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The plastic fetal pituitary

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A chronically adverse intrauterine environment can foster a fetal hypercortisolemia that persists after stressful conditions are removed and well after a transient, stress-associated elevation in adrenocorticotrophic hormone (ACTH) has passed (1,2). This observation, among others, strongly suggests that chronic intrauterine stress can reprogram the fetal hypothalamo-pituitary-adrenal (HPA) axis. As Butler and colleagues show in this issue of the *JCI* (3), the development of a phenotypically novel cellular subpopulation within the pituitary may explain, at least in part, this profound and long-lasting change in the endocrine environment. Butler et al. demonstrate here that the fetal ovine pituitary possesses a developmental malleability that allows a remodeling of its corticotroph population. The particular alterations seen depend upon the stage of fetal life during which stressful stimuli are experienced, but some persist late into gestation and may well be permanent.

Imposing intrauterine stress

The ovine embryo can be subjected to reduced vascular perfusion and substrate deprivation by being allowed to develop within a uterus that has been antenatally carunclectomized, or surgically nearly depleted of its possible placental attachment sites. Fetuses that cannot compensate through placental hypertrophy will ultimately experience varying degrees of chronic metabolic disease including hypoxemia, hypoglycemia, and acidemia (4).

Butler and colleagues report here on the independent and combined effects on fetal corticotroph development of maternal carunclectomy itself and chronic hypoxemia of late gestation. Perhaps their most remarkable finding relates to the developmental plasticity of the normal ovine pituitary, as judged by the development of corticotrophin-releasing hormone–responsiveness (CRH-responsiveness) in vitro. CRH is a 41 amino acid hypothalamic peptide that acts as the central regulator of the body's response to stress. By binding to specific receptors (CRHR1, CRHR2) on pituitary corticotrophs, it facilitates the release of ACTH, which, in turn, stimulates adrenal corticosteroid production. Butler et al. observed that cultured fetal ovine pituicytes that have been subjected to toxic ablation of all CRH-receptor positive cells can nevertheless regain CRH responsiveness, suggesting that the fetal pituitary contains multipotential precursor cells capable of differentiation late into gestation. In addition, the authors found that a new population of fetal pituitary corticotrophs emerges in ovine fetuses subjected to the aberrant intrauterine environment produced by carunclectomy. These unique corticotrophs, which were unresponsive to CRH and have a relatively high constitutive secretion of ACTH, developed whether or not hypoxemia eventually occurred, suggesting that an early insult associated with carunclectomy sufficed to redirect corticotroph ontogeny. Unlike the cells that emerged in cultures from non-carunclectomized fetuses, these corticotrophs could not restore CRH sensitivity after the ablation of CRH-responsive cells. Hence, it appears that very early intrauterine stress can trigger a cascade of terminal differentiation that limits the developmental plasticity of the pituitary, precluding the alterations seen in response to later insults.

In the present study, fetal ovine chronic hypoxemia was associated with diminished ACTH synthesis within the CRH-responsive ovine corticotrophs. It should be noted that the level of hypoxemia in the fetuses studied was insufficient to induce hypoglycemia or acidemia, so the decrease in ACTH synthesis probably cannot be attributed to concurrent metabolic disease. The observation that peripheral ACTH levels were unaffected is consistent with previous work in which arginine vasopressin–responsive (AVP-responsive) corticotrophs were found to be responsible for the majority of baseline ACTH secretion, while CRH-responsive corticotrophs were responsible for ACTH release in response to an acute superimposed stress (5).

Fetal HPA activation and parturition

A hallmark of the normal maturation of the fetal neuroendocrine system is a heightened activity of the fetal HPA which occurs in late gestation. HPA development is associated with increased levels of ACTH and cortisol in the fetal circulation and increased expression of CRH mRNA in the hypothalamus (6). The placenta secretes a significant amount of CRH in late gestation (7), and the overall maternal bioavailability of this hormone at term is further increased by a simultaneous drop of its neutralizing binding

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Nonstandard abbreviations used: adrenocorticotrophic hormone (ACTH); hypothalamo-pituitary-adrenal (HPA); corticotrophin-releasing hormone (CRH); arginine vasopressin (AVP); glucocorticoid receptor (GR).

protein, CRH-BP (8). CRH secretion by placental trophoblast cells is paradoxically increased by glucocorticoids, as well as by prostaglandins, cytokines, and catecholamines, and is decreased by nitric oxide and progesterone. It has been suggested that the inhibitory effect of progesterone upon myometrial activity is exerted through binding to the glucocorticoid receptor (GR) in trophoblast cells. At term, the newly abundant cortisol may displace progesterone bound to GR. In addition to its potential as a predictor of gestational length (9), CRH itself may modulate myometrial contractility in a manner depending upon the affinity and second messenger of its receptor subtypes (10, 11).

Fetal cortisol: more is not necessarily better

Cortisol contributes to the maturation of organ systems required for extrauterine survival. However, excessive levels, derived either from maternal administration of synthetic corticosteroids or sustained endogenous fetal cortisol production, compromise cellular proliferation, resulting in intrauterine growth retardation and an increased risk for future metabolic disease (12–16). Fetuses exposed to maternal betamethasone in late gestation demonstrate hypertension, insulin resistance, and exaggerated adrenal responsiveness within six months of birth (17, 18). Among babies born at term, low birth weight predicts cardiovascular risk factors and disease in adulthood. In addition, babies born prematurely, whether or not they have intrauterine growth retardation, are similarly predisposed (19). This suggests that there is a critical window of susceptibility late in fetal development during which time a stress — whether it be in utero as with chronic hypoxemia or ex utero after a pre-term delivery — can reprogram the fetus in a manner predisposing it to the "metabolic syndrome" of hypertension, hyperglycemia, and insulin resistance. Understanding the negative potential of glucocorticoids administered prenatally, obstetricians are using them with increasing restraint, carefully weighing the benefits of their maturational effects against possible long-term cardiovascular sequela (20).

Plasticity of the HPA in the fetus and beyond

As Butler et al. have found, the CRH-responsive corticotrophs of stressed fetuses that subsequently become chronically hypoxemic fail to manufacture normal levels of ACTH. Hence, the ability to develop a new host of corticotrophs that constitutively secrete large amounts of ACTH in response to an early intrauterine stress is a seemingly beneficial adaptation, allowing for heightened glucocorticoid production in fetuses that would otherwise be incapable of stimulating the required biosynthetic pathways. Although, the hypoxemic fetuses in Butler's study did on average manifest higher cortisol levels than the non-hypoxemic fetuses, a carunclectomized environment exerted no independent positive effect upon cortisol levels. Therefore, the corticotroph subpopulation engendered by carunclectomy does not seem necessary to mount a hypercortisolemic response against later hypoxemia. Since cortisol was only measured late in gestation, it is unknown whether these novel corticotrophs enhanced cortisol secretion at an earlier time point in fetuses within a carunclectomized environment. As Butler and colleagues have not explored the longer-term sequela of these changes in their sheep model, the significance of these novel corticotrophs remains to be elucidated.

The work of Butler and colleagues demonstrates that early suboptimal intrauterine conditions can permanently alter the cohort of anterior pituitary corticotrophs, irrespective of whether chronic fetal hypoxemia ensues. Further work is needed to clarify whether these particular changes prove detrimental to the adult. Indeed, a more thorough understanding of the nature, mechanisms, and sequela of intrauterine stress is needed to optimize the antepartum treatment of maternal-fetal disease.

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