The Influence of Corticotropin-Releasing Hormone on Human Fetal Development and Parturition

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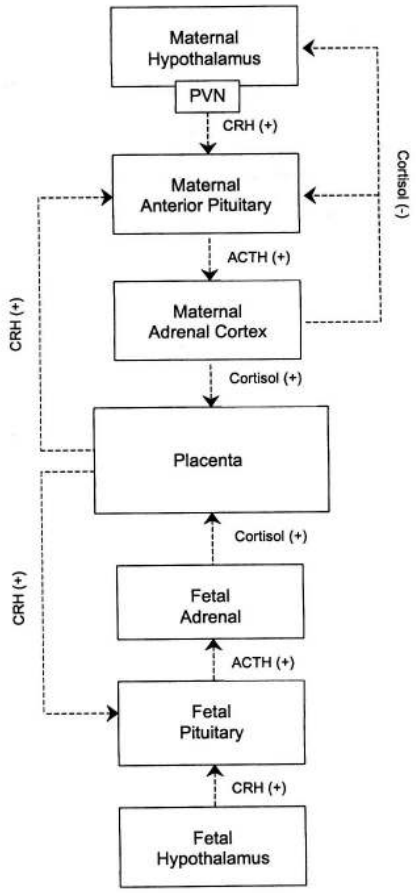
Full Text: Headnote ABSTRACT: Hypothalamic corticotropin-releasing hormone (CRH) is a neuropeptide that has a central role in responses to stress. During pregnancy, CRH also is synthesized by the placenta. This paper focuses on the effects of placental CRH on two outcomes: timing of onset of parturition and fetal development. It appears that premature elevation of placental CRH during pregnancy may contribute to shorter gestational lengths. Also, CRH may affect fetal development. Our data show that the fetuses of women with CRH concentrations exceeding the normal range show different responses to stimulation than fetuses of women with concentrations in the normal range. This finding is consistent with other work demonstrating the importance of the intrauterine environment in long-term health and development. Corticotropin-releasing hormone (CRH) is a neuropeptide, first discovered in the paraventricular nucleus of the hypothalamus (Vale, Spiess, Rivier, &Rivier, 1981), that plays a central role in regulating the hypothalamic-pituitary-adrenal axis and responses to stress (Chrousos, 1992). Stress activates the expression of hypothalamic CRH, which stimulates the anterior pituitary and precipitates the release of adrenocorticotropic hormone (ACTH) and beta endorphin. The release of ACTH, in turn, stimulates the adrenal cortex increasing synthesis and release of cortisol, resulting in an energy redistribution and preparing the organism for the "fight or flight" response. In addition, these increased levels of cortisol down regulate the brain and pituitary, by negative control, inhibiting the synthesis and release of CRH and ACTH (See Figure 1). Pregnancy is characterized by dramatic physiological changes including the development of the placenta, an organ of fetal origin that is a source of extrahypothalamic CRH. Starting at the seventh to eighth week of gestation the placenta begins to synthesize and release CRH into the maternal and fetal compartments (Challis, Matthews, Van Meir, &Ramirez, 1995; Petraglia, Florio, Nappi, &Genazzani, 1996) and as a result, maternal plasma CRH concentrations reach levels observed in the brain only during physiological stress (Lowry, 1993). Placental CRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity (Petraglia, et al., 1996). However, there is one crucial difference in the regulation of hypothalamic and placental CRH (See Figure 1). In contrast to the negative control on hypothalamic CRH, glucocorticoids stimulate the production of placental CRH, establishing a positive feedback loop that allows for the simultaneous increase of CRH, ACTH, and cortisol over the course of gestation (Petraglia, Florio, Nappi, &Genazzani, 1996; Robinson, Emanuel, Frim, &Majzoub, 1988)1. We believe that increases in CRH concentration may play two important roles in pregnancy: One involving the timing of onset of spontaneous delivery and the other involving fetal brain and organ development. Our program of research has focused on both of these aspects of the influence of placental CRH during pregnancy. We have examined the association between CRH and the timing parturition and the influences of CRH on fetal behavior. The Role of CRH in the Timing of Onset of Parturition McLean and colleagues introduced the concept of a placental clock that plays a role in controlling the timing of birth (McLean et al., 1995). In a groundbreaking paper the authors report that rising levels of CRH serve as a marker of the progress of this clock, and that as early as sixteen to twenty weeks into human pregnancy, these levels may predict the length of gestation. Specifically, their data demonstrate that higher-than-normal levels of CRH are associated with a shorter gestation, while lower-than-normal levels are associated with a longer gestation. Subsequent research, including our own, has replicated and expanded this finding, reinforcing the important role of CRH in the timing of parturition (McLean, et al. 1999; Wadhwa, Porto, Garite, Chicz-DeMet, &Sandman, 1998). We and others now believe that CRH is not only a marker of the placental clock, but a critical part of the process of parturition. CRH may act both through

paracrine and endocrine mechanisms, affecting prostaglandin in the myometrium and stimulating the fetal HPA axis to produce the DHEA sulfate, a substance necessary for estrogen synthesis (Challis, Patel, &Pomini, 1999; Karalis, Goodwin, &Majzoub, 1996; Smith, R., Mesiano, Chan, Brown, &Jaffe, 1998; Smith, R., Wickings, Bowman, Belleoud, Dubreuil, Davies &Madsen, 1999; Stevens, Challis &Lye, 1998).



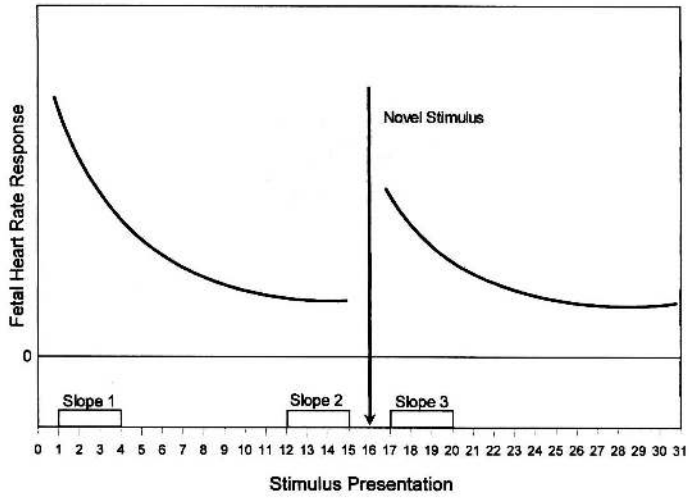
The Role of CRH in Development The effects of CRH on human fetal development are poorly understood. However, there exists evidence from other species that exposure to CRH can dramatically alter development. For example, high levels of CRH administered to pregnant rats result in offspring that exhibit developmental anomalies as infants, including the inability to respond normally to environmental challenge (Williams, Hennessey, &Davis, 1995). There also is evidence that CRH determines the rate of metamorphosis in tadpoles (Denver, 1997). CRH could affect human fetal brain development either directly or indirectly. A direct influence of CRH is plausible because there is rich expression of CRH receptors in parahippocampal and limbic areas during mid to late gestation (Wong, Licinio, Pasternak, &Gold, 1994). Moreover, the immature nervous system is especially sensitive to CRH. For instance, selective death of CA3 pyramidal cells in the parahippocampal regions occurs in the immature, but not the mature, nervous system after exposure to high levels of CRH (Baram &Ribak, 1995; Ribak &Baram, 1996). Thus, one possible avenue for the effects of CRH on development is that areas of the fetal brain rich in CRH receptors are directly affected by higher-than-normal levels of placental CRH during critical periods of development, and this exposure is neurotoxic. However, there is also support for the possibility that the influence of CRH on the fetal nervous system is mediated by cortisol. In primate fetuses at mid-gestation, CRH is capable of stimulating fetal glucocorticoid secretion (Berghorn, Albrecht, &Pepe, 1991; Smith, R., et al., 1998). Further, considerable evidence indicates that elevated levels of glucocorticoids also are neurotoxic to hippocampal CA3 pyramidal cells (Margarines, McEwen, Flugge, &Fuchs, 1996; Sapolsky, Krey, &McEwen, 1985; Sapolsky, Uno, Rebert, &Finch, 1990), and fetal exposure to high levels of glucocorticoids produces irreversible damage to the hippocampal area (Uno, et al., 1994). Thus, it could also

be that elevations in placental CRH influence the fetal nervous system indirectly, by stimulating the release of glucocorticoids. The Study of Human Fetal Behavior Scientific debate concerning whether or not the human fetus could perceive sound began in the late 1800's. However, it was not until the mid-1980's that this issue was fully resolved (for a review, see Kisilevsky &Low, 1998). We now know that fetuses do in fact detect and respond to ex utero stimulation. Fetal arousal in response to external stimulation has been observed by 22 weeks (Leader, Stevens, &Lumbers, 1988) and can be elicited reliably by 30 weeks in normal development (Gagnon, Hunse, &Patrick, 1988). The habituation paradigm is a sophisticated method of studying the fetal response to stimulation and is a measure of fetal cognition. Habituation is the response decrement following repeated exposure to a stimulus (typically with the human fetus, the stimulus is acoustic or vibroacoustic and the response is heart rate or movement). Properly tested, habituation is evidence of learning and a reflection of higher central nervous system (CNS) integrity (Sokolov, 1963). It requires that an organism detect and respond to information and then systematically ignore and cease responding to subsequent, identical information. The fetus, to accomplish this, must compare contemporary information from the recent past by forming a representation, or memory, of the stimulus. Several studies have evaluated habituation to external stimuli during fetal development (Kisilevski &Muir, 1991; Leader, 1994; Madison, et al., 1986; Madison, Madison, &Adubato, 1986; Shahidulah &Hepper, 1994; Shalev, Weiner, &Serr, 1990) and it has been shown that the rate of habituation increases with development (Shalev, Bennett, Megory, Wallace, &Zuckerman, 1989). Few studies of the fetus have determined whether the observed response decrement to repeated stimulation can be attributed to habituation, which is a process of the CNS, or receptor fatigue, a peripheral process. The dishabituation paradigm employs one of the few behavioral controls for distinguishing between response decrements resulting from sensory adaptation and fatigue and the contribution of the CNS (Graham, Anthony, &Zeigler, 1983; Thompson &Spencer, 1966; Tighe &Leaton, 1976). Dishabituation is the reemergence of a previously habituated response (Mackintosh, 1987; Thompson, Groves, Teyler, &Roemer, 1973). This reemergence is typically elicited by the sensitizing or arousing effects of a novel stimulus or an altered context. Novelty is presumed to increase the level of arousal and potentiate the weak, habituated response (Mackintosh, 1987). Our Fetal Habituation Paradigm Eighty-three women with a singleton pregnancy in the 31st and 32nd week of gestation were tested. Transabdominal transducers were attached for measuring fetal heart rate (FHR). Vibroacoustic stimuli (VAS) were presented during a 45-minute testing period while the mother listened to pure tone music presented through headphones to mask the auditory stimulus (see Figure 2). The first 15 VAS (S1; 63 db, 300 Hz) were presented for two seconds on the mother's abdomen over the area of the fetal head (determined by ultrasonography) with pseudorandom intervals between trials of 20-45 seconds. On the 16th trial, a novel VA stimulus (S2; 68 db, 400 Hz) was presented, differing from S1in intensity and frequency. The second series of trials (17-31) repeated the S1 series with a different pseudorandom arrangement. Fetal heart rate was estimated by auto-correlation over 3-second epochs providing the beat-to-beat rate. The average FHR of the 5second interval before each stimulus was used as the prestimulus value for each trial and subtracted from the average value during the trial to isolate the specific influence of successive stimulation from changing baseline levels (Kisilevsky &Muir, 1991; Sandman, Wadhwa, Hetrick, Porto, &Peeke, 1997). Fetal Habituation Pattern Overall the data suggest that the fetuses did habituate to S1. The first VA stimulus elicited an average FHR increase of 8 bpm. The initial increase was followed by a decrement in FHR with successive presentations of S1. This decrement is reflected in an average slope of -1.33 over the first four trials (Slope 1; See Table 1). We can assess dishabituation by comparing FHR responses immediately before (Slope 2) and after (Slope 3) the presentation of the novel stimulus (see Figure 2). If the presentation of the novel stimulus did not affect responding, then there should not be a difference between the two slopes. Conversely, if the dishabituating stimulus did affect responding, then there should be a difference in the slopes. Slope 2 was statistically different from Slope 3 suggesting that dishabituation did occur (See Table 1). Further, Slope 1 was not statistically different from Slope 3 indicating that the initial response to SI was similar to the response to the second series

of SI presentations following the novel stimulus. Last, Slope 1 did differ from Slope 2, again a pattern consistent with habituation. Viewed together, these data suggest that the human fetus exhibits a response decrement to repeated stimulation that can be attributed to habituation and not to sensory adaptation or fatigue.

Figure 2

An Example of a Normal Fetal Heart Rate Habituation Response to Stimulation.



Note: S1 Is Presented for Trials 1–15. Slope 1 (First Four Presentations of S1) Is Negative Reflecting the Response Decrement. Slope 2 Represents the End of the First Series of S1 Presentations (trials 12–15). It Is Relatively Flat and the Heart Rate is Close to the Prestimulus Baseline Indicating that the Fetus Is No Longer responding to S1. Following the Presentation of the Novel Stimulus (S2) on Trial 16, the Response to S1 Reemerges (Dishabituation) and Is Reflected in the Increase in FHR and a Negative Value for Slope 3 (Trials 17–20).

Table 1
Means and standard errors for FHR slopes

	M	*SEM*	*Comparison*
Slope 1	−1.333	.394	Slope 2 ($p < .001$)
			Slope 3 ($p < .12$)
Slope 2	0.828	.336	Slope 3 ($p < .01$)
Slope 3	−0.423	.356	

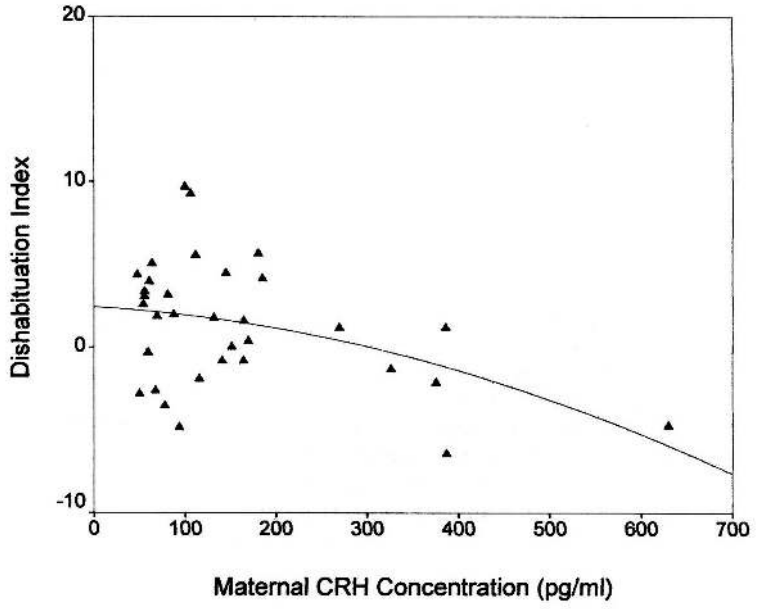
Note: Slope 1 = rate of FHR change for trials 1–4, Slope 2 = rate of FHR change for trials 12–15 (period immediately before the presentation of the novel stimulus), Slope 3 = rate of FHR change for trials 17–20 (period immediately following presentation of the novel stimulus). Adapted from "Human Fetal Heart Rate Dishabituation Between Thirty and Thirty-two Weeks Gestation," by C.A. Sandman, P. Wadhwa, W. Hetrick, M. Porto, & H.V.S. Peeke, 1997. *Child Development, 68,* p. 1036.

CRH and Habituation For a subset of individuals (N = 33) we examined the effects of maternal CRH concentrations on dishabituation (for a discussion of the collection and assay of CRH, see Wadhwa, et al., 1998). We measured dishabituation with an index (Slope 2-Slope 3) for which a positive value is consistent with a normal habituation pattern (Sandman, Wadhwa, Chicz-DeMet, Porto, &Garite, 1999). Figure 3 shows the relationship between CRH concentrations and the dishabituation index (r^sub quad^ = .42, p <.05). None of the positive values for the index (those consistent with habituation) are found among the fetuses of mothers who had CRH concentrations that exceeded the normal range (CRH >200 pg/ml). Only those fetuses who had been exposed to maternal CRH concentrations in the normal range had an index score that indicated a typical

habituation pattern. These data are consistent with the notion that exposure to CRH affects fetal responding to stimuli.

Figure 3

The Relation Between the Dishabituation Index and Maternal CRH concentrations.



Note: Adapted from "Maternal Corticotropin-Releasing Hormone and Habituation in the Human Fetus," by C.A. Sandman, P. Wadhwa, A. Chicz-DeMet, M. Porto, & T.J. Garite, 1999. *Developmental Psychobiology, 34,* p. 167.

The Influence of the Maternal Environment Even in the absence of environmental perturbations, maternal/placental stress hormones appear to affect fetal development and the timing of delivery. However, we also believe that exposure to stressors in the maternal environment may alter the rate of increase in CRH during pregnancy, affecting timing of delivery and perhaps fetal development (Glynn, Wadhwa, Dunkel-Schetter, Chicz-DeMet, Sandman, 2000). In humans, there is some evidence that placental CRH is related to stress. For example, during pregnancy, maternal psychosocial factors such as stress and social support influence maternal pituitaryadrenal stress hormones that may regulate placental CRH (Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto, &Sandman, 1996; Wadhwa, Sandman, Chicz-DeMet, &Porto, 1997). In addition, one study has shown a relation between maternal stress at mid-gestation and amount of placental CRH production from mid to late gestation (Hobel, Dunkel-Schetter, Roesch, Castro, &Arora, 1999). While there is no direct evidence in humans suggesting that CRH mediates the effects of environmental stress on development, there is one striking example from the non-human literature suggesting that this may be the case. Tadpoles, when stressed by habitat dessication, respond by accelerating metamorphosis. In an elegant series of studies, Denver (1997) has shown that this acceleration can be attributed to CRH. Western spadefoot toad tadpoles injected with CRH-like substances exhibited accelerated metamorphosis. Further, when subjected to habitat dessication tadpoles treated with a CRH antagonist failed to show the expected increase in metamorphosis rate. Thus, it appears that in the case of the tadpole, CRH transmits environmental stress affecting the rate of development. It seems plausible that CRH plays a similar role in humans and other mammals. Stress in the maternal environment might result in increases in CRH concentrations. These increases in CRH might speed development or time to parturition (or both) and thus facilitate the fetus's escape from an unfavorable environment2. The Importance of the Intrauterine Environment on Development Our work on CRH and fetal development provides one plausible

mechanism through which the prenatal environment might influence postnatal outcomes. The influence of the prenatal and early environment has received increasing attention and has proved to be an important source of variance in developmental and health outcomes. For example, the work of Barker (1998) provides convincing evidence that morbidity in humans, specifically risk of cardiovascular disease and stroke, can be programmed early in life by prenatal development and early childhood events. Francis, Diorio, Liu, and Meaney (1999) have shown that the functioning of the hypothalamic-pituitary-adrenal axis in the rat can be nongenomically transmitted across generations through early maternal care. Those offspring who receive less care from their mothers show different endocrine responses to stress than those who receive more care. Research comparing monozygotic twins that share a single placenta with those that have separate placentas provides another source of compelling evidence for the substantial and long-lasting influence of the prenatal environment. This work shows higher rates of concordance for a wide range of outcomes, including IQ, personality, schizophrenia, and cholesterol, for monochorionic monozygotic twins than for dichorionic monozygotic twins (for a review, see Phelps, Davis, &Schartz, 1997). Viewed together this work strongly suggests that the prenatal and early environment is a powerful contributor to long term health and development and highlights the need for future research to fully characterize intrauterine and early developmental influences. Footnote 1 Within the brain, the production of CRH in both the central nucleus of the amygdala and the lateral bed nucleus of the stria terminalis, like the placenta, are also under positive control of glucocorticoids (Makino, Gold &Schulkin, 1994a, 1994b). 2 For both the human and the tadpole, escape from an unfavorable environment through acceleration of parturition or metamorphosis, respectively, may be adaptive in the short term, but may also be associated with long-term costs. Premature birth in humans is associated with morbidity, mortality and developmental disabilities (Knoches &Doyle, 1993; Robison &Gonzalez, 1999). Similarly, accelerated metamorphosis in tadpoles is associated with smaller body size at emergence which is correlated with reduced adult fitness in areas such as age at first reproduction and jumping ability (Denver, 1997, John-Alder &Morin, 1990; Newman, 1989; Smith, D.C., 1987). References REFERENCES Baram, T.Z., &Ribak, C.E. (1995). Peptide-induced infant status epilepticus causes neuronal death and synaptic reorganization. Neuroreport, 26, 277-280. Barker, D.J.P. (1998). Mothers, Babies and Health in Later Life. Edinburgh: Churchill Livingstone. Berghorn, K.A., Albrecht, E.D., &Pepe, G.J. (1991) Responsivity of the baboon fetal pituitary to corticotropin-releasing hormone in utero at midgestation. Endocrinology, 129, 1424-1428. Challis, J.R., Matthews, S.G., Van Meir, C., &Ramirez, M.M. (1995). Current topic: The placental corticotrophin-releasing hormone-adrenocorticotropin axis. Placenta, 16, 481-502. Challis, J.R., Patel, F.A., &Pomini, F. (1999). Prostaglandin dehydrogenase and the initiation of labor. Journal of Perinatal Medicine, 27, 26-34. Chrousos, G.P. (1992). Regulation and dysregulation of the hypothalamic-pituitary-adrenal axis: The corticotropin-releasing hormone perspective. Endocrinology &Metabolism Clinics of North America, 21, 833-58. Denver, R.J. (1997). Environmental stress as a developmental cue: Corticotropin-releasing hormone is a proximate mediator of adaptive phenotypic plasticity in amphibian metamorphosis. Hormones and Behavior, 31, 169-179. Francis, D., Diorio, J., Liu, D., &Meaney, M.J. (1999). Nongenonmic transmission across generations of maternal behavior and stress responses hi the rat. Science, 286, 1155-1158. Gagnon, R., Hunse, C., &Patrick, J. (1998). Fetal responses to vibratory acoustic stimulation: Influence of basal heart rate. American Journal of Obstetrics and Gynecology, 158, 75-79. Glynn, L.M., Wadhwa, P.D., Dunkel-Schetter, C., Chicz-DeMet, A., &Sandman, C.A. (2000). When stress happens matters: Effects of earthquake timing on stress responsivity in pregnancy. Manuscript submitted for publication. Graham, F.K., Anthony, B.J., &Zeigler, B.L., (1983). The orienting response and developmental processes. In D, Siddle (Ed.), Perspectives in Human Research (pp. 371-430). New York: Wiley. Hobel, C.J., Dunkel-Schetter, C., Roesch, S.C., Castro, L.C., and Arora, C.P. (1999). Maternal plasma corticotropin-releasing hormone associated with stress at 20 weeks' gestation in pregnancies ending in preterm delivery. American Journal of Obstetrics and Gynecohgy, 180, S257-263. John-Alder, H.B., &Morin, P.J. (1990). Effects of larval density on jumping ability and stamina in newly metamorphosed Bufo-Woodhousi-fowleri. Copeia, 1990, 856-

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