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Corticotropin-Releasing Hormone during Pregnancy Is Associated with Infant Temperament

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Abstract
During pregnancy corticotropin-releasing hormone (CRH) is released into maternal and fetal circulation from the placenta. Elevated concentrations of placental CRH are associated with spontaneous preterm birth, but the consequences for infant development, independent of birth outcome, are unknown. In this study, the effects of placental CRH on infant temperament were examined in a sample of 248 full-term infants. Maternal blood samples were collected at 19, 25 and 31 weeks of gestation for CRH analysis. Infant temperament was assessed with measures of fear and distress at 2 months of age. Infants of mothers with low CRH at 25 weeks of gestation scored lower in fear and distress at 2 months. CRH at 19 and 31 weeks' gestation was not significantly associated with measures of infant temperament, suggesting the possibility that there is a sensitive period for its effects. These data suggest that prenatal exposure to CRH may exert influences that persist into the postnatal period.

Maternal stress during pregnancy has been studied as a risk factor that may have developmental and health consequences persisting throughout the lifespan. Animal and human studies have demonstrated that maternal stress during pregnancy has consequences for cognition and learning [Laplante et al., 2004; Weinstock, 1996], stress reactivity [Clarke et al., 1994], behavioral responses to novelty [Davis et al., 2004; Schneider, 1992] and other emotional and behavioral disturbances [O'Connor et al. 2003; Schneider et al., 1992; Van den Bergh and Marcoen, 2004; Weinstock, 2001] in the offspring. A primary pathway by which stress effects the fetus appears to be the hypothalamic-pituitary-adrenal (HPA) axis [Ward and Phillips, 2001; Welberg and Seckl, 2001]. However, few studies have examined the effect of HPA axis activity during the prenatal period on human postnatal development [de Weerth et al., 2003].

HPA axis activity is regulated by the release of hypothalamic corticotropin releasing hormone (CRH). CRH is a 41-amino acid neuropeptide that stimulates the biosynthesis and release of adrenocorticotropin hormone (ACTH) and β-endorphin from the anterior pituitary. ACTH triggers glucocorticoid (cortisol in primates) production and release from the adrenal cortex [Chrousos and Gold, 1992; Vale et al., 1981]. In addition to the hypothalamus, CRH has been identified in other areas of

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the brain with high quantities localized in the central nucleus of the amygdala and the bed nucleus of the stria terminalis [Avishai-Eliner et al., 2002; Schulkin, 1999].

During primate pregnancy CRH is also released from the placenta into the bloodstream. The human placenta contains mRNA for CRH as early as the 7th week of gestation [Petraglia et al., 1987]. Fetal and maternal levels are correlated because the active peptide is released into both the maternal and fetal circulation [Economides et al., 1987; Gitau et al., 2004; Goland et al., 1988; Stalla et al., 1989]. Placental CRH is identical to hypothalamic CRH in structure, immunoreactivity and bioactivity [Petraglia et al., 1996]. There is, however, a crucial difference. In contrast to the negative control on hypothalamic CRH, glucocorticoids stimulate the expression of hCRH mRNA in the placenta. Placental CRH is released establishing a positive feedback loop that allows for the simultaneous increase of CRH, ACTH, and cortisol in the maternal and fetal compartments over the course of gestation [King et al., 2001a; Petraglia et al., 1996]. As pregnancy advances, levels of CRH in plasma reach those observed within the hypothalamic-pituitary portal system during stress [Lowry, 1993]. Hypothalamic CRH is not, however, detectable in the peripheral circulation. Plasma CRH is of placental origin [King et al., 2001b]. It is because of this HPA and placental circuit that there are increasing levels of CRH, ACTH, and cortisol in the maternal and fetal compartments during pregnancy. CRH has been proposed as one mechanism by which prenatal stress influences fetal and infant development [Avishai-Eliner et al., 2002; Sandman et al., 1999].

An increasing number of studies have reported that women who have high concentrations of placental CRH for their gestational stage are at significantly elevated risk for premature delivery [Erickson et al., 2001; Hobel et al., 1999; Holzman et al., 2001; Inder et al., 2001; McLean et al., 1995; Moawad et al., 2002; Smith et al., 2003; Wadhwa et al., 2004]. Placental CRH also has a direct effect on the fetus and plays a role in fetal development and maturation [Mastorakos and Ilias, 2003]. For instance, it was found that prenatal exposure to elevated CRH resulted in impaired ability of the human fetus to distinguish a novel tone from familiar tones at 32 weeks' gestation [Sandman et al., 1999]. Animal models suggest that the influence of prenatal exposure to elevated levels of CRH persists to the postnatal period. Stress-related increases of CRH accelerate the developmental trajectory of other species such as the western spadefoot tadpole. However, this acceleration comes at the cost of long-term impairment in survival skills for the mature toad [Denver, 1997]. Additionally, prenatal administration of CRH in the rodent delays growth and increases vocalizations in response to isolation [Williams et al., 1995]. These findings are particularly interesting because the rodent placenta does not produce CRH and exposure does not result in premature delivery. Thus the influences noted in these studies of prenatal CRH treatment reflect effects on the fetal CNS without complications of premature birth.

The effects of placental CRH on human postnatal development have not been investigated. Research with both human and nonhuman primates has demonstrated that an important consequence of prenatal exposure to stress and stress hormones is an increase in fearful or reactive behavior [Davis et al., 2004; Schneider, 1992; Welberg and Seckl, 2001]. It has been further illustrated that the effects of prenatal stress on development are related to the timing of exposure [Schneider et al., 1992; Laplante et al., 2004]. We examined, first, whether elevated maternal CRH during pregnancy might predict increased fear and distress in the offspring and second, whether there was a critical period during fetal development for the effects of CRH on infant temperament. CRH was measured at three time points during pregnancy starting at the 19th week of gestation. Infant fear and distress behaviors were evaluated at 2 months of age. It has been documented that placental CRH influences length of gestation and that infants born prematurely or small for gestational age (GA) are at risk for a wide variety of developmental problems [Peterson et al., 2003]. Because we were interested in examining the impact of placental CRH on infant development independent of birth outcome, only full-term infants were included in this study.

Methods

Participants

Two hundred and forty-eight women with healthy singleton term pregnancies were recruited serially between 1999 and 2003 from two obstetrics clinics in Southern California prior to the 16th week of pregnancy. Women gave informed consent for all aspects of the protocol, which was approved by the institutional review board for protection of human subjects. At delivery, mothers ranged in age from 18 to 43 years (mean = 30.8, SD = 5.3), 72% of the women were married and 59% were primiparous. Annual household income for this sample ranged from USD 5,000 to over USD 100,000. Ninety-eight percent of women had graduated from high school and 48% were college graduates. Forty-nine percent of the women were non-Hispanic White, 20% were Hispanic White, 11% were African American and 9% were Asian. This sample is representative of low-risk pregnancies seen at these clinics. The infants of these women (116 girls and 132 boys) were assessed at 8 weeks

of age (SD = 2.1). All infants were born at term (mean GA = 39.5 weeks, SD = 1.1 weeks; mean weight = 3,540.02 g, SD = 505.5 g), 71% were delivered vaginally. Infants in this sample were stable at the time of delivery and had a median 5-min Apgar score of 9 (range = 4–9).

Procedures

Maternal plasma samples were collected at 3 time points during pregnancy (19.1 ± 0.8, 24.9 ± 0.84, 30.8 ± 0.98 weeks of gestation) for analysis of CRH concentration. Infant temperament and maternal psychological state were assessed at 8 weeks postpartum (SD = 2.1).

Measures

Placental CRH Assessment. Blood samples (20 ml/draw) were withdrawn by antecubital venipuncture into EDTA (purple top) vacutainers and chilled on ice immediately. Samples were centrifuged at 2,000 *g* (15 min) and the plasma decanted into polypropylene tubes containing 500 kIU/ml aprotinin (Sigma Chemical Co., St. Louis, Mo., USA) and stored at –70°C until assayed.

CRH concentrations (pg/ml) were determined by radioimmunoassay (RIA; Bachem Peninsula Laboratories, San Carlos, Calif., USA). Plasma samples (1–2 ml) were extracted with three volumes of ice-cold methanol, mixed, allowed to stand for 10 min at 4°C and then centrifuged at 1,700 *g* for 20 min at 4°C by the modified method of Linton et al. [1995]. The pellets were washed with 0.5 ml methanol, and the combined supernatants dried down (Savant SpeedVac concentrator): Reconstituted samples in assay buffer were incubated with anti-CRH serum (human) for 48 h at 4°C followed by a 24-hour incubation with ^{125}I-CRH. Both labeled and unlabeled CRH were collected by immunoprecipitation with goat anti-rabbit IgG serum and normal rabbit serum after 90 min incubation at room temperature. Samples were centrifuged at 1,700 *g* (20 min) at 4°C and the aspirated pellets were quantified with a gamma scintillation counter. The CRH assay had less than 0.01% cross-reactivity with ovine CRH, 36% cross-reactivity with bovine CRH, and non-detectable reactivity with human ACTH. The intra-assay and inter-assay coefficient of variance ranges from 5 to 15% respectively. Data reduction for the RIA assay was with a computer assisted four-parameter logistics program [Rodbard and Hutt, 1974].

Infant Temperament. Infant temperament was assessed using a modified version of two of the subscales of the Infant Behavior Questionnaire, a standardized instrument designed to assess temperament in infancy by maternal report [Gartstein and Rothbart, 2003]. The 8-item fear scale assesses the extent to which infants display fearful reactions to novel or surprising stimuli (e.g., How often during the past week did the baby startle to a loud sound or sudden noise?). The 12-item distress scale assesses levels of fussiness or irritability (e.g., How often during the past week did the baby fuss or show distress while in a confining place or position?). Mothers rated their infant on each item using a 5-point Likert scale ranging from 1 (never) to 5 (always). Responses to items from each scale were averaged to create a score for fear and a score for distress. Published reliability and validity data for the Infant Behavior Questionnaire indicates that this instrument has strong psychometric properties. Cronbach α-coefficients for these scales were 0.90 and 0.81 and intercorrelation between ratings given by the primary and secondary caregiver were 0.75 and 0.57 for fear and distress, respectively [Gartstein and Rothbart, 2003].

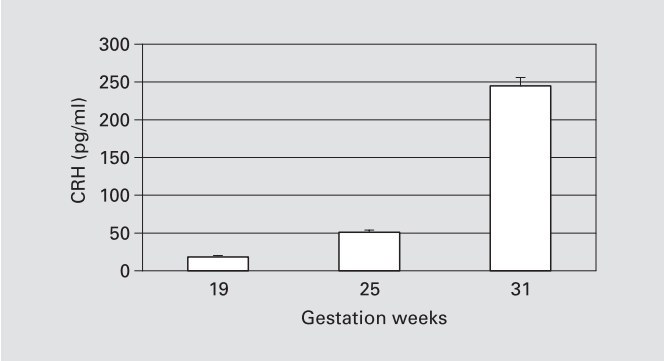

Fig. 1. Mean CRH levels at 19, 25 and 31 weeks of gestation.

Maternal Psychological Assessments. To control for the influence of maternal affect during the postnatal period on ratings of infant temperament, maternal anxiety and depression also were measured. Maternal postpartum depression was evaluated using the short form of the Center for Epidemiological Studies Depression Inventory [Santor and Coyne, 1997]. Responses to each of the 9 items in this measure were recorded on a 4-point Likert scale with a range of 0–3. Anchor points, in terms of days per week, were 'rarely or none of the time (less than 1 day)' to 'most or all of the time (5–7 days)'. The final score could span from 0 to 27, with a higher score indicating greater impairment. This measure has been extensively used and published studies demonstrate both internal consistency (Cronbach's α = 0.84) and validity of this measure [Santor and Coyne, 1997].

State anxiety was measured using the State Anxiety subscale of the State-Trait Anxiety Inventory [STAI; Spielberger, 1983]. This 10-item scale assessed the extent to which participants had experienced anxiety-related symptoms or emotions using a 4-point Likert scale ranging from 1 (not at all) to 4 (very much). State anxiety scores could range from a minimum of 10 to a maximum of 40. The STAI has been used for research purposes with both pregnant [Rini et al., 1999] and non-pregnant samples. The STAI has good internal consistency with a Chronbach's α-coefficient of 0.92 [Spielberger, 1983].

Results

Placental CRH Assessment

As illustrated in figure 1, levels of CRH increased significantly from 19 to 25 weeks' GA [$t(247) = 12.5$, $p < 0.001$] and from 25 to 31 weeks' GA [$t(247) = 18.6$, $p < 0.001$]. Median CRH levels were 15.2 pg/ml at 19 weeks, 33.1 pg/ml at 25 weeks and 187.7 pg/ml at 31 weeks. CRH levels at the three measurement periods were modestly correlated (with r ranging from 0.24 to 0.30, $p < 0.001$). A square root transformation was employed to reduce the skew of the CRH values.

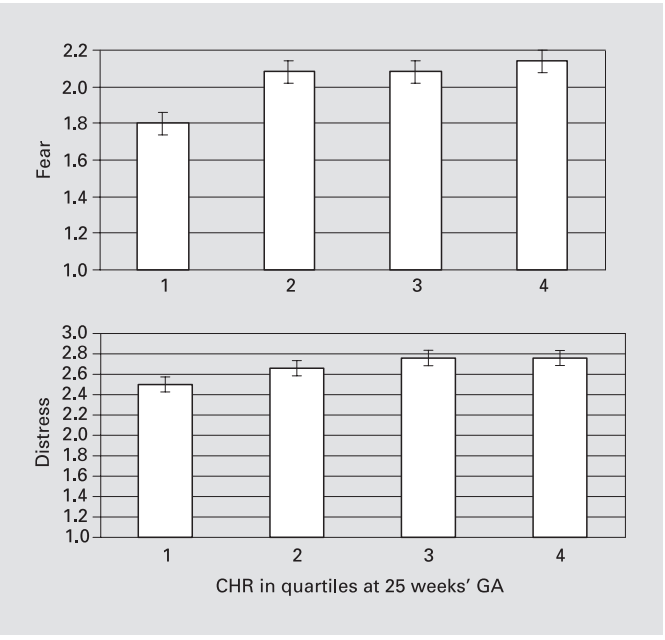

Fig. 2. CRH and temperament. GA = Gestational age.

Infant Temperament

Infant fear scores ranged from 1.3 to 3.4 (mean = 2.0, SD = 0.45). Infant distress scores ranged from 1.2 to 4.3 (mean = 2.6, SD = 0.59). Fear and distress were moderately correlated [$r(248) = 0.40$, $p < 0.001$]. At 2 months, mean levels of fear and distress did not differ significantly based on sex of the infant [$t(247) = 0.45$, $p = 0.66$ and $t(247) = 0.17$, $p = 0.87$, respectively], method of delivery [vaginal vs. cesarean section, $t(247) = 0.77$, $p = 0.44$ and $t(246) = 0.69$, $p = 0.48$], or parity [$t(247) = 1.6$, $p = 0.13$ and $t(246) = 1.5$, $p = 0.10$]. Furthermore, annual household income, used as an index of socioeconomic status, was not correlated with infant temperament [$r(246) = 0.05$, $p = 0.31$ and $r(246) = 0.06$, $p = 0.024$].

Placental CRH and Infant Temperament

To determine whether CRH levels during pregnancy affected infant temperament we examined whether the offspring from mothers with higher levels of placental CRH during pregnancy displayed higher levels of fear or distress. Three regression analyses indicated that placental CRH only at 25 weeks, but not at 19 or 31 weeks, significantly predicted infant temperament: fear ($R^2 = 0.04$, $\beta = 0.15$, $t = 2.4$, $p < 0.01$) and distress ($R^2 = 0.03$, $\beta = 0.16$, $t = 2.5$, $p < 0.01$). Further, there was evidence that these associations were nonlinear (i.e. a cubic solution accounted for more variance). Thus, temperament measures were compared in groups of infants divided into quartiles based on levels of CRH at 25 weeks of GA. Group 1 comprised individuals with low levels of CRH at 25 weeks (n = 63), groups 2 (n = 61) and 3 (n = 60) contain individuals with middle levels of CRH and group 4 (n = 64) contained individuals with high levels of CRH. As illustrated in figure 2, differences among the 4 groups were significant for ratings of fear [$F(3,244) = 3.3$, $p < 0.05$] and there was a non-significant trend for the four groups to differ in ratings of distress [$F(3,244) = 2.4$, $p = 0.07$]. The group with the lowest level of CRH at 25 weeks displayed the lowest levels of fear and distress in infancy. Tukey corrected post hoc tests indicated that group 1 displayed significantly lower levels of fear than groups 2, 3 and 4 (all p values <0.05). Similarly, measures of infant distress were significantly lower for group 1 than groups 3 and 4 (all p values <0.05).

There is evidence that maternal psychological state during the postpartum period may independently influence infant temperament and the maternal perception of infant temperament [Pauli-Pott et al., 2003]. The contribution of these factors to the relation between CRH and infant temperament was examined to assess this alternative explanation. Ratings of infant fear behavior were associated with maternal postpartum anxiety [$r(248) = 0.15$, $p < 0.05$], but not maternal postpartum depression [$r(248) = 0.12$, $p = 0.07$]. Ratings of infant distress were correlated with both postpartum maternal anxiety [$r(248) = 0.29$, $p < 0.001$] and depression [$r(248) = 0.31$, $p < 0.001$]. Postpartum maternal anxiety and depression were entered as covariates and the relation between CRH at the 25th week of gestation and infant temperament was re-examined. Including maternal mood as covariates did not change the relations between CRH and infant temperament [fear ratings: $F(3,243) = 3.2$, $p < 0.05$ and distress ratings: $F(3,243) = 2.4$, $p = 0.07$].

Discussion

The HPA axis is altered dramatically during pregnancy because the placenta expresses the genes for CRH (hCRH mRNA). In contrast to the negative control on hypothalamic CRH, glucocorticoids stimulate the expression of hCRH mRNA in the placenta, establishing a positive feedback loop that allows for the simultaneous increase of CRH, ACTH, and cortisol over the course of gestation [Petraglia et al., 1996]. By this mechanism the effects of stress may be amplified during pregnancy and

thereby increase the synthesis and release of CRH. Consistent with previous studies we found that levels of maternal plasma CRH increase over the course of pregnancy, with the greatest increase occurring in the third trimester. Maternal plasma CRH during pregnancy is of placental, not hypothalamic origin. Hypothalamic contributions, even after extreme stress, are diluted after leaving the portal system and are not detectable in the peripheral circulation [King et al., 2001a].

During pregnancy CRH has been proposed to regulate a placental clock that initiates a cascade of events leading to parturition [Smith et al., 2003]. Significant elevations in CRH are associated with preterm delivery [Hobel et al., 1999; Holzman et al., 2001; McLean et al., 1995; Wadhwa et al., 1998, 2004; Sandman, 1998]. A precocious rise in CRH may signify a hostile environment [Denver, 1997] and precipitate a cascade of events that influences the fetal nervous system. A rodent model has demonstrated that prenatal treatment with CRH alters behavior in the offspring [Williams et al., 1995]. Furthermore, we have shown that elevated CRH during the prenatal period, in humans, is related to delayed habituation in the human fetus [Sandman et al., 1999].

The data presented here suggest that exposure of the human fetus to CRH affects infant temperament. Fetuses exposed to lower levels of maternal CRH at 25 weeks of gestation were rated by their mothers as exhibiting less fear and distress behavior in infancy. Importantly all infants in this study were born at term and thus, this finding is not related to the established consequences of preterm delivery. CRH levels at 19 and 33 weeks were not significantly associated with infant temperament indicating that there may be a critical period for observing programming influences of CRH on infant temperament. These data indicate that CRH may influence fetal CNS development and are consistent with the few existing studies showing that elevated CRH during the prenatal period is related to impairments in learning and behavior [Sandman et al., 1999; Williams et al., 1995].

Observational studies, such as this one, rely on naturally occurring variations in maternal hormones rather than experimental manipulations. Thus, the possibility that the association between CRH and infant temperament is due to other factors cannot be eliminated. Neither SES, based on annual household income, nor parity were related to infant temperament in this sample. Postnatal maternal anxiety and depression were associated with report of infant fear and distress behavior. However, after controlling for postpartum maternal psychological state the relation between placental CRH and infant temperament was not altered, supporting our conclusion that prenatal experiences were responsible for this association.

The mechanisms underlying the associations between placental CRH and fear and distress behaviors in infancy are unknown. One possible explanation is that CRH acts directly on regions of the brain that underlie these temperament characteristics. There is evidence that CRH may cross the adult blood-brain barrier [Kastin and Akerstrom, 2002]. Furthermore, the blood-brain barrier is immature during fetal development and thus it is more likely to be permeated by peptides such as CRH [Ohtsuki, 2004; Stonestreet et al., 2000]. Furthermore, CRH receptor mRNA is widely distributed in the brain [Wang et al., 2001] suggesting that the fetal nervous system is a plausible target for placental CRH. Limbic regions, including the amygdala, are rich in CRH receptors [Eghbal-Ahmadi et al., 1998; Schulkin, 1999] and intra-amygdala administration of CRH is anxiogenic [Dunn and Berridge, 1990]. Animal studies have shown that exposure to elevated CRH during critical periods of an organism's maturation influences the development of these regions [Avishai-Eliner et al., 2002]. Thus it is possible that the association between placental CRH and infant temperament may be due to effects of CRH on these limbic regions.

However, human studies, such as this one, cannot distinguish between direct effects of CRH on the fetal CNS and those effects that might result from the impact of CRH-induced release of ACTH and cortisol. Fetal hypothalamic and placental CRH stimulate fetal pituitary ACTH secretion, which controls adrenocortical functional development [Mastorakos and Ilias, 2003]. CRH could alter infant behavior through programming of the development of the fetal HPA axis and the ensuing effects of cortisol production. In support of this possibility, prenatal exposure to glucocorticoids leads to an increase in fearful or reactive behavior in the offspring [Ward et al., 2000; Welberg and Seckl, 2001]. Additionally, prenatal treatment with glucocorticoids increases CRH mRNA levels in the central nucleus of the amygdala, a key locus for the effects of the neuropeptide on the expression of fear and anxiety [Welberg et al., 2001].

In summary, these data suggest that there may be a sensitive period for the effect of placental CRH on infant temperament. The time course of development of CRH receptors in the CNS is unknown [Avishai-Eliner et al., 2002]. We found associations between CRH and infant temperament at 25 weeks of GA (the end of the 2nd trimester) but not at 19 or 33 weeks of GA, suggesting that this may be a period of vulnerability to exposure to ele-

vated levels of CRH. Several studies with human and nonhuman primates have suggested that the fetus is more susceptible to the effects of stress during the second trimester of pregnancy [DiPietro, 2004; Schneider, 1992]. Our findings support these observations and suggest that the second trimester may be a time when the fetus is vulnerable to the influences of stress signals such as CRH.

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