Roles of the placenta in fetal brain development

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Following on the seminal observations of Barker and associates (1), maternal hormonal and nutrient environment has been systematically implicated in effects on the developing fetus that ultimately influence susceptibility to a wide range of metabolic, neurodevelopmental, and psychiatric diseases in adulthood (2, 3). There is a growing appreciation that perturbations in the maternal environment are conveyed to the fetus by changes in placental function (4). Two recent studies have identified functions of the murine placenta as the interface between the maternal environment and the developing CNS (5, 6). In response to acute maternal food deprivation, Broad and Keverne (5) find that a program of catabolic gene expression is initiated in the placenta, whereas the hypothalamus is largely spared. These observations raise the possibility that, in circumstances of reduced maternal nutrient availability, the placenta itself may be catabolized to provide critical fuel and structural molecules to the developing hypothalamus. Levitt and collaborators (6) used a novel ex vivo preparation to demonstrate that the placenta can convert maternal tryptophan into the neurotransmitter serotonin (5-hydroxytryptophan; 5-HT), providing the primary source of 5-HT for the developing mouse forebrain at midgestation. Together these studies suggest that the traditional view of the placenta as a passive site of transport of maternal nutrients, growth factors, and hormones needs to be expanded to include a role in supporting CNS development through adaptive responses to the maternal environment.

Fetal Consequences of Perturbations in Maternal Metabolism

Studies of long-term outcomes in offspring exposed to maternal undernutrition and stress caused by the Dutch Hunger Winter of 1944 to 1945 revealed an increased prevalence of metabolic diseases, such as glucose intolerance, obesity, and cardiovascular disease, as well as emotional and psychiatric disorders (7, 8). Animal models have been developed to assess the long-term consequences of a variety of maternal challenges, including under- and overnutrition, hyperglycemia, chronic stress, and inflammation. Exposures to a wide range of insults during gestation are associated with convergent effects on fetal growth, neurodevelopment, and metabolism. Maternal undernutrition and stress are associated with reduced fetal growth (9). Low birth weight, particularly when compensated by early catch-up growth, is linked to increased prevalence of metabolic diseases, such as obesity and diabetes, as well as affective and neurodevelopmental disorders (1–3). On the other end of the spectrum, maternal factors that lead to increased fetal growth, such as high-fat diet, diabetes, and proinflammatory cytokines, have also been associated with increased prevalence of insulin resistance and/or hypertension in offspring (2, 10).

Broad and Keverne propose a mechanism for placental adaptations to adverse maternal environments.

Maternal perturbations are conveyed to the fetus via the placenta, most notably in the expression of transporters that regulate the flux of glucose, amino acids, vitamins, and ions required for growth and development (4, 11). Hormonal signals of maternal status, including glucocorticoids, insulin-like growth factors (IGFs), insulin, and leptin, are sensed by the placenta and transmitted to the fetus predominantly through effects on placental function. For example, maternal undernutrition reduces placental 11-β-hydroxysteroid dehydrogenase activity, which normally acts to buffer the fetus from maternal glucocorticoids, leading to intrauterine growth restriction and subsequent development of insulin resistance and high blood pressure (2). IGF-1 and -2 are produced in maternal, placental, and fetal tissues, and their expression is affected by nutrient availability, glucocorticoids, insulin, and thyroid hormone (11). Interactions between IGF signals from these tissues likely play a critical role in ensuring that placental function and fetal growth are congruent with the maternal environment. The observation that maternal nutrient and hormonal signals appear to converge on similar sets of placental genes that regulate the flux of nutrients to the fetus (11) could contribute to similarities in fetal outcomes resulting from different maternal challenges.

In addition to affecting fetal growth, maternal nutrient status has also been reported to directly influence neuronal development during gestation. Maternal high-fat diet affects neuropeptide expression in offspring brain regions that control energy homeostasis and affective states (12). In addition, maternal hyperinsulinemia, even in the absence of obesity, influences the differentiation of critical neuronal lineages regulating food intake and energy expenditure (13). To date, among the missing pieces of the puzzle has been the question of how changes in placental gene expression are conveyed to the developing fetus to influence formation and function of neuronal circuits. As mentioned above, two recent papers provide evidence that the placenta–in addition to serving as a conduit for maternally-derived molecules–can itself synthesize critical substrates for the developing forebrain.

Placental Adaptations Defend Fetal Brain Development

In PNAS, Broad and Keverne (5) propose a mechanism for placental adaptations to adverse maternal environments that protect the developing murine hypothalamus at midgestation (embryonic days 11–13), an important period of neuronal proliferation and differentiation (14). The authors notice a strong correlation between the set of genes that are differentially regulated in the hypothalamus and placenta at midgestation and propose that critical developmental processes in these two organs are shaped by the same environmental cues. This synchronization in gene expression profiles is disrupted by acute (24 h) maternal food deprivation. For example, in response to a 24-h maternal fast, genes involved in the ubiquitin–proteosome system, which promote protein degradation, are up-regulated in the placenta and not in the fetal hypothalamus. At the same time, expression of genes encoding several transporter proteins is down-regulated in the placenta and up-regulated in the fetal hypothalamus.

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Precedent for such reciprocal regulation of a gene in response to metabolic circumstance is provided by the responses of adipocyte and muscle lipoprotein lipase to caloric restriction (15).

The authors (5) focus on the maternally imprinted gene *Peg3* because its inactivation in mice is associated with reduced fetal growth, followed by increased fat deposition at the expense of lean mass, deficits in thermoregulation, and delayed puberty (16). Like other, paternally expressed genes in the placenta, such as *Igf-2* and the amino acid transporter *Slc38a*, *Peg3* expression promotes fetal growth (4). Interestingly, many of the changes in placental gene expression seen in response to maternal food deprivation are recapitulated in *Peg3* hypomorphs: notably, increased expression of catabolic genes. Based on these studies, the authors (5) propose that (*i*) under conditions of reduced nutrient availability, the placenta is cannibalized to provide nutrients and critical structural substrates for hypothalamic development; and (*ii*) *Peg3* plays a critical role in this adaptive response. Defining the relationship between hypothalamic *Peg3* expression and the development of circuits regulating food intake and body weight is an important area for future research. As epigenetic changes in the developing hypothalamus could exert permanent effects on food intake and metabolic functions of female offspring, they could contribute to a mechanism whereby effects of early exposure to maternal stress or food deprivation could be conveyed transgenerationally via transplacental effects of the types alluded to by Pentinat et al. (17).

Placenta Synthesizes Neutrotrophic Factors for the Developing Forebrain

In response to maternal nutrient deprivation, many amino acid and other metabolite transporters are down-regulated in the placenta (5). A recent paper from Levitt and coworkers (6) provides evidence that the placenta is the primary source of 5-HT for the developing murine hypothalamus from days 10.5 to 15.5 of gestation. By using an ex vivo preparation, the authors (6) demonstrate that the placenta can synthesize the neurotransmitter 5-HT from maternal metabolites at midgestation. As 5-HT has been shown to affect neuronal proliferation and axonal outgrowth during this period, the placenta could provide substrates regulating brain development (18). 5-HT is also reported to play a central role in the maturation of circuits that modulate emotional function in mice (19), and polymorphisms in genes related to 5-HT function are associated with depressive symptoms in humans (20). Thus, changes in placental 5-HT production could influence neurodevelopmental endpoints.

The observation that the placenta preferentially provides 5-HT to the forebrain and not the caudal CNS raises the possibility that there is specific transmission of other nutrients or signals to the forebrain as well. If so, this could explain the apparent preferential effects of maternal programming on psychiatric or metabolic outcomes, which are controlled by forebrain structures, compared with physiological phenotypes regulated by caudal brain structures (e.g., locomotion or respiration). Cross-disciplinary studies are needed to understand the relationships among altered maternal metabolic status, placental transport and production of nutrients and signals, development of forebrain circuits, and physiological outcomes. These could provide novel mechanistic (and potentially actionable) insights into the observation that maternal stress, diet, and inflammation influence susceptibility of offspring to metabolic and affective disorders.

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