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Review

Actions and interactions of estradiol and glucocorticoids in cognition and the brain: Implications for aging women

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ABSTRACT

Menopause involves dramatic declines in estradiol production and levels. Importantly, estradiol and the class of stress hormones known as glucocorticoids exert countervailing effects throughout the body, with estradiol exerting positive effects on the brain and cognition, glucocorticoids exerting negative effects on the brain and cognition, and estradiol able to mitigate negative effects of glucocorticoids. Although the effects of these hormones in isolation have been extensively studied, the effects of estradiol on the stress response and the neuroprotection offered against glucocorticoid exposure in humans are less well known. Here we review evidence suggesting that estradiol-related protection against glucocorticoids mitigates stress-induced interference with cognitive processes. Animal and human research indicates that estradiol-related mitigation of glucocorticoid damage and interference is one benefit of estradiol supplementation during peri-menopause or soon after menopause. The evidence for estradiol-related protection against glucocorticoids suggests that maintaining estradiol levels in post-menopausal women could protect them from stress-induced declines in neural and cognitive integrity.

Contents

Abbreviations: GC, glucocorticoids; HPA axis, hypothalamic–pituitary–adrenal; HPG axis, hypothalamic–pituitary–gonadal; E2, 17β-estradiol; TSST, Trier Social Stress Test; CPT, cold pressor task; Aβ, beta-amyloid; OVX, ovariectomized; WHI, Women’s Health Initiative; WHIMS, Women’s Health Initiative Memory Study; WHISCA, Women’s Health Initiative Study of Cognitive Aging; fMRI, functional magnetic resonance imaging; ACTH, adrenocorticotropic hormone; DEX, dexamethasone; CRH, corticotropin releasing hormone.

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1. Introduction

Women's transition into reproductive senescence is marked by reductions in ovarian function and output; referred to as menopause (Rannevik et al., 1986). However; the dramatic declines in estradiol production and estradiol levels occurring during menopause (Rannevik et al., 1986) may alter more than just reproductive capability. The systems governing stress and fluctuations in female reproductive hormones and the primary hormones of each system (glucocorticoids and estradiol; respectively) intimately interact and influence one another. Thus; as one system changes; the nature of the interactions between them may also change.

Research on how glucocorticoids and estradiol affect the brain, body, and cognition spans a number of species, ranging from rodents to humans. However, how glucocorticoids (GC) and estradiol interact to change the effect and action of the other on the brain, body, and cognition in human females is less studied. Due to the dramatic change in the production and release of estradiol in human females with age, understanding whether and how these systems interact to affect women is of importance.

In addition to interacting, glucocorticoids and estradiol also exert opposing effects on various bodily systems, in males and females. For instance, development of metabolic syndrome (Pasquali et al., 2006; for review see, Rosmond, 2005), unhealthy alterations in fat distribution (Rebuffe-Scrive et al., 1992), promotion of hyperglycemia and hyperinsulinemia (McGuinness et al., 1993; Rebuffe-Scrive et al., 1992), promotion of bone resorption (O'Brien et al., 2004), and maintenance of bone degrading osteoclasts (Jia et al., 2006) have been associated with long-term GC exposure. In contrast, opposite patterns of less unhealthy fat distribution (Green et al., 2004; Musatov et al., 2007), lesser occurrence of hyperglycemia and hyperinsulinemia (Krotkiewski et al., 1983; Musatov et al., 2007), and promotion and maintenance of bone mineral density (Delmas et al., 1997; Felson et al., 1993; Sowers et al., 1998), have been linked to estradiol, the primary estrogen in females (see Table 1).

Similar contrasting effects of GCs and estradiol occur in neural tissue and cognition, where chronic or extreme GC exposure leads to dendritic retraction, and neuropil and neuron damage or loss (Behl et al., 1997; Filipovic et al., 2013; Hillerer et al., 2013; MacPherson et al., 2005; Magarinos et al., 2011; Stein-Behrens et al., 1992; for review see, Tata and Anderson, 2010; see also, Tombaugh et al., 1992; Tynan et al., 2013; Tynan et al., 2010; Woolley et al., 1990b), and impairments in cognitive performance (Alexander et al., 2007; Duncko et al., 2009; Elzinga and Roelofs, 2005; Luethi et al., 2009; Oei et al., 2006; Schoofs et al., 2009; Young et al., 1999). In contrast, estradiol promotes neural growth and protection (Brinton et al., 2000; Chen et al., 2006; Gerstner et al., 2007; Hao, 2006; Saravia et al., 2007) and improvement of cognitive function (Baker et al., 2012; Krug et al., 2006; Shaywitz et al., 2003; Velázquez-Zamora et al., 2012; Wolf et al., 1999).[1]

Due to the fluctuations and eventual loss of estradiol throughout the adult lifespan of human females, it is important to understand the implications of the opposing effects of stress and estradiol on the brain and cognition. Much of the literature reviewed here will span from basic research findings to findings in human research, and explore patterns of these hormone effects in males and females. We will focus on the negative effects of stress on neural tissue and cognition in both males and females, and discuss whether the opposing effects of estradiol in the same domains may offer some protection against these effects. We propose that estradiol loss after menopause leaves women more vulnerable to developing dysfunctional stress responses and therefore, larger effects of stress on cognition. We also argue that the loss of estradiol in midlife leaves peri- and post-menopausal women more vulnerable to the negative effects of stress hormone exposure, accelerating age-related declines in neural and cognitive integrity.

2. Interactions of the stress and estradiol systems

2.1. The "stress system"

The hypothalamic–pituitary–adrenal (HPA) axis governs response to stressors. Emotional or physiological challenges cause the paraventricular nucleus of the hypothalamus to release corticotropin-releasing hormone. The portal system carries the neuropeptide to the anterior pituitary, causing release of andrenocorticotropic hormone. Andrenocorticotropic hormone travels via the bloodstream to the adrenal glands, causing release of GCs from the adrenal cortex (the outer layers of the adrenal gland) and the catecholamines epinephrine and norepinephrine from the adrenal medulla (for review see, Lupien et al., 2009). Due to our interest in the effects of GCs, and interactions between GCs and estradiol, we will focus on this portion of the stress response.

During the stress response, GCs assist in the fight-or-flight response by providing immediate energy to the body via assistance converting protein to glucose, fat to usable energy, and shunting blood flow from immediately nonessential systems, such as the gut, to skeletal muscles for energy. Cortisol, the primary GC in humans, also is responsible for terminating the HPA response to a stressor via negative feedback. Glucocorticoids initiate shutdown of the HPA response by exerting direct inhibition of the hypothalamus and pituitary gland, as well as recruiting additional brain regions, particularly the prefrontal cortex and hippocampus, to send inhibitory signals.

2.2. The "estradiol system"

Unlike the HPA axis, the hypothalamic–pituitary–gonadal (HPG) axis terminates at different targets for males and females, the testes or ovaries, respectively. Here we will focus on the female HPG axis,

[1] GCs also are necessary for normal neuronal functioning (Nadeau and Rivest, 2003), and are beneficial for memory of emotional stimuli or events (e.g., Buchanan and Lovallo, 2001). Similarly, estradiol can damage already compromised neural tissue (Chen et al., 2006), and is associated with worse emotional memory (for review see, Sakaki and Mather, 2012).

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