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Short communication

Behavioral effects of chronically elevated corticosterone in subregions of the medial prefrontal cortex

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HIGHLIGHTS

- Corticosterone implants in prelimbic or infralimbic cortices reduce open arm exploration.
- Elevated corticosterone in the anterior cingulate cortex didn't affect plus-maze behavior.
- All behavioral effects of corticosterone were specific to open arm exploration.
- Corticosterone's effects in the medial prefrontal cortex are anatomically specific.

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ABSTRACT

The medial prefrontal cortex is a key mediator of behavioral aspects of the defense response. Since chronic exposure to elevated glucocorticoids alters the dendritic structure of neurons in the medial prefrontal cortex, such exposure may alter behavioral responses to danger as well. We examined the effects of chronically elevated corticosterone in discrete regions of the medial prefrontal cortex on exploration of the elevated plus-maze. Chronically elevated corticosterone in the prelimbic or infralimbic cortices reduced open arm exploration. This effect was specific to the ventral regions of the medial prefrontal cortex as corticosterone had no effect on plus-maze exploration when administered into the anterior cingulate cortex. Taken together, these findings demonstrate clear regional differences for the effects of corticosterone in the medial prefrontal cortex.

1. Introduction

The defense response is a highly conserved process that promotes survival of the organism by activating a complex neural circuit. At the most basic level, this response consists of threat detection along with adaptive physiological and behavioral responses to danger [1,2]. The autonomic and endocrine responses to a diverse array of threats have been well characterized and the neural circuits mediating these effects are beginning to emerge. However, less is known about how glucocorticoids released during the defense response affect the neural circuit itself. Glucocorticoids secreted in response to danger cross the blood brain barrier and may alter activity of the defense circuitry to subsequent threats [3,4].

The medial prefrontal cortex is a key mediator of behavioral aspects of the defense response and expresses both type I and type II glucocorticoid receptors [5,6]. Glucocorticoids administered directly into the anterior cingulate cortex (ACC) identified this structure as a negative feedback site for hypothalamic pituitary adrenal axis regulation [5]. Knockdown studies of glucocorticoid receptors in the prelimbic (PLC) and infralimbic corteces (ILC) reveal clear regional differences in glucocorticoid receptor mediated feedback and behavior in the forced swim test [7]. Chronically elevated glucocorticoids reduce the volume of the medial prefrontal cortex and alter dendritic morphology in this region of the brain [8,9]. Such structural changes likely modify function of the medial prefrontal cortex and possibly include altered behavioral responses to danger.

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Glucocorticoid receptors in the medial prefrontal cortex are involved in regulating endocrine and behavioral components of the defense response. Further, glucocorticoids secreted during chronic exposure to threats may increase the sensitivity of the neural circuit underlying behavioral responses to danger. Our previous work suggests the amygdala and dorsolateral bed nuclei of stria terminalis represent components of the defense circuit affected in this way [10,11]. However, the behavioral effects of chronically elevated glucocorticoids within the medial prefrontal cortex remain largely unexplored.

As part of our ongoing efforts to understand the potential role of glucocorticoids on the defense circuit, we implanted corticosterone micropellets into distinct subregions of the medial prefrontal cortex. In a series of three experiments we systematically examined the effects of glucocorticoids in the ACC, PLC, and ILC on exploration of the elevated plus-maze.

2. Methods

2.1. Animals

Sixty-seven Male Wistar rats (Charles River Laboratories, Wilmington, MA) weighing 325–350 g were habituated to the animal facility for at least 1 week prior to surgery then acclimated to the testing room for one additional week. All rats were handled and weighed daily. Rats were then randomly assigned to receive stereotaxic implantation of cholesterol (control) or corticosterone micropellets into one of three regions of the medial prefrontal cortex: anterior cingulate (ACC), prelimbic (PLC) or the infralimbic (ILC) region. All procedures were approved by the Towson University IACUC.

2.2. Micropellets

Micropellets of crystalline corticosterone and cholesterol were constructed according to the procedure developed and characterized in our laboratory [10–13]. Briefly, the pellet is constructed by tamping cholesterol or corticosterone into a 25-guage stainless steel cannula then the cannula is mounted in a standard electrode holder. Once the cannula is lowered into the target tissue the micropellet is extruded by inserting a stylet into the cannula. The cannula is removed from the brain leaving the pellet behind. The pellet is clearly visible in tissue sections at the end of the one week treatment period and micropellet placement was verified histologically for each animal at the end of the study (Fig. 1). This procedure yields a micropellet containing 30 μg of corticosterone with a diffusion radius of 0.75 mm measured ventral to the pellet in the amygdala. Tissue levels of corticosterone are in the high physiologic range [14]. The cytoarchitecture of the amygdala and frontal cortex are different and may affect the diffusion characteristics of corticosterone. Diorio et al. [5] found corticosterone diffusion up to 0.9 mm caudal to the implantation site in the ACC. This raises the possibility that diffusion from our micropellet may be greater in the cortex than in the amygdala. Alternatively, diffusion of corticosterone may be ovoid rather than spherical with more diffusion in the rostral caudal plane.

2.3. Stereotaxic surgery

Rats received bilateral implants containing 30 μg of cholesterol or corticosterone in the ACC (2.9 mm rostral to bregma, +1.5 mm lateral to midline, −2.6 mm ventral), PLC (2.9 mm rostral to bregma, +1.7 mm lateral to midline, −3.9 mm ventral) or ILC (2.9 mm rostral to bregma, +2.0 mm lateral to midline, −5.1 mm ventral). Rostral/Caudal coordinates are with respect to bregma and ventral

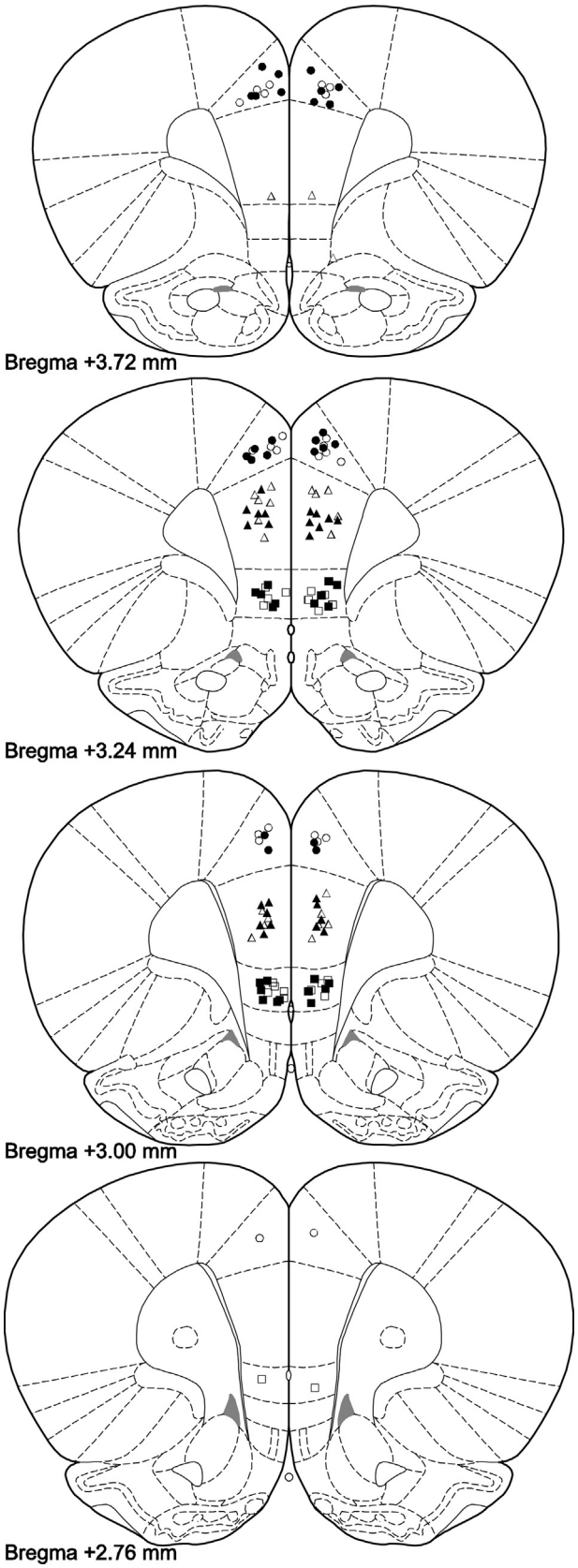

Fig. 1. Location of micropellet implants from all three experiments. Different symbols indicate the site targeted for each experiment. Implants for the cingulate cortex from experiment 1 are indicated with circles. The prelimbic (triangles), and infralimbic (squares) cortices are from experiments 2 and 3 respectively. Corticosterone or cholesterol (control) were implanted in all three experiments. Black markers represent corticosterone micropellets and grey indicates cholesterol.