

Developmental origins of adult mental diseases biology essay

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Abstract:

Dysfunction of brain serotonin (5-HT) signaling contributes to the pathophysiology of several psychiatric disorders. However, before 5-HT acts as a neurotransmitter/neuromodulator in the adult brain, increasing evidence suggests that it plays crucial roles in the modulation of essential neurodevelopmental processes. It was recently demonstrated that the placenta synthesizes 5-HT from maternally derived tryptophan during pregnancy. Therefore, genetic and environmental perturbations that affect placental tryptophan metabolism could alter neurodevelopmental processes in the developing embryo, and contribute to the developmental origin of psychiatric disorders. Here we discuss how disruptions of the placental tryptophan metabolic pathway may lead to abnormal brain development and function in adult life. **Keywords:** Placenta, Serotonin, Tryptophan, Schizophrenia, Autism, Stress, Fetal Programming, Fetal brain.

Introduction:

The concept of prenatal programming of adult diseases, also known as the "Barker hypothesis" in some circles, has really only started to emerge over

the last 20 years (1) . Based on the initial observation that the intrauterine environment influences blood pressure in adulthood (2), it was postulated that adverse prenatal events can influence health trajectories throughout life in the offspring. Subsequently, numerous epidemiological studies in humans have shown an association between several types of adverse prenatal events and increased risk for a wide range of adult diseases (3, 4). Particularly strong evidence for the fetal origin of adult mental diseases comes from human epidemiological studies demonstrating that adverse prenatal events experienced during pregnancy increase the risk of developing specific mental disorders throughout the life of the offspring. For instance maternal stress, infection or malnutrition experienced during the 1st trimester of pregnancy appear to significantly increase the risk of developing schizophrenia in the adult offspring (5-7). More recently, there is some indication that maternal fever experienced during the 1st trimester of pregnancy significantly increases the risk of autism in the offspring (8). Interestingly, similar events during other stages of pregnancy lead to different outcomes; influenza infection during the 2nd or 3rd trimesters were reported to increase the risk of major depressive disorders in the offspring (9). Thus, it has been suggested that there are sensitive developmental time periods for the fetal programming of specific mental illnesses. This could be correlated to differential temporal effects of these events on the maternal, fetal or materno-fetal (i. e. placental) physiology, which are known to change dramatically throughout the course of pregnancy (see (10)). Several perspectives have emerged to account for how prenatal events induce long-term physiological changes that lead to different mental diseases in

adulthood. Dysfunction of the placental maternal-fetal interface appears to be a somewhat common adverse prenatal event (11). For example, placental insufficiency – which causes intrauterine growth restriction – occurs in ~5% of human infants born every year in the United States(12, 13). This condition is also associated with significantly increased risk for varied diseases in the adult offspring, such as metabolic, cardiovascular or even mental disorders (3, 14). Thus, the placenta is now thought to be a central mediator for the fetal programming of adult diseases. Indeed, accumulating evidence from animal studies support this possibility (10, 15). Helping to understand how the placenta may influence fetal programming, it was recently demonstrated that the placenta is a source serotonin (5-HT) in mice and humans (16).

Earlier studies have shown that before it acts as the well-known neurotransmitter in the adult brain, 5-HT is in fact an important trophic factor for the fetal brain (17–19). For instance, developmental disruption of 5-HT signaling in specific regions of the fetal brain leads to abnormal wiring of major axonal pathways (17, 20) and altered cell division and laminar organization in the neocortex (21). Furthermore, manipulating 5-HT receptor expression during critical neonatal periods has long-term consequences on adult brain function; a series of elegant studies demonstrated that disrupting 5-HT_{1A} receptor expression, exclusively in the neonatal period, increases anxious behaviors in adult mice (22). During development, these 5-HT signaling effects may be an important mediator for the fetal programming of adult mental diseases. Since the placenta is an essential source of 5-HT for the fetal brain, altered placental tryptophan metabolism could in turn be an important molecular pathway for the fetal programming of brain

development (23, 24). In humans and mice, tryptophan hydroxylase I (TPH1) and amino acid decarboxylase (AADC) enzymes are expressed in the placenta (16, 25). Simple biochemical experiments demonstrated that the organ can indeed rapidly convert the essential amino acid tryptophan to 5-HT; furthermore in mice, ex vivo dual perfusions of isolated, live placentas (26) demonstrated that placentally-neosynthesized 5-HT is rapidly released into the fetal blood stream through the umbilical vein (16). Placental-specific pharmacologic inhibition of TPH1 activity in vivo showed that, once released into the umbilical vein, placental 5-HT reaches the fetal forebrain through the fetal blood stream. Since the blood-brain barrier is not yet fully functional in this fetal period (27), placentally-derived 5-HT may signal through receptors expressed during early brain development; in particular receptors of the 5-HT₁ subtype (17, 28). Although it remains to be fully demonstrated, placental 5-HT, and more generally placental tryptophan metabolism, may be critical for normal fetal brain development. This also suggests that placental tryptophan metabolism may constitute a new molecular pathway by which adverse prenatal events can alter the development of specific brain circuits. For instance, studies in rats have shown that a chronic mild stress during pregnancy increases the fraction of free tryptophan in the maternal blood and the concentration of 5-HT in the fetal brain; importantly, gestational stress also increases anxiety in the adult offspring (29–31). Thus, maternal blood tryptophan concentration appears as a determinant factor in the fetal programming of adult anxiety disorders. Mechanistically, increased free plasma tryptophan due to maternal stress may, through placental neosynthesis of 5-HT, lead to increased delivery of placental 5-HT to the

developing forebrain, ultimately altering developmental processes such as circuit formation (see Fig. 1). It should be noted that although normal fluctuations in maternal tryptophan blood level do occur (32), homeostatic regulation of placental tryptophan metabolism may take place during typical development to prevent random fluctuations in placental 5-HT output to the fetus. Studies in our laboratory currently focus on adverse prenatal environmental (e. g. chronic stress, inflammation) events, which combined with specific genetic (e. g. SERT polymorphisms) conditions, may affect placental tryptophan metabolic regulation, leading to 5-HT-mediated negative programming events in the fetal brain. It is important to note that the period of placental 5-HT contribution to the fetal forebrain in mice corresponds roughly to the first and early second trimesters in humans: periods that are associated with greater risk for mental illnesses due to maternal perturbations (33, 34). Thus, examining maternal, fetal and placental tryptophan availability throughout normal and abnormal pregnancies may provide new clues for the etiology of several neurodevelopmental disorders. There is already sparse evidence that genetic conditions associated with abnormal tryptophan metabolism during pregnancy have long-term consequences for the offspring. For instance, mutations in the tryptophan 2, 3-dioxygenase enzymes (TDO1/2) involved in tryptophan metabolism through the kynurenine pathway in the placenta (35), affect neurogenesis, increase anxious behaviors in mice (36), and, in humans, are associated with increased risk for schizophrenia, bipolar disorder, and autism (37, 38). In conclusion, maternal tryptophan metabolism in the placenta (and thus release of placental 5-HT or other

tryptophan metabolites to the fetus) may be an important mechanism of fetal programming, and may contribute to the neurodevelopmental origins of mental disorders such as schizophrenia in the adult offspring.