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Review

The neurodevelopmental effects of serotonin: A behavioural perspective

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HIGHLIGHTS

- Mood-related behavioural changes are observed after both prenatal and postnatal SSRI exposure.
- Autism-related features arise in response to early postnatal increases in serotonin levels.
- Sexual behaviour is affected by SSRI exposure during the late postnatal period.

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ABSTRACT

Serotonin is well known for its role in psychiatric disorders like depression and autism, but it is less clear how aberrant behaviour associated with these disorders are shaped by serotonergic alterations during prenatal and postnatal development. The use of serotonergic antidepressant agents and other drugs during pregnancy and breastfeeding can change brain development, and the behavioural consequences may depend on the stage of development; prenatal, early and late postnatal. The aim of this review is to provide an overview of the behavioural consequences of changes in serotonin levels during these three critical developmental stages. The studies together demonstrate that risk for mood disorders (including social deficits) is related to serotonergic perturbations during the prenatal and postnatal phases, whereas risk for autism-like features and sexual abnormalities increases when serotonin levels are increased during the postnatal period. This insight may inform timed strategies to reduce risk for psychiatric disorders.

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Abbreviations: 5-HT, 5-hydroxytryptamine serotonin; SSRI, selective serotonin reuptake inhibitors; 5-MT, 5-methoxytryptamine; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino) tetralin; CGS-120066B, 4-(4-methyl-piperazin-1-yl)-7-trifluoromethyl-pyrrolo[1,2-a]quinoxaline dimaleate; *m*CPP, *meta*-chlorophenylpiperazine; WAY-100635, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridyl)cyclohexanecarboxamide; GR-127935, 2′-methyl-4′-(5-methyl-[1,2,4]oxadiazol-3-yl)-biphenyl-4-carboxylic acid [4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide; 5,7 DHT, 5,7-dihydroxytryptamine; 5-HTP, 5-hydroxytryptophan; THP, tryptophan hydroxylase; 5-HTT, serotonin transporter; 5-HIAA, 5-hydroxyindoleacetic acid; MAO-A, monoamine oxidase A; *p*CPA, *p*-chlorophenylalanine; AR, androgen receptor; GnRH, Gonadotropin-releasing hormone; DHS, developmental hyperserotonemia; OT, oxytocin; PVN, paraventricular nucleus; CGRP, calcitonin-gene related peptide; CeA, central nucleus of the amygdala; BDNF, brain-derived neurotropic factor; TrkB, tropomyosin related kinase B; LU, Lu 10-134-C; GABA(A)R, gamma-aminobutyric acid-A receptor; REM, rapid eye movement; ASD, autism spectrum disorders.

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1. Introduction

Serotonin (5-hydroxytryptamine; 5-HT) is known as a monoamine neurotransmitter that plays a major role in neural plasticity. The 5-HT system can be manipulated by different types of drugs like antidepressant agents, which cause alterations in 5-HT levels and thereby influence many brain regulated functions such as mood, cognition, perception, sleep and appetite. In recent years, it has been well established that 5-HT not only influences brain functioning as a monoamine neurotransmitter but also brain development as a neurotrophic factor [1–3]. This is of fundamental interest and increases our understanding of disorders with a neurodevelopmental fundament like anxiety, depression and autism. This also helps to elucidate whether antidepressant treatment – targeting the 5-HTergic system – during pregnancy and/or breastfeeding has detrimental consequences for the development of children [4,5].

Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed drugs for the treatment of depression and anxiety-related disorders. They are mainly prescribed because of their proven safety in adults and are for that reason the preferred drug for the treatment of depressed pregnant and postpartum women [6]. Pregnancy is a risk factor for depression, and given that depression is detrimental for both the mother and unborn child it has to be treated. From the 10–16% of pregnant woman that suffer from depression [7], 25% continue antidepressant use during pregnancy and 0.5% just start to use them during this time [5]. SSRIs can cross the placenta [8] and can be transferred via breast milk [9]. The exposure to these antidepressant drugs not only lead to neonatal withdrawal-related complications, like low birth weight and pulmonary hypertension, but also influence the whole neurodevelopmental process [10,11]. Given that SSRIs increase 5-HT levels by inhibiting its re-uptake [12] and that 5-HT is a major neurotrophic factor [1–3], prenatal and early postnatal SSRI exposure may affect neurodevelopment of the unborns and newborns, respectively [13,14]. Indeed, autism is characterized by hyperserotonemia, which is hypothesized to be related to increased 5-HT levels in the embryonic brain [15]. Prenatal SSRI exposure in humans also increases the risk for autism [16]. Furthermore, anxiety and depression are ascribed to constitutive alterations in 5-HTergic tone. Hence, early life alterations in 5-HT levels can contribute to a constellation of psychiatric disorders. Strikingly, this opposes the effects of SSRIs when given during adulthood, because in adults SSRIs are used to treat depression, anxiety-related symptoms and autism [17].

Developmental effects of 5-HT may well be different across developmental stages, because during each stage specific processes take place. While some previous reviews have touched upon the consequences of 5-HT alterations during development [4,18–20], it remains open whether there are critical stages in the neurodevelopmental effects of 5-HT, and whether behavioural consequences are dependent on the neurodevelopmental stage during which 5-HT levels are altered. In this review we focus on the 2nd half of pregnancy (hereafter referred to as 'prenatal') and the early and late postnatal developmental phases in rodents, which correspond to the second and third trimesters of human pregnancy [19,21]. The development of the serotonergic system starts halfway pregnancy in rodents (~the second trimester of human pregnancy), and the outgrowth and guidance of the serotonergic neurons to its final targets occurs during the course of the remainder of the rodent pregnancy. During the early/late postnatal phases in rodents (~third trimester of human pregnancy) the development of neurons are refined (Fig. 1). Given these progressing neurodevelopmental processes across neurodevelopmental stages it is likely that that the later life behavioural consequences of neurodevelopmental SSRI exposure are dependent on the developmental stage during which this exposure takes place. Therefore, the outstanding question we aim to answer is: "Are the behavioural consequences of developmental SSRI exposure dependent on its timing?"

To understand the behavioural consequences of timed neurodevelopmental SSRI exposure, rodents provide several experimental advantages. First, whereas it is difficult to control the timing of developmental SSRI exposure in humans, this timing can be controlled in rodents. Second, rodents can overcome the long life cycle of humans. The other side of the coin is that results from animal studies need to be translatable to humans. Given that placental transfer of SSRIs is similar in rodents and in humans [22,23], and that plasma SSRI levels are similar in rodents and humans [23] translation is expected to be realistic. For these reasons and the aim to answer the outstanding research question we concentrate on rodent studies that (1) investigated manipulations of specifically the serotonergic system and (2) applied manipulations that were limited to a certain developmental period; the prenatal phase, the early and/or late postnatal phase and the entire prenatal plus postnatal phase. Manipulations of the serotonergic system will be monitored through the use of different SSRIs or tricyclic antidepressants (clomipramine). Additionally, we review studies that manipulated the 5-HTergic system during the developmental time windows of interest using 5-HT agonists (5-MT, 8-OH-DPAT, CGS-120066B, *m*CPP), 5-HT antagonists (WAY-100635, GR-127935), neurotoxins (5,7 DHT), tryptophan depletion, 5-HTP (a metabolic intermediate in 5-HT synthesis), and 5-HT antibodies, because these studies contribute to the answering of the outstanding question.

2. 5-HT and brain development in rodents

Before 5-HT is synthesized by the brain itself, at embryonic day 10.5 (E10.5), 5-HT is derived from the placenta [24]. It has been

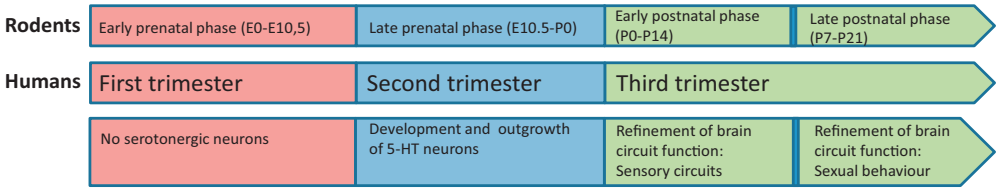

Fig. 1. Schematic overview of the developmental time points and the processes that mainly take place during rodent and human pregnancy and early life referring to the serotonergic system [1,4,14,24–43]. Development and outgrowth of 5-HT neurons is not finished at P0/end of second trimester but at P21.