REGULATION OF PITUITARY CYCLIC AMP, PLASMA PROLACTIN AND POMC-DERIVED PEPTIDE RESPONSES TO STRESSFUL CONDITIONS

J.L. Meyerhoff, G.J. Kant, B.N. Bunnell, and E.H. Mougay

Neurochemistry & Neuroendocrinology Branch
Department of Medical Neurosciences
Division of Neuropsychiatry
Walter Reed Army Institute of Research
Washington, DC 20307-5100

INTRODUCTION

We have been investigating the role of pituitary cyclic AMP in regulating the stress-induced release of pituitary hormones in vivo. This paper will review a series of experiments describing the effects of both physical and psychological stressors on these responses and exploring possible mechanisms of regulation. Exposure to stressful conditions elevates plasma levels of corticosterone (CS) (1-3), and increases plasma levels of several hormones secreted from the anterior pituitary, including adrenocorticotropic hormone (ACTH), beta-endorphin (β-EP), beta-lipotropin (β-LPH), and prolactin (PRL) (3-8). ACTH, β-LPH and β-EP are derived from a common precursor, a 31,000 dalton glycoprotein currently referred to as proopiomelanocortin (POMC) (9,10). β-LPH is a 91 amino acid peptide (11) which contains β-EP as the 61-91 segment (12). In the rat, the three POMC-derived peptides are co-localized in the same secretory granules in anterior pituitary corticotrophs (13,14), while the intermediate lobe contains and releases predominantly β-EP (15-18). Plasma levels of β-EP are high relative to β-LPH (8,19), but exposure to stressors markedly increases plasma levels of all three POMC-derived peptides (5,8,19).

The release of the POMC-derived peptides from the pituitary gland is believed to be chiefly regulated by corticotropin-releasing factor (CRF), a 41 amino-acid peptide (20) secreted from the hypothalamus into the portal circulation. In cultured anterior pituitary cells, CRF stimulates cyclic AMP accumulation, cyclic AMP-dependent protein kinase activity, and release of ACTH into the culture medium (21-25). The incubation of pituitaries with cyclic AMP releases ACTH into the medium (26), and cyclic AMP is believed to function as a second messenger (27) involved in the synthesis of anterior pituitary POMC (28) as well as the release of the peptide hormones derived from POMC (26,29). In the sections which follow, we will present data which

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suggest that cyclic AMP is a mediator in vivo of CRF-stimulated neuroendocrine responses to stressful conditions.

PHYSICAL STRESSORS INCREASE PITUITARY CYCLIC AMP AND RELEASE PITUITARY HORMONES IN VIVO

We have reported that exposure to physical stressors, such as forced running, immobilization, or footshock produces elevations of pituitary cyclic AMP in vivo in rats (8,30–35). These increases were localized to the anterior lobe of the pituitary (36), persisted at least 15 minutes following termination of footshock (37), and were associated with increased plasma levels of ACTH, β-EP and β-LPH.

To determine whether the cyclic AMP response was proportional to the intensity of the stressor, we subjected rats to increasing intensities of footshock for 15 minute periods and measured pituitary cyclic AMP and plasma hormonal responses (31). The data are displayed in Figures 1 and 2. On the basis of these data, 1.6 mA was chosen as an optimal shock intensity to be used in subsequent experiments using footshock.

PSYCHOLOGICAL STRESSORS INCREASE PITUITARY CYCLIC AMP AND RELEASE PITUITARY HORMONES IN VIVO

If the pituitary cyclic AMP response to physical stressors represents a critical step in mediating hypothalamic-pituitary-adrenal responses in general, then pituitary cyclic AMP levels should also increase in animals subjected to purely psychological stressors. To examine this question, we

![Pituitary CAMP Response to Graded Foot Shock](image)

**Figure 1.** Pituitary cyclic AMP response to increasing intensities of footshock for 15 minutes (31). Values represent mean ± SEM of 6 rats per group. Controls (C) were sacrificed upon removal from home cage.

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b In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.