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A Placenta-Specific Genetic Manipulation Reprograms Offspring Brain Development and Function

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Epidemiological and experimental approaches have identified associations between adverse gestational conditions and the onset of health complications in the offspring. The concept of developmental origins (or so-called fetal programming) of adult diseases in humans goes back many years, with, for example, a seminal study linking prematurity and low birth weight to neurological disorders (1). Later, larger-scale epidemiological studies demonstrated associations between a broad range of adverse gestational conditions (e.g., maternal stress, maternal infection, bereavement, prenatal teratogens, famine) and a host of health complications, including mental disorders such as schizophrenia, in the developing and adult offspring (2,3). Subsequently, some of these correlations have been supported causally with animal studies (4,5), indicating that adverse gestational conditions can have wide-ranging impacts on the developing fetus. The physiological and molecular mechanisms by which adverse prenatal events affect fetal brain development, either directly or indirectly by affecting maternal–fetal interactions through the placenta, remain obscure. Adding to the complexity, many prenatal insults appear to have sex-specific effects on offspring development and health. This field of research is gaining a lot of attention, and new mechanisms driving functional interactions among maternal, placental, and fetal compartments are progressively being elucidated.

The article by Bronson *et al.* (6) in this issue of *Biological Psychiatry* is a striking example. Maternal diabetes and obesity are pregnancy complications that predispose offspring to male-biased neurodevelopmental disorders such as attention-deficit/hyperactivity disorder, autism, and schizophrenia (7). Because abnormal insulin signaling is common to these complications and has been implicated in adverse fetal outcomes, Bronson *et al.* hypothesized that impaired insulin signaling specifically in the placenta might be linking maternal metabolic dysfunction to male-biased neurodevelopmental reprogramming. Bronson *et al.* used a Cre recombinase driver mouse line to knock down the insulin receptor (*InsR*) gene expression specifically in fetal trophoblastic cells of the placenta, and thus only during fetal development. Strikingly, *InsR* deficiency suppresses expression in 25 gene sets involving a range of physiological functions such as lipid homeostasis, vascular function, amino acid transport, and metabolism in male placentas but not in female placentas.

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Evaluating endpoints related to neurodevelopmental disorders, the study identifies potential new mediators of the long-term, sex-specific alterations in behaviors related to prefrontal cortex function in the offspring. Notably, the trophoblast-specific *InsR* knockdown results in reprogramming of prefrontal cortex gene expression, increased hypothalamus-pituitary-adrenal axis stress response, and impaired sensorimotor gating in male mice but not in female mice. These male-specific effects are remarkable and highlight the importance of placental function in neurodevelopmental programming. Importantly, Bronson *et al.* observe that *InsR* deficiency in male placentas downregulates the expression of genes involved in placental synthesis and clearance of serotonin, an important trophic factor for the fetal brain (8) and a potent vasoconstrictor implicated in the etiology of gestational diabetes (9). Altered placental serotonin synthesis was recently shown to drive abnormal development of serotonergic and other neuronal systems in the context of maternal inflammation during pregnancy (10). Although fetal brain concentrations of this biogenic amine were not measured in the study by Bronson *et al.*, the impact of deficient placental insulin receptor expression on the placental serotonin metabolic pathway could contribute directly to adverse developmental effects on the fetal brain. Consistent with this possibility, gene expression profiles in the embryonic brain reveal reduced expression of genes modulating cytoskeletal dynamics and cell motility specifically in male embryos with placental *InsR* knockdown. Given that these processes are required for neuronal proliferation, migration, and axon growth and targeting during gestation, these findings suggest a placentally derived mechanism disrupting fetal brain development specifically in male mice, and possibly involving placental serotonergic function.

Overall, the report by Bronson *et al.* is one of the first studies to directly link placental-specific gene dysregulation to offspring brain function and provides important data to further our understanding of the developmental origins of mental disorders. They demonstrate that the genetic perturbation of insulin receptor expression specifically in placental trophoblasts, which can also occur because of maternal metabolic conditions, is sufficient to disrupt stress sensitivity and prefrontal cortical development in male mice but not in female mice. These findings provide compelling evidence for the critical involvement of placental insulin signaling in sex-specific neurodevelopment programming; the molecular mechanisms specifically linking decreased insulin receptor expression in the placenta to these (sex-specific) outcomes remain elusive, but the results open up an avenue for future investigations, including the possibility of targeting the placental insulin signaling pathway in fetal or early postnatal therapies (at least initially in animal models) to prevent some of the long-term neurodevelopmental effects of deficient placental function.

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