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Corticotropin-Releasing Hormone (CRH) Programs the Fetal and Maternal Brain

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Corticotropin-releasing hormone (CRH) is a 41-amino acid neuropeptide that is synthesized primarily in the paraventricular nucleus of the hypothalamus and has a major role in regulating pituitary-adrenal function and the physiological response to stress [1,2]. The hypothalamic-pituitary-adrenal (HPA) axis participates in a remarkable surveillance and response system which has evolved and is conserved, so that many species from the desert dwelling Western Spadefoot tadpole to the human fetus can detect threats to survival and adjust their developmental trajectory [3,4]. For instance, rapidly evaporating pools of desert water result in elevation of CRH in the pathway between the brain and the pituitary gland (median eminence) of the tadpole, initiating metamorphic climax to escape imminent peril [5,6]. If the CRH response is blocked during environmental desiccation, then the rate of development is arrested and the tadpole's survival is compromised. There are long-term consequences for the tadpole that survives this stressful challenge because its growth is stunted and it is at a disadvantage in competing with a normally developing toad foraging for food or reproducing.

Normally, as described for the tadpole, stress activates the expression of hypothalamic CRH which stimulates the cascade of events preparing the organism for “fight or flight”. The maternal HPA system is altered dramatically during human pregnancy because the placenta expresses the genes for CRH. Placental CRH (pCRH) increases several hundred-fold as pregnancy advances and reaches levels in the maternal circulation at term observed only in the hypothalamic portal system during physiological stress [7]. In contrast to the inhibitory influence of maternal stress signals (e.g. cortisol) on expression of the CRH gene in the hypothalamus, maternal cortisol activates the promoter region in the placenta and stimulates its synthesis [8,9]. This positive feedback system contains both a signal to the fetus (elevated cortisol) that the host environment (the mother) is threatened [10], and a measurable response from the fetus (increased pCRH production). The rapid increase in pCRH that is stimulated by stress signals from the mother begins a cascade of events resulting in myometrial activation and in extreme cases, premature birth [11]. Human infants born early suffer a similar fate as the tadpole including a panoply of motor, sensory and neurological impairments that persist for a lifetime [12,13].

There are well-established neurological consequences associated with preterm birth, however it is the intrauterine conditions that determine the birth phenotype and alter the developmental trajectory. The fetus whether born early or at term, participates in its own development by incorporating messages about the nature of the maternal and intrauterine milieu and adapting its developmental program to prepare for postnatal survival. In addition to the growing acceptance that a significant proportion of variation in infant and adult health outcomes and disease risk is attributable to developmental processes during fetal life in response to a variety of environmental, social, psychological, physiological and genetic influences, there is newer information that the host, the mother, also is programmed by the processes specific and unique to pregnancy.

FETAL PROGRAMMING

The human fetus expresses an estimated eight-fold more cell divisions before term compared with the remainder of life [14]. Between 8 and 16 weeks of gestation, migrating neurons form the subplate zone, awaiting connections from afferent neurons originating in the thalamus, basal forebrain, and brainstem. Concurrently, cells accumulating in the outer cerebral wall form the cortical plate which eventually will become the cerebral cortex. By week twenty of gestation, axons form synapses with the cortical plate. This process continues so that by 24 weeks cortical circuits are organized. The enormous growth of the human fetal nervous system is characterized by the proliferation of neurons estimated to increase at a rate of 250,000 per minute [15]. The rate of synaptogenesis reaches an astonishing peak so that by week 34 there is an increase of 40,000 synapses per second [16]. Because of these changes, the human fetus is particularly vulnerable both to organizing and disorganizing influences which have been described as “programming” [17].

Programming is a process by which a stimulus or insult during a critical developmental period has a long-lasting or permanent influence. Tissues develop in a specific developmental sequence and different organs are sensitive to programming influences at different times depending upon their rate of cell division. Thus, the timing of the stimulus during development coupled with the time-table for organogenesis, determine the nature of the programmed effect. Fetuses exposed to maternal stress signals at various times during gestation are at subsequent risk for later cardiovascular disease, hypertension, hyperlipidemia, insulin resistance, non-insulin dependent diabetes mellitus, obesity, serum cholesterol concentrations, shortened life span, and other poor health outcomes [14,18,19,20,21]. Research from our group [10,22-29] indicates that a primary pathway of the effects of stress on the human fetus is the HPA stress axis.

Our program of research has explored the influences of maternal psychosocial stress and maternal stress hormones on human development beginning with neurological effects on the fetus. In a recent study [30], we reported that at 25 weeks' gestation, fetuses who had been exposed earlier in gestation to low (optimal) levels of pCRH exhibited enhanced neurological maturity in response to stimulation. Previously we reported that fetuses of women with elevated CRH during the third trimester were less responsive to the presence of a novel stimulus [31]. In a third study we reported that fetuses in maternal environments with high levels of stress hormones from the maternal pituitary (not the placenta) also were less sensitive to environmental stimulation [25]. These findings suggest that a stress-sensitive system controlled by the maternal central nervous system exerts an influence on fetal neurological maturity.

Our prospective studies of the newborn and developing infant further supported the role of pCRH in fetal programming. In a sample of 158 newborns, increased levels of CRH at 31 gestational weeks were associated with decreased physical and neuromuscular maturity [32]. Delayed newborn neuromuscular development has been associated with impaired newborn brain development and abnormalities in motor development that persist at least until age four. In addition to affects on physical and neuromuscular development, effects of exposure to the pCRH appear to extend to infant temperament. We reported that infants exposed to lower (optimal) levels of CRH at 25 weeks of gestation exhibited less fearful behavior at two months of age [33]. These findings are congruent with our results for the fetus, strongly suggesting that pCRH exerts persisting influences on the developing nervous system independent from the effects of preterm birth. We are actively following our cohort of children as they age with brain imaging and behavioral measures of cognition, temperament and social development (HD-51852).

MATERNAL PROGRAMMING

The dramatic maternal endocrine alterations that accompany pregnancy have implications not only for the maintenance of gestation, optimal fetal development and successful parturition, but also have implications for the maternal brain and behavior, a process we refer to as maternal programming [34-36]. Little is known about the influence of prenatal hormone exposures on the human maternal brain, with some evidence indicating a role for gonadal and adrenal hormones in determining the quality of postnatal maternal care [37,38]. However, even less is known about the possible role of pCRH. In the non-pregnant state, CRH is believed to play a role in the etiology of depression. Depressed individuals have an increased number and hypersensitivity of CRH neurons in the paraventricular nucleus of the hypothalamus [39,40]. Because of the dramatic increase in pCRH during pregnancy and the link between CRH and depression, our group has examined the possible risk pCRH may present for post-partum depression (PPD). In a cohort of 100 women followed prospectively five times beginning early in pregnancy, elevations in pCRH at 25 weeks' gestation, but not earlier or later, were associated with an increased risk of developing symptoms of PPD. Specifically, pCRH levels of at 25 weeks' accurately identified 75% of women who subsequently would develop PPD symptoms [41]. These findings add new support to the small but emerging literature indicating that the maternal brain is susceptible to changes associated with normal human pregnancy. Moreover, this new finding has important clinical implications suggesting that mid-gestation pCRH may be a possible diagnostic tool to identify women who are at risk for PPD.

Taken together, these studies indicate that the mother and her fetus are each susceptible to adverse consequences because of exposure to elevated pCRH. The finding that fetal and maternal programming may occur in parallel raises interesting possibilities related to long-term consequences. One possibility is that infants/children who are products of pregnancies characterized by elevations in pCRH may be subjected to double biological jeopardy. Fetuses that have had their development compromised by exposures to elevated pCRH, also are at increased risk for receiving parenting from a depressed mother. Thus, the infant who is already at risk for adverse developmental outcomes, and who has the greatest need of competent mothering, is most likely to receive compromised quality of maternal care. A second and perhaps more intriguing possibility, involves the adaptive significance of fetal programming. Just as the tadpole adjusts its development to maximize its chances of survival in a hostile environment, the human fetus may adjust its development in response to prenatal maternal stress signals in anticipation of a hostile or non-nurturing postnatal environment. The fetus that is stressed in utero and adjusts its development accordingly to prepare for a hostile environment, may cope better in the presence of lower quality of maternal care than the fetus that was not exposed to prenatal stress signals and did not make this anticipatory adjustment to its trajectory. Consideration of these possibilities in determining health and well-being are not currently part of a comprehensive medical history, but because of the growing acceptance of the fetal origins of disease and the new results related to maternal programming, these factors will become an expected component of patient care.

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