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Steroid abnormalities and the developing brain: Declarative memory for emotionally arousing and neutral material in children with congenital adrenal hyperplasia

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Summary

Steroid hormones modulate memory in animals and human adults. Little is known on the developmental effects of these hormones on the neural networks underlying memory. Using Congenital adrenal hyperplasia (CAH) as a naturalistic model of early steroid abnormalities, this study examines the consequences of CAH on memory and its neural correlates for emotionally arousing and neutral material in children. Seventeen patients with CAH and 17 age- and sex-matched healthy children (ages 12–14 years) completed the study. Subjects were presented positive, negative and neutral pictures. Memory recall occurred about 30 min after viewing the pictures. Children with CAH showed memory deficits for negative pictures compared to healthy children ($p < 0.01$). There were no group differences on memory performance for either positive or neutral pictures ($p > 0.1$). In patients, 24 h urinary-free cortisol levels (reflecting glucocorticoid replacement therapy) and testosterone levels were not associated with memory performance. These findings suggest that early steroid imbalances affect memory for negative material in children with CAH. Such memory impairments may result from abnormal brain organization and function following hormonal dysfunction during critical periods of development.

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1. Introduction

Previous findings report that steroid hormones may influence cognitive function (McEwen, 1994; Cherrier, 2005; Lupien et al., 2007). Acute elevations in glucocorticoids (cortisol in humans) and androgens were shown to modulate declarative memory for emotional and neutral material (e.g., Vazquez-Pereyra et al., 1995; Naghdi et al., 2001; Cherrier, 2005; de Kloet et al., 2005; Lupien et al., 2007). Declarative memory refers to the conscious or voluntary recollection of previously learned information (Milner et al., 1998). Glucocorticoids and androgens may influence declarative memory for emotional and neutral material through their interactions with a large number of their receptors located in the frontal cortex, hippocampus and amygdala (Handa et al., 1994; Beyenburg et al., 2000; Lupien and Lepage, 2001; Roozendaal, 2003; de Kloet et al., 2005; Wilson and Davies, 2007), three brain structures implicated in declarative memory and the processing of emotional information (Milner et al., 1998; Davidson, 2002; Phelps, 2006).

Steroids can have two types of effects, organizational and activational effects. The organizational effects refer to permanent changes in brain structure, organization or function *in utero* or during critical periods of development. The activational effects refer to the acute effects of circulating steroids during adulthood. Although most research on the mnemonic effects of steroids focused on the activational mechanisms of these hormones (e.g., Vazquez-Pereyra et al., 1995; Naghdi et al., 2001; Cherrier, 2005; see de Kloet et al., 2005; Lupien et al., 2007), organizational influences of steroids on declarative memory are now widely accepted (Welberg and Seckl, 2001; Owen et al., 2005).

Indeed, animal models provide important evidence that dysfunction of glucocorticoids pre-natally or early in life can induce organizational changes in structure and function of the hippocampus, a central neural substrate of declarative memory, and amygdala, a key to emotional coding. Altered hippocampal architecture, such as neuronal degeneration of hippocampal pyramidal neurons or reduced hippocampal glucocorticoid gene expression, was observed following pre-natal and early life chronic exposure to elevated glucocorticoid levels in young rat offspring (Francis et al., 1999; Matthews, 2001; Welberg and Seckl, 2001). This animal model was also associated with increased glucocorticoid gene expression in the amygdala of juvenile offspring (Welberg and Seckl, 2001). Behaviorally, pre-natal and early life chronic glucocorticoid excess was found to be associated with increased anxiety behaviors in threatening situations and deficits in discrimination learning and spatial memory tasks in young rodents (Owen et al., 2005; Welberg and Seckl, 2001).

Though a few studies report on the organizational effects of glucocorticoid insufficiency on brain structure and function in juvenile mammals, such findings remain scarce. Interestingly, however, data reported so far show that removal of glucocorticoids by adrenalectomy (ADX) leads to similar consequences as those observed in young offspring exposed to elevated glucocorticoid levels. Hence, reduced number and branching of dendrites in hippocampal cells were reported following neonatal ADX in juvenile rodents (Hashimoto et al., 1989). Moreover, degeneration in granule cells throughout the dentate gyrus of the hippocampus was

reported in rat pups submitted to ADX during the early post-natal period (Gould et al., 1991; Sloviter et al., 1993). No studies measured the effects of early post-natal ADX on the amygdala in young offspring. Behaviorally, glucocorticoid depletion in early post-natal life was associated with impaired fear expression to threat in rat pups tested a few days after ADX (Takahashi, 1994; Moriceau et al., 2004).

Androgen levels in pre-natal and early life were also found to influence structure and function of both hippocampus and amygdala in animals. More specifically, these organizational effects were shown to modulate synaptic plasticity in hippocampal CA1 cells in juvenile rats (Hebbard et al., 2003). Moreover, sex differences in the shape and synaptic organization of the medial amygdala are influenced by pre-natal and early life androgen levels in young rodent offspring (Cooke et al., 1998; Cooke and Woolley, 2005; Wilson and Davies, 2007). Behaviorally, elevated levels of pre-natal and early life androgens were shown to reduce social memory performance (Hebbard et al., 2003), and to sexually differentiate the development of spatial memory abilities (Roof, 1993) and visual discrimination learning (Hagger and Bachevalier, 1991) in young and late puberty juvenile mammal offspring.

Despite animal findings documenting organizational effects of glucocorticoids and androgens on the hippocampus or amygdala, and on learning performance, no studies examined such consequences in humans. An initial step could be the study of declarative memory in children with congenital steroid dysfunction such as CAH.

Classic CAH is an autosomal recessive disorder with a prevalence rate estimated at one in 15,000 live births (Merke and Bornstein, 2005). Classic CAH due to 21-hydroxylase (OH) deficiency is characterized by a deficiency in cortisol biosynthesis and severe androgen excess. In addition, a rodent model of CAH reports that the lack of cortisol negative feedback results in overproduction of corticotropin-releasing hormone (CRH)mRNA in the hypothalamus, as well as overproduction of proopiomelanocortin (POMC)mRNA (precursor of adrenocorticotrophic hormone (ACTH) in the pituitary; Tajima et al., 1999). Such overproduction of ACTH stimulates the adrenals and leads to excess adrenal androgen production (Merke and Bornstein, 2005).

Pre-natal dysfunction of glucocorticoids and androgens in CAH patients has led to the notion that brain organization, behavior and cognition may be affected in this population. With respect to brain organization, we recently reported irregularities in the structure and function of the amygdala in children with CAH. Specifically, we documented reduced volume in both male and female patients (Merke et al., 2003), and enhanced response to negative facial emotions in female patients (Ernst et al., 2007). Behaviorally, some studies have suggested that prenatal androgen excess masculinizes the brain of females with CAH, as these young girls exhibit male-like behaviors in their play interests, report themselves as being more aggressive and have enhanced spatial abilities compared to their healthy counterparts (Berenbaum, 2001; Hines et al., 2003; Cohen-Bendahan et al., 2005). Cognitively, research in CAH patients has reported inconsistent results. Johannsen and collaborators (2006) found that adult patients with the most severe form of classic CAH, and especially those who

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