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Exogenous prenatal corticosterone exposure mimics the effects of prenatal stress on adult brain stress response systems and fear extinction behavior

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Summary Exposure to early-life stress is a risk factor for the development of cognitive and emotional disorders later in life. We previously demonstrated that prenatal stress (PNS) in rats results in long-term, stable changes in central stress-response systems and impairs the ability to extinguish conditioned fear responding, a component of post-traumatic stress disorder (PTSD). Maternal corticosterone (CORT), released during prenatal stress, is a possible mediator of these effects. The purpose of the present study was to investigate whether fetal exposure to CORT at levels induced by PNS is sufficient to alter the development of adult stress neurobiology and fear extinction behavior. Pregnant dams were subject to either PNS (60 min immobilization/day from ED 14—21) or a daily injection of CORT (10 mg/kg), which approximated both fetal and maternal plasma CORT levels elicited during PNS. Control dams were given injections of oil vehicle. Male offspring were allowed to grow to adulthood undisturbed, at which point they were sacrificed and the medial prefrontal cortex (mPFC), hippocampus, hypothalamus, and a section of the rostral pons containing the locus coeruleus (LC) were dissected. PNS and prenatal CORT treatment decreased glucocorticoid receptor protein levels in the mPFC, hippocampus, and hypothalamus when compared to control offspring. Both treatments also decreased tyrosine hydroxylase levels in the LC. Finally, the effect of prenatal CORT exposure on fear extinction behavior was examined following chronic stress. Prenatal CORT impaired both acquisition and recall of cue-conditioned fear extinction. This effect was additive to the impairment induced by previous chronic stress. Thus, these data suggest that fetal exposure to high levels of maternal CORT is responsible for

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many of the lasting neurobiological consequences of PNS as they relate to the processes underlying extinction of learned fear. The data further suggest that adverse prenatal environments constitute a risk factor for PTSD-like symptomatology, especially when combined with chronic stressors later in life.

1. Introduction

Post-traumatic stress disorder (PTSD) is a disabling affective disorder that occurs as a consequence of a physically or emotionally traumatic experience. It is characterized by intrusive memories, a state of hyper-vigilance, and an inability to inhibit fear responses to trauma-associated cues. An estimated 9 million people in the United States suffer from PTSD, yet this is only a portion of those who experience trauma (Kessler et al., 2005). Therefore, other factors are likely to confer vulnerability to developing PTSD subsequent to traumatic stress, including experiential, environmental, or biological predispositions. Clinical studies suggest that early life stressors, such as childhood exposure to trauma, low socioeconomic status, and familial instability increase susceptibility to PTSD later in life (Breslau et al., 1999; Koenen et al., 2007). Prenatal stress (PNS) is an adverse early life event that has been associated with increased risk for anxiety, ADHD, schizophrenia, developmental delays, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation in humans; however, very little is known about its role as a potential risk factor for PTSD (Davis and Sandman, 2012; Talge et al., 2007).

Animal studies suggest that PNS programs the adult stress system to create a stress-reactive phenotype, showing fear- and depression-like behaviors that resemble aspects of PTSD (Weinstock, 2008). PNS has been shown to permanently program the brain corticosteroid and brain monoamine systems, both of which are implicated in the formation and extinction of fear memories. PNS can reduce glucocorticoid receptor (GR) and/or mineralocorticoid receptor (MR) expression in adult offspring (Brunton and Russell, 2010; Green et al., 2011; Harris and Seckl, 2011; Weinstock, 2008). PNS also alters catecholamine release in brain areas associated with behavioral and cognitive components of the stress response. It has been shown to decrease basal and stress-induced norepinephrine release in the prefrontal cortex (PFC) and locus coeruleus (LC) as well as dopamine in the LC (Carboni et al., 2010; Takahashi et al., 1992). In addition to these biochemical effects, PNS causes enduring behavioral changes, including anxiety-like behavior on the elevated plus maze, an increase in freezing behavior following footshock, and compromised performance in cognitive tasks like the Morris water maze (Brunton and Russell, 2010; Kofman, 2002; Salomon et al., 2011; Takahashi et al., 1992; Weinstock, 2008).

This altered physiological and behavioral response to stress may create a state of vulnerability to chronic stressors later in life and thus increase the risk for PTSD. Indeed, after experiencing a traumatic stress, many individuals continue to endure a secondary, persistent state of chronic stress that is produced by intrusive memories, nightmares, and increased physiological stress responses to cues associated with the initial trauma. In individuals who may be impaired in their ability to cope with stress, this persistent chronic stress may facilitate the transition from acute stress disorder to chronic PTSD (Davidson and Baum, 1986; Wessa and Flor, 2007). Likewise, chronic stress may also impair the ability to extinguish trauma-associated fear memories. Preclinical studies in rodents have demonstrated that chronic stress in adulthood facilitates conditioned fear behavior and impairs the retention of subsequent extinction of conditioned fear (Farrell et al., 2010; Garcia et al., 2008). We recently showed that both PNS and adult chronic stress independently impaired acquisition of fear-extinction. These effects appeared to be additive, such that rats receiving both PNS and adult chronic stress were consistently the most impaired in their ability to extinguish fearful associations, a hallmark trait of PTSD in humans (Green et al., 2011).

Fetal exposure to maternal glucocorticoids represents one potential mechanism whereby PNS may program the adult stress response in utero. During PNS, glucocorticoids are released by the dam, and, at high concentration, can cross the placental barrier to exert direct effects on gene transcription in the fetus (Harris and Seckl, 2011; Takahashi et al., 1998). Fetal exposure to high levels of glucocorticoids results in long-term impairments in cognitive and emotional regulation (Alexander et al., 2012). Both the direct administration of glucocorticoids and the inhibition of placental barrier enzymes mimic some of the effects of PNS (Welberg et al., 2000). Likewise, maternal adrenalectomy is able to prevent some of the lasting effects of PNS (Barbazanges et al., 1996; Salomon et al., 2011). However, it is unknown if prenatal glucocorticoid exposure mimics the effects of PNS on the formation and extinction of fear memories in the adult offspring. It is also unknown whether a history of prenatal glucocorticoid exposure interacts with later stress to further impair fear extinction, i.e., creating vulnerability for a PTSD-like phenotype. To address these questions, we compared the effects of prenatal corticosterone (CORT) administration in the absence of maternal stress to those of PNS. We first determined a dose of exogenous CORT, delivered to the mother, that best mimics both fetal and maternal circulating CORT levels induced by PNS. To determine if CORT treatment mimics the neurobiological consequences of PNS, we then measured the mRNA and protein expression of the GR, corticotrophin releasing factor (CRF), brain-derived neurotrophic factor (BDNF), and tyrosine-hydroxylase (TH) in the brains of the adult male offspring. Finally, we measured the effect of prenatal CORT exposure on fear conditioning and extinction behavior in the adult offspring, with and without exposure to chronic stress. We hypothesized that prenatal CORT exposure would mimic the neurobiological effects of PNS and create an additive detrimental effect on fear conditioning and extinction behavior when combined with chronic stress later in life.

2. Methods

2.1. Animals

Timed-pregnant female Sprague-Dawley rats (Harlan, Indianapolis) arrived on embryonic day (ED) 6 and were