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CORTICOTROPHIN-RELEASING HORMONE DECREASES SYNAPTIC TRANSMISSION IN RAT SENSORIMOTOR CORTEX *IN VIVO*

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Abstract—Corticotrophin-releasing hormone is a key regulator of the mammalian stress response. Although its actions on behavior are well documented, the actions of corticotrophin-releasing hormone in cortical neuronal systems are poorly understood. In the present experiments, adult male Sprague–Dawley rats were anesthetized and field excitatory post-synaptic potential recordings were made from sensorimotor cortex layer II/III and layer V cells. Infusions of corticotrophin-releasing hormone (100 ng/nl) directly into the sensorimotor cortex produced a significant depression of the initial excitatory component of evoked responses that could be prevented by prior administration of a corticotrophin-releasing hormone antagonist. Although requiring the activation of corticotrophin-releasing hormone receptors, the depression was also dependent upon *N*-methyl-D-aspartate receptor activity and could be blocked by the competitive *N*-methyl-D-aspartate antagonist −3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonate. These findings demonstrate that corticotrophin-releasing hormone has a novel depressant-like action in sensorimotor cortex *in vivo* that may play a role in modulating motor activity during periods of stress. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: neocortex, plasticity, hormones, LTP, LTD, stress.

Corticotrophin-releasing hormone (CRH) is a 41 amino acid polypeptide that was first described by Vale et al. (1981) in isolated rat hypothalamus. It is a key regulator of the mammalian stress response, and is the major hypothalamic peptide controlling pituitary adrenocorticotropic hormone (ACTH) secretion. In addition to the hypothalamus, CRH immunoreactive cells and mRNA have been identified in several neocortical structures including the frontal, cingulate, precentral motor, somatosensory, auditory, and visual cortices (Swanson et al., 1983; Chalmers et al., 1995; Brunson et al., 2002).

In these regions, CRH appears to act as a neuromodulator, or possibly even a neurotransmitter, and is involved in mediating increased arousal, learning, and anxiety while simultaneously decreasing food intake and sexual behavior and altering locomotion (Koob and Heinrichs, 1999; Smagin et al., 2001; Roozendaal et al., 2002). Many of these effects may be mimicked with intraventricular administration of CRH (Sherman and Kalin, 1987; Takahashi et al., 1989; Dunn and Berridge, 1990; Koob and Heinrichs, 1999), however the mechanisms mediating these behavioral effects remain unclear, and little is known of the impact of CRH on neural activity in many parts of the brain.

Early reports suggested that CRF has predominantly excitatory actions in locus coeruleus, hippocampus, cortex, and some regions of hypothalamus, where its main action is to reduce after-hyperpolarizations by blocking Ca^{2+}-dependent K^{+}-conductances (Siggins et al., 1985). In fact, this excitatory effect is powerful enough that the administration of high doses of CRH intraventricularly can even produce epileptiform activity in the amygdala and hippocampus (Siggins, 1989). More recently, intrahippocampal infusions of lower doses of CRH have been shown to produce a long-lasting increase in synaptic efficacy in the dentate gyrus (Wang et al., 1998). Even more interesting is the fact that this CRH induced LTP requires protein synthesis (Wang et al., 2000), making it analogous to that induced following the application of conditioning stimuli in this region (Otani and Abraham, 1989).

In addition to producing excitation, CRH can also reduce the occurrence of spontaneous action potentials in certain (unspecified) populations of somatosensory neurons (Cahusac et al., 1998). It remains unclear as to whether this effect is due to the actions of CRH on principal cells directly, or whether CRH acts to tonically increase inhibition in somatosensory cortex. Like the hippocampus, this region of the neocortex is also capable of supporting synaptic plasticity, and both LTD and LTP have been demonstrated in horizontal connections of layers IV and V (Urban et al., 2002) and II/III (Hess, 2002; Rioult-Pedotti et al., 1998, 2000; Hess and Donoghue, 1996). LTD has also been demonstrated in the vertical pathways of both somatosensory and motor cortices (Castro-Alamancos et al., 1995). Both LTP (Chapman et al., 1998; Trepel and Racine, 1998) and LTD (Froc et al., 2000; Froc and Racine, 2004, 2005) have been demonstrated in sensorimotor cortex of awake rats. Current source density analyses show that, in sensorimotor cortex, positive-going layer V responses reflect a passive source in deep layer V and negative-going layer II/III responses reflect an active sink in upper layer V. LTP of this monosynaptic component involves enhancement in layer V synaptic strength (Chapman et al., 1998). In the present series of experiments we examine how direct intracortical microinfusions of CRH

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Abbreviations: CPP, −3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonate; CRH, corticotrophin-releasing hormone; NMDA, *N*-methyl-D-aspartate.

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affect evoked responses in layers II/III and layer V of sensorimotor cortex in the anesthetized rat.

EXPERIMENTAL PROCEDURES

All of the procedures used in these experiments were in accordance with the Canada Council on Animal Care and approved by the University of British Columbia Animal Care Committee. All experiments were conducted in accordance with Canadian and International standards for animal care. All efforts were made to minimize the number and suffering of any animals used in these experiments. Male Sprague–Dawley rats (300–400 g) were obtained from University of British Columbia (UBC) animal care services and were housed individually, fed *ad libitum*, and maintained on a 12-h light/dark cycle. All experimentation was performed during the light cycle.

Surgery

Rats were anesthetized with Somnotol (sodium pentobarbital, 65 mg/kg i.p.) and placed in a stereotaxic unit. Monopolar stimulating and recording electrodes were constructed from Teflon-coated stainless steel wire (120 μm diameter) and implanted into either the sensorimotor cortex (M1 bordering on S1) or the white matter in the same coronal plane, respectively (Fig. 1A). Sensorimotor cortex electrodes were placed 2.0 mm anterior to bregma

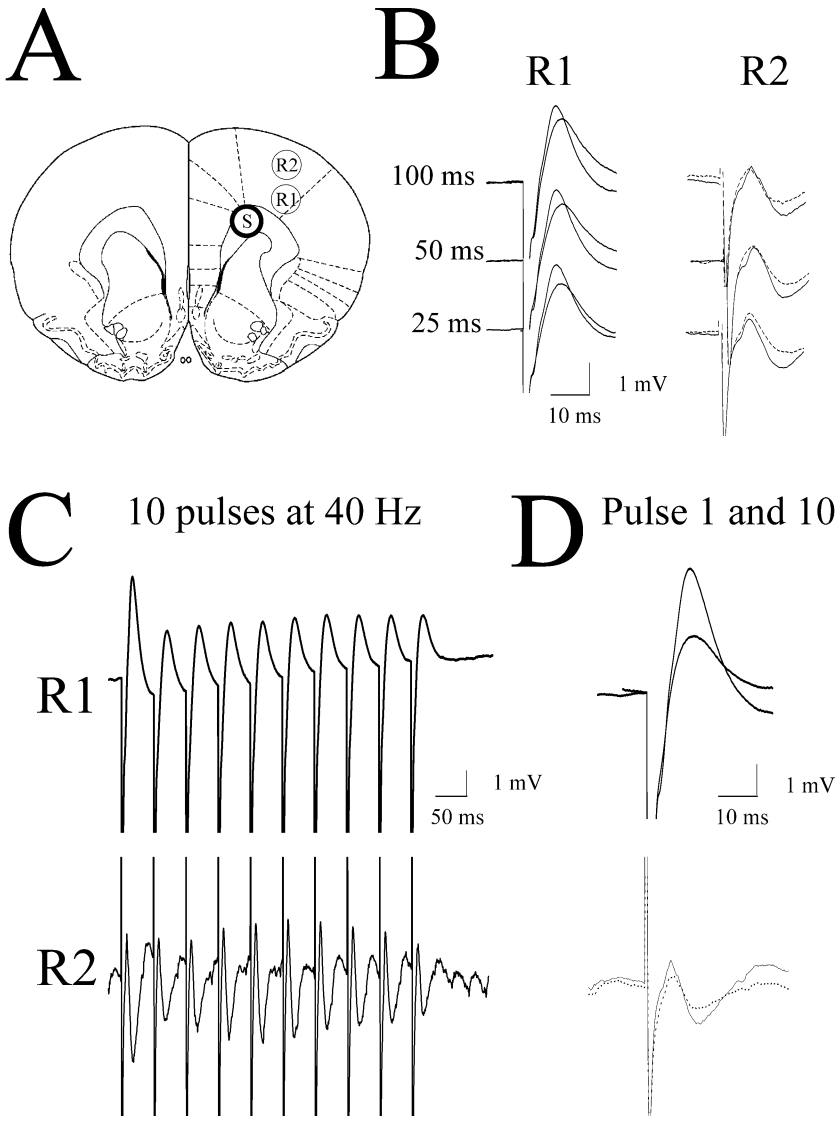

Fig. 1. Sensorimotor cortex electrophysiological responses in the anesthetized rat. Activation of nearby white matter (S) elicits a monosynaptic response from layer V (R1) and layer II/III (R2) in the sensorimotor cortex of the anesthetized rat. (A) Schematic of a rat brain slice taken 2.0 mm anterior to bregma illustrating the electrode and infusion cannula (I.C.) placements. The stimulating electrode was positioned in the nearby white matter 2.0 mm lateral to the midline at a depth of 3.0 mm and the recording electrodes were implanted in the motor cortex 4.0 mm lateral to the midline at a mean depth of 0.5 mm (layer II/III; R2) and 2.0 mm (layer V; R1) from the pial surface. (B) Representative traces showing that responses evoked in layer V (R1) and layer II/III (R2) of the motor cortex were attenuated but followed at frequencies up to 40 Hz indicating that they were monosynaptic. (C) Representative sweeps showing that paired-pulse stimulation using 25, 50 and 100 ms inter-pulse intervals elicits a paired-pulse depression of evoked responses in both layer V (R1) and layer II/III (R2) suggesting that these synapses exhibit a high probability of neurotransmitter release. (D) Superimposition of first and tenth responses taken from the 40 Hz train.