Gestational Factors Throughout Fetal Neurodevelopment

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Serotonin (5-HT) is a critical player in brain development and neuropsychiatric disorders. Fetal 5-HT levels can be influenced by several gestational factors, such as maternal genotype, diet, stress, medication, and immune activation. In this review, addressing both human and animal studies, we discuss how these gestational factors affect placental and fetal brain 5-HT levels, leading to changes in brain structure and function and behavior. We conclude that gestational factors are able to interact and thereby amplify or counteract each other's impact on the fetal 5-HT-ergic system. We, therefore, argue that beyond the understanding of how single gestational factors affect 5-HT-ergic brain development and behavior in offspring, it is critical to elucidate the consequences of interacting factors. Moreover, we describe how each gestational factor is able to alter the 5-HT-ergic influence on the thalamocortical- and prefrontal-limbic circuitry and the hypothalamo-pituitary-adrenocortical-axis. These alterations have been associated with risks to develop attention deficit hyperactivity disorder, autism spectrum disorders, depression, and/or anxiety. Consequently, the manipulation of gestational factors may be used to combat pregnancy-related risks for neuropsychiatric disorders.

Keywords: gestation ; serotonin ; neurodevelopment ; neural circuit formation ; neuropsychiatric disorders

1. Aim of Review

We performed an extensive literature search up to February 2020 using the PubMed database. The key characteristics of referred human and animal studies are shown in Table S1 and S2, respectively. The objective of this review is to carry out a comprehensive approach towards gestational factors affecting the fetal 5-HT system and as a result may affect an offspring's brain development and behavior regarding neuropsychiatric disorders. We first introduce this topic by providing background information concerning 5-HT-ergic neuromodulatory effects on brain development (Section 2). Thereafter, we highlight what is currently known about the effects of gestational factors on an offspring's brain 5-HT system and neuropsychiatric disorders related to brain development and behavior (Section 3). Gestational factors include maternal 5-HT-ergic genotype, 5-HT-related diet composition, stress, 5-HT-related medication, and immune activation. Finally, we discuss the (interactive) impact of the gestational factors on the placenta-derived and offspring's raphe-produced 5-HT content, the related brain circuit development, and how these effects may provide risk of the onset of specific neuropsychiatric phenotypes later in life (Section 4). Noteworthy paternal and postnatal environmental factors, such as paternal genotype and maternal

2. Gestational Factors Influence Fetal Development during the Embryonic Period and After Birth

2. 5-HT-ergic Maternal Genotype Influences the 5-HT System, Neurodevelopment, and Behavior in the Offspring

As proposed previously by Gleason and colleagues, maternal genetic variations affecting the 5-HT system (hereafter called maternal 5-HT-ergic genotype) are able to influence fetal development[1]. Changes in the 5-HT system can occur through alterations in placental and fetal 5-HT levels or through transmission of risk alleles. The effects of the transmission of risk alleles on an offspring's brain development and behavior are discussed in other reviews (e.g.,[2]). In short, maternal 5-HT-ergic genotype perturbs fetal 5-HT homeostasis by increasing or decreasing 5-HT supply. The animal studies addressed below suggest that the thalamocortical circuitry is particularly sensitive to maternal variance in 5-HT-ergic genotype.

2.2 Maternal 5-HT-ergic-Related Diets Influence the Tryptophan Pathway, Neurodevelopment, and Behavior in the Offspring

Another route via which the mother can influence her offspring's development involves her diet. Nutrients received from the mother via the placenta or during lactation are crucial for an offspring's health and growth[3][4]. In the following sections, we describe the effects of maternal tryptophan-related diets, high-fat diets, and alcohol consumption on 5-HT-ergic brain development of the offspring. In short, depending on the composition of the diet, the mother can perturb fetal 5-HT homeostasis by increasing or decreasing fetal 5-HT availability and influencing the fetal 5-HT system in the hippocampus, hypothalamus, amygdala, the raphe nuclei, and the mPFC.

2.3 Maternal Stress Affects the 5-HT System, Neurodevelopment, and Behavior in the Offspring

Maternal stress (defined as physical and/or psychosocial stress during pregnancy) can negatively influence child health and a variety of pediatric aberrations have extensively been reported (for review[5]). The effects of maternal stress on the maternal HPA-axis resulting in excessive fetal cortisol levels has been most extensively described in literature. In recent reviews, the effects of maternal stress on the placental and fetal 5-HT systems is briefly discussed as potential underlying factor as well. These 5-HT alterations may affect fetal brain development and increase the risk of the onset of neuropsychiatric disorders, such as ASD, depression, and anxiety[5][6][7]. In the following sections, we will review human and animal studies describing the effects of maternal stress on 5-HT-related brain development and function in the offspring. In animals, stressors used include electric foot shocks, restraint under bright light, auditory stimuli, cold water immersion, forced swim, wet bedding, crowding, saline injection, and cage rotation. Some studies use one of these stressors to mimic maternal stress, while others make use of chronic unpredictable stress models whereby, in general, animals are exposed to up to two of these stressors daily. In short, maternal stress is associated with both increases and decreases in 5-HT levels in the offspring. Increases in 5-HT levels affect development of the thalamocortical circuitry, whereas decreases in 5-HT levels affect development of the prefrontal-limbic circuitry. The HPA-axis is affected in almost all maternal stress models, irrelevant of the offspring's 5-HT level changes.

2.4 Maternal Intake of 5-HT-ergic Medication Alters 5-HT Levels in Offspring and Affects their Neurodevelopment and Behavior

Pregnant women suffering from depression, migraine, or schizophrenia are sometimes in need of medication during pregnancy. Medication is taken during 6% of all pregnancies[8]. Over the years, multiple reviews have been written trying to disentangle the effects attributable to prenatal SSRI exposure from the underlying maternal disorder and the maternal-child transmission of risk alleles to neuropsychiatric disorders. Due to inconsistent study results, review outcomes differ. There is a tendency, however, towards viewing SSRI exposure as a plasticity rather than a risk factor[9][10][11][12][13][14][15]. This means that SSRI exposure can positively or negatively influence offspring's 5-HT system depending on other gestational factors. In the following sections, we describe the effects of maternal intake of 5-HT receptor (ant)agonists and SSRIs during pregnancy on offspring's 5-HT-ergic brain development and neuropsychiatric disorders-related behaviors, referring to both human and animal studies. In short, there is quite some overlap between human and animal findings. Maternal SSRI intake alters fetal 5-HT levels; however, the direction remains unclear. Nevertheless, these fetal brain 5-HT alterations could explain the remarkable changes in fetal brain development related to the thalamocortical and prefrontal-limbic circuits, as well as the HPA-axis that we address in this review.

2.5 Maternal Immune Activation Affects the Tryptophan Pathway and Neurodevelopment of Offspring

Recent reviews have proposed a role for maternal immune activation in the aetiology of ADHD, ASD, and depression and suggest a potential mediating role for the 5-HT system[16][17]. Immune activation during pregnancy occurs either upon a viral or a bacterial infection, or when there is a condition such as pre-eclampsia[18]. Pre-eclampsia is a complex multisystem disorder unique to the second half of pregnancy and marked by low platelet 5-HT levels[19]. Pre-eclampsia has been shown to play an important role in the development of neuropsychiatric disorders such as ASD[20][21][22]. In the following sections, we describe the effects of induced maternal immune activation on 5-HT-ergic brain development of the offspring of rodents. In short, maternal immune activation causes a decrease in an offspring's brain 5-HT levels throughout life, independent of the method used and gestational period studied. During the embryonic period an acute increase in brain 5-HT levels may occur. The tryptophan and 5-HT-related brain areas that seem to be affected by maternal immune activation are located in the thalamocortical and the prefrontal-limbic circuits.

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