tonic LC output, thereby elevating NE levels throughout the forebrain (Curtis et al., 1997; Valentino and Foote, 1988; Page and Abercrombie, 1999; Palamarchouk et al., 2000; Zhang et al., 1998). ICV administration of CRF induces changes that mimic many of the behavioral responses observed during stress (Buwalda et al., 1997; Sherman and Kalin, 1988), including disruption of sensory processing (Conti et al., 2002; Risbrough et al., 2004).

The goal of the current study was to examine the effect of varying ICV doses of CRF on sensory-driven responses in the visual thalamus. The responses of dorsal lateral geniculate (dLGN) neurons to light stimuli were recorded before and after ICV CRF in the anesthetized rat. The results show that ICV CRF decreases the latency, increases the magnitude of light evoked responses according to an inverted-U dose–response relationship, and causes a dose-dependent increase in the number of dLGN cells responding to a previously subthreshold light stimulus. A separate group of animals was pretreated with the CRF antagonist DpheCRF, via direct application onto the LC ipsilateral to the monitored dLGN prior to administration of 3.0 μg CRF ICV. This prevented or attenuated many of the modulatory actions normally observed after administration of CRF. These results, together with those obtained with intra-LC application of CRF, indicate that the observed changes in dLGN neuron responsiveness to light stimuli are likely due to CRF-mediated activation of the LC-NE system.

2. Results

Action potential waveforms from individual cells were recorded from the dLGN thalamus in 36 anesthetized animals. ICV drug treatments in these animals were as follows: 0.1 μg ($n=5$), 0.3 μg ($n=7$), 1.0 μg ($n=6$), 3.0 μg ($n=6$), 10.0 μg CRF ($n=6$), and intra-LC CRF antagonist treatment prior to administration of 3.0 μg CRF: DpheCRF+3.0 μg ($n=6$). A sample of 156 cells at various drug doses [0.1 μg ($n=26$), 0.3 μg ($n=28$), 1.0 μg ($n=25$), 3.0 μg ($n=25$), 10.0 μg ($n=26$), DpheCRF+3.0 μg ($n=26$)] was deemed suitable for subsequent analysis, i.e. having well discriminated waveforms recorded for the duration of experimental protocols (described in methods). Another set of experiments was performed using multiple doses of CRF (3, 10, 100 ng in 100 nL aCSF) infused locally into the LC ipsilateral to the dLGN recording site. A detailed analysis was conducted on the cells recorded from animals receiving 10 ng CRF ($n=6$, 25 cells), a dose that has been shown in prior experiments to increase LC output similar to moderate doses of CRF ICV (Curtis et al., 1997). Placement of dLGN recording electrodes (Fig. 1) and location of LC cannulae (Fig. 2) were confirmed post-mortem.