Effects of selective serotonin reuptake inhibitors on neurodevelopment

Robin Dennebos
University of Groningen
Supervisor: Dr. Ing. Jocelien D.A. Olivier
Department of Neurobiology
Groningen Institute for Evolutionary Life Sciences (GELIFES)
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Abstract

The neurotransmitter and neurotrophic factor serotonin is involved in many processes in multiple brain regions. During mammalian development, serotonin can regulate the formation of serotonergic and non-serotonergic circuitry which are important for the maturation of these brain regions. Disruption of serotonin signalling during development may affect the wiring of the brain which can result in abnormal behaviour in the offspring. Selective serotonin reuptake inhibitors (SSRIs) are widely used as anti-depressant treatment and they are also used to treat depression during pregnancy. The precise effects of SSRI treatment on the developing child are not clear, both short and long term, and a significant amount of research has been done trying to understand the risks and effects of SSRI use during pregnancy. One factor that is most likely important for treatment of depression is the period of neurodevelopment in which the child is exposed to SSRIs. Exposure to SSRIs in specific developmental stages may affect the developing child differently. Therefore these drugs may have a variety of effects on specific brain regions which may result in different behavioural outcomes. However, distinguishing between depression and SSRI effects on the developing child is important for exactly understanding the possible risks that SSRI may bring. Importantly, not only serotonin levels of the developing child should be considered as both placental and maternal serotonin levels can be found in the developing brain. Therefore, placental and maternal serotonin signalling may be important for the neurodevelopment of the child as well. To which extent and how precisely SSRIs can affect neurodevelopment however still remains elucidated.

Table of contents

Introduction

The neurodevelopmental role of serotonin

During mammalian development of the central nervous system (CNS) one key player is the neurotransmitter serotonin (5-HT). In the human brain, high levels of 5-HT are found early in development and 5-HT levels increase in the first two years of life (Hedner et al. 1986). Two years after birth 5-HT levels decline again, reaching adult levels 5 years after birth (Hedner et al. 1986). These 5-HT concentrations indicate 5-HT may function differently early in development compared to adulthood (Toth & Fekete 1986). Serotonergic (5-HTergic) neurons can already be found as early as 5 weeks after the start of gestation (Sundström et al. 1993). Hereafter 5-HTergic neurons increase in number throughout the 10^{th} week of gestation and after 15 weeks the organization of 5-HTergic cells in the raphe nuclei, a cluster of nuclei which contain large populations of 5-HTergic cells, can be seen (Kontur et al. 1993; Takahashi et al. 1986; Hornung 2003). 5-HTergic cells in these nuclei can project to multiple target regions in the forebrain and midbrain (Vertes & Linley 2008; Bang et al. 2012). Furthermore, 5-HTergic neurons, and 5-HT, can be found in different brain regions including the hypothalamus, midbrain, pineal gland and the substantia nigra indicating a role for 5-HT in multiple processes throughout the brain (Steinbusch 1981).

Serotonin does not solely function as a neurotransmitter, it can also act as a neurotrophic factor (Yan et al. 1997). For instance, during early development of the CNS, 5-HT is thought to be modulating the response of axons to their guidance cues important in development of neuronal circuitry (Bonnin et al. 2007). 5-HT can bind to a variety of receptors which can mediate different responses. Activation of the 5-HT receptors 5-HT_{1A} and 5-HT_7 can lead to neurite outgrowth and neuronal survival, suggesting 5-HT may contribute to these processes during development as well (Fricker et al. 2005; Rojas et al. 2014). Furthermore, 5-HT is involved in the formation of both 5-HTergic and non-5-HTergic circuitries during neurodevelopment (Daubert & Condron 2010). In addition, 5-HT also seems to be important for neural progenitor differentiation, proliferation and survival (Ishizuka et al. 2014; Benninghoff et al. 2010). These finding suggest that although 5-HT acts as a neurotransmitter, 5-HT also seems to play an important role in the neurodevelopment.

Serotonin on the molecular level

The majority of the receptors to which 5-HT can bind are G-protein coupled receptors, including G_i/G_0, G_q and G_s coupled receptors (Barnes & Sharp 1999). As these receptors can be found in different locations throughout the brain, 5-HT may mediate different responses in specific brain regions. Examples of the receptors include the 5-HT_{1A} receptor (G_i/G_0) which is implicated in anxiety, mood and cognitive functions (memory and learning) (Ögren et al. 2008), the 5-HT_{2C} receptor (G_q) implicated in anxiety and mood (Dekeyne et al. 2008) and the 5-HT_6 receptor which is implicated in cognition (Hirst et al. 2006). In addition, the 5-HT_{1A} receptor for instance can be found in the hippocampus, raphe nuclei and cerebral cortices while it can also be found in lower levels in the thalamus and basal ganglia (Ito et al. 1999). The 5-HT_{1A} receptor can be present on both pre- and postsynaptic neurons. In presynaptic cells the 5-HT_{1A} receptor can negatively regulate 5-HTergic neuronal activity (Liu et al. 1999) and inhibit neuronal firing (Bayliss et al. 1997). For example, in mice lacking 5-HT_{1A} receptors neuronal firing is enhanced and these mice showed anxiety-like behaviour, although it did not alter 5-HT release (Richer et al. 2002). This behaviour was likely caused by the absence of 5-HT_{1A}

receptors in the postsynaptic cells, as 5-HT release appeared to be normal. Therefore the 5-HT_{1A} receptors seems to be of importance for physiological and behavioural processes in both pre- and postsynaptic cells. In addition to the G-protein coupled receptors two other 5-HT receptors have been identified. First, the 5-HT_3 receptor, which is an ligand-gated ion channel, can contain five different subunits all with different properties and can functions (Thompson & Lummis 2006). The 5-HT_3 receptor can be found in both pre- and postsynaptic cells and its activation can stimulate the release of multiple neurotransmitters, such as dopamine (Blandina et al. 1989), cholecystokinin (Paudice & Raiteri 1991) and Gamma-aminobutyric acid (GABA) (Nayak et al. 1999; Katsurabayashi et al. 2003). 5-HT can activate the 5-HT_3 ligand-gated ion channel, allowing sodium and potassium to pass the cell membrane and elicit fast synaptic transmission (Jackson & Yakel 1995). Furthermore, the 5-HT_3 receptor is expressed and functional in a relatively large group of GABAergic interneurons in the neocortex (Lee et al. 2010). These GABAergic interneurons are thought to be important for processing information in cortical circuits (Rudy et al. 2011). In addition, $5HT_3$ receptor expression has been found in glutamatergic Cajal-Retzius cells in the cortex as well (Lee et al. 2010). During CNS development the Cajal-Retzius cells are present in specific regions of the neocortex and hippocampus and are thought to be important for cell migration and neuronal outgrowth (Frotscher 1997; Marín-Padilla 1998). Secondly, 5-HT can interact with the 5-HT transporter (in literature both described as SERT or 5-HTT). The 5-HT transporter is responsible for the reuptake of 5-HT back into the presynaptic cell after its release in the synaptic cleft (Holmes, Murphy, et al. 2003). This removal of 5-HT from the synaptic cleft by the SERT thus ends the effects of 5-HT on the postsynaptic cell. As a consequence, the presynaptic neuron can reuse the 5-HT that has re-entered the cell for future release into the synaptic cleft. The SERT has been found in almost all brain regions in humans (Kish et al. 2005). Interestingly, SERT knockout mice show abnormal anxiety-like behaviour in combination with reduced exploratory activity (Holmes, Yang, et al. 2003). Moreover, antagonizing the 5-HT_{1A} receptor in these SERT knockout mice reversed this abnormal anxiety-like behaviour, but not the reduced exploratory activity. These findings suggest a role for the SERT in anxiety-like behaviour and a role for the 5-HT_{1A} receptor in mediating this abnormal behaviour. The wide distribution of 5-HT and its multiple receptors in different brain areas indicates the importance of 5-HT signalling in both development and homeostasis.

Disruption of serotonin signalling

The disruption of 5-HT signalling is widely implicated in behaviour and behavioural disorders. Examples include implications of 5-HT in cognition, mood, sleep, aggressiveness and social behaviour (Schmitt et al. 2006; Cowen & Sherwood 2013; Young & Leyton 2002; Portas et al. 2000; Kiser et al. 2012). Furthermore, disruption of 5-HT signalling in the (developing) mammalian brain may be important in the onset of multiple psychiatric and developmental disorders including autism, schizophrenia and depression (Harrington et al. 2013; Iqbal & van Praag 1995; Caspi et al. 2003; Albert & Benkelfat 2013). As a result, alteration of the 5-HT signalling has been used as a target for the treatment of many of these disorders, for example depression. It has been shown that inhibiting the reuptake of 5-HT from the synaptic cleft can counteract the symptoms of depression, the SERT is therefore an important target for antidepressant treatment (Schloss & Williams 1998) as it has been shown that this transporter can be inhibited by the use of selective serotonin reuptake inhibitors (SSRIs) and these SSRIs seem to have a positive effect on depressive symptoms in depressive patients (Qin et al. 2014). Maternal depression during pregnancy can affect the developing child, and sometimes treatment

of depression during pregnancy is unavoidable (Kinsella & Monk 2009). However, since 5-HT is not only a neurotransmitter but also a neurotrophic factor involved in many developmental processes of the brain, it is most likely that SSRIs can have an effect on the development of the child. It has been shown that SSRI exposure during pregnancy (in both humans and rodents) is associated with an increased risk to develop depression (Gaspar et al. 2003), anxiety-like behaviour (Croen et al. 2011) and autism spectrum disorders (Gur et al. 2013) in the offspring. In addition, it has been shown that *in utero* exposure to SSRIs is associated with an increased risk of autism (Rai et al. 2013). Therefore it is most likely that disruption of 5-HT signalling, as a consequence of SSRI treatment of maternal depression during depression, may contribute to the development of behavioural disorders in the offspring. In addition, it is not well understood which periods of neurodevelopment are most vulnerable for SSRI treatment induced alterations in 5-HT signalling. In this essay the possible effects of SSRIs on 5-HT signalling during neurodevelopment, and primarily its role as a neurotrophic factor, are discussed.

Selective serotonin reuptake inhibitors and their effect on the developing child

Use of SSRIs in treatment of maternal depression

The prevalence of depression during pregnancy can be as high as 20% and approximately 5% of pregnant women suffer from major depression (Ryan et al. 2005; Melville et al. 2010). The underlying mechanisms of depression are thought to be of both environmental influences and genetic susceptibility (Lopizzo et al. 2015). In some cases, treatment of maternal depression during pregnancy is necessary for the wellbeing of both the mother and the developing child. Treatment of depression using SSRIs are considered to be safe as they have few side effects and good efficacy (Barbey & Roose 1998). However, the effects of SSRIs on the neurodevelopment of the developing child are still not well understood. SSRIs can pass the placenta and may thus have an direct effect on the unborn child (Hendrick et al. 2003). The effects of SSRIs on the developing child may depend on the developmental stage in which the developing child is when exposed to SSRIs. Pregnancy in humans can be divided into three trimesters (figure 1). In comparison, mice and rats can be used as a model for human pregnancy stages regarding neurodevelopment, as these follow a roughly similar process (although the last stage of development is after birth) (figure 1). For example, the expression of the SERT in neurons of the raphe nuclei can be found from early gestation to adolescence in primates, while in rodents (mice and rats) the SERT expression can be found as early as in mid gestation (Homberg et al. 2010).

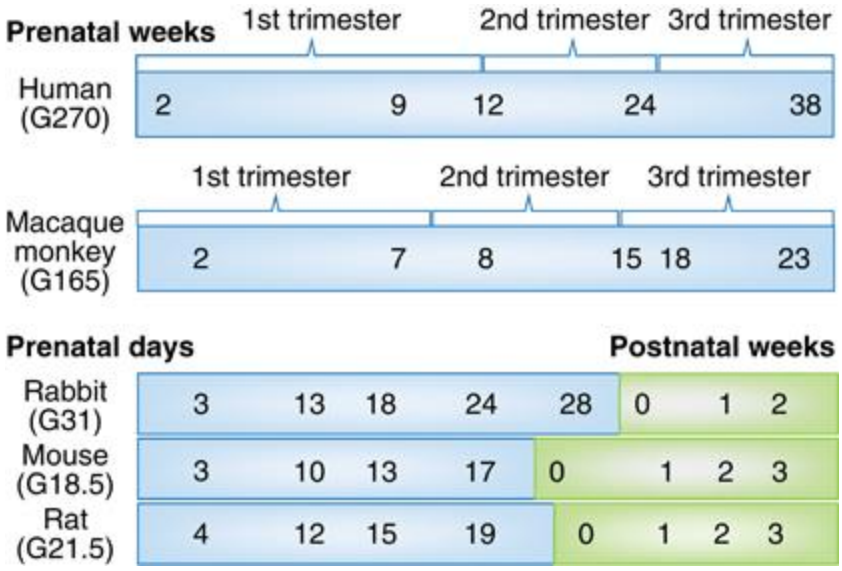

Figure 1: The developmental stages during pregnancy in different animal species. These stages can be divided into three trimesters shown in weeks for human and macaque monkeys, and in days for rabbits, mice and rats. The rodent equivalent of the third trimester is postnatal (shown in green). © Neuropsychopharmacology reviews (2015) 40, 61-87 ; doi:10.1038/npp.2014.147 (Ross et al. 2015).

Furthermore, a small percentage of pregnant women may already use SSRIs when they become pregnant or start before they know they are pregnant. In this case the developing child is exposed to SSRIs directly from the start of the pregnancy, or shortly after. The neurodevelopment of the child may thus be exposed to the already affected 5-HT regulation of the mother and the developing child may be exposed to SSRIs before 5-HT related processes

in the developing brain begin. These conditions may have a significant impact on the development of the child as well.

Effects of SSRIs in different developmental stages

Very early in pregnancy (approximately day 10.5), preceding the start of the 5-HTergic circuitry formation in the developing brain, maternal 5-HT is able to cross the placenta and necessary for normal murine development (Côté et al. 2007). This maternal 5-HT seems to play a role in controlling morphogenesis and what could be more important, knockout of tryptophan hydroxylase 1 (necessary for 5-HT production) in mothers but not the offspring of these mothers resulted in abnormal development in mice (Côté et al. 2007). These findings suggest that the phenotype of the offspring depends more on the mothers phenotype than on the offspring's phenotype. Therefore, very early neurodevelopment does not necessarily depend on 5-HT expressing cells in the developing brain but rather on the maternal 5-HT present (Côté et al. 2007). Importantly, these findings may mean that interference in 5-HT signalling in the mother may have consequences for the developing child and SSRI induced alterations in the mother may also indirectly affect the offspring. Therefore, the effects of SSRIs on the pregnant mother may be important for the wellbeing of the developing child.

In addition to the maternal 5-HT being of importance in early development, placental 5-HT also seem to be important in the early stages of normal neurodevelopment. Differences in 5-HT levels seen in the forebrain and hindbrain during both early and late developmental stages are thought to have a placental, but not maternal, origin in both mice and humans (Bonnin et al. 2011). During neurodevelopment, 5-HT derived from the placenta accumulates in the forebrain and hindbrain. Interestingly, placental 5-HT is likely to be important for early neurodevelopment as the SERT, 5-HT receptors and enzymes that are involved in the synthesis and breakdown of 5-HT are expressed before 5-HT producing neurons are present in these regions in mice (Bonnin et al. 2011). During this period outgrowth and guidance of axons is starting and is partly mediated by 5-HT in mice (Bonnin et al. 2007). Therefore it is likely that placental 5-HT is necessary for normal axon outgrowth and guidance mediated by 5-HT during early neurodevelopment. Thus SSRIs may interfere not only with fetal 5-HT signalling, but also with placental 5-HT signalling, and thereby they might alter normal development of the forebrain and hindbrain in the offspring via alterations in placental 5-HT signalling. Therefore the use of SSRIs before and during the start of embryonic development may, besides fetal 5-HT signalling, affect maternal and placental 5-HT signalling and subsequently alter 5-HT signalling involved processes in the early stages of the developing brain. It has been shown that the SSRI fluoxetine can significantly reduce placental tissue 5-HT content in rats from prenatal day 11 to 21 (Fornaro et al. 2007). Placental 5-HT has been implicated in both placentation (Oufkir et al. 2010) and embryogenesis (Cikos et al. 2011), thus disruption of 5-HT regulation in the placenta may affect the developing child. Therefore SSRIs may not only act directly on the brain of the developing child, but may also act indirectly on neurodevelopment via alterations in placental 5-HT signalling during early development. As a consequence the forebrain and hindbrain 5-HT levels, normally derived from the placenta during early development, may be affected and hindering the 5-HT mediated outgrowth and guidance of axons in these regions. Moreover, expression of genes in the placenta involved in multiple processes including cellular function and maintenance, growth and proliferation and cell death and survival were differently regulated in women treated with SSRIs during pregnancy compared to their matched controls (Olivier et al. 2015).

During human neurodevelopment the SERT plays an important role. In the developing human cortex the SERT can be seen from week 8 of gestation in humans (Verney et al. 2002). Interestingly, the SERT is expressed in embryonic thalamic and cortical neurons which do not express the SERT in adulthood, indicating that SERT and possibly 5-HT are important in these neurons during development (Cases et al. 1996; Lebrand et al. 1996; Narboux-Nême et al. 2008). Importantly, in mice the SERT was seen in raphe 5-HTergic neurons by day 12.5 of gestation, followed by expression of the SERT in the specific regions of the cortex, hippocampus and the dorsal thalamus by day 15.5 of gestation. The broad expression of this 5-HT related transporter, and the finding that the SERT is also expressed in neurons which do not express 5-HT, suggests that SSRIs might act on many neurons and brain regions. Furthermore, mice deficient for monoamine oxidase A, an enzyme responsible for degrading neurotransmitters, or the SERT leads to failure of normal segregation of thalamocortical axons (Cases et al. 1996). Moreover, decreasing 5-HT levels rescued this segregation suggesting 5-HT may inhibit this process. Inhibition of 5-HT reuptake may also lead to this failure of normal segregation of thalamocortical axons (Cases et al. 1996). As been mentioned before, 5-HT is also involved in the navigation of thalamocortical axons to the cortex and their response to netrin-1, a guidance cue (Bonnin et al. 2007). In addition, during formation of the somatosensory cortex in mice the temporary expression of the SERT mediates storage and reuptake of 5-HT in the developing thalamic neurons (Lebrand et al. 1996). This 5-HT uptake and storage seems to be necessary for normal development and fine tuning of cortical sensory maps in the development in rodents (Gaspar et al. 2003). These thalamic neurons can take up extracellular 5-HT and do not synthesize 5-HT themselves. In addition, the precision of thalamocortical circuitry projections toward the barrel cortex were reduced in SERT knockout rats (Miceli et al. 2013). Inhibiting the uptake of 5-HT could alter their 5-HT signalling and maturation of the thalamic neurons which may lead to alterations in circuitry involved in sensory information processing. Moreover, 5-HT innervation patterns in specific regions in the thalamus suggests that 5-HTergic neurons may affect emotional and cognitive functions (Linley et al. 2013). Therefore, administration of SSRIs during pregnancy might alter development of circuitry to and from the cortex. Interestingly, administration of the SSRI paroxetine in rats from postnatal day 0 to 8 (equivalent of the third trimester in humans) affected the development of neural circuitry in the somatosensory cortex when thalamocortical synapses were formed (Xu et al. 2004). However, inhibiting SERT using the SSRIs racemic citalopram and paroxetine to have an effect on the responsiveness of thalamic axons to guidance cues in development did not completely depend on SERT inhibition and thus these SSRIs may affect processes independent of 5-HT signalling (Bonnin et al. 2012).

Removing 5-HT during very early development in rats results in a reduction of neuron number in the adult hippocampus and cortex (Lauder & Krebs 1976). In addition, 5-HT is also important for dendritic development in the hippocampus and cortex (Yan et al. 1997). 5-HT concentrations in the hippocampus increase during the first two week of pregnancy, however decreasing these 5-HT levels using a neurotoxin reduced hippocampal type II corticosteroid receptor binding (Mitchell et al. 1990). Reduced levels of this receptors has been associated with psychotic depression (Schatzberg et al. 1985) and mood disorders (Webster et al. 2002). Furthermore, the spine density of dendrites from specific mouse neurons in the hippocampus can be reduced by the use of SSRIs during late development (treatment on postnatal days 4 to 22) (Zheng et al. 2011). Interestingly, the spine density in the hippocampus of these SSRI treated mice was increased at postnatal day 90 compared to untreated mice. The long term effect

observed in these mice due to SSRI treatment were anxiety and an impaired locomotor activity. In addition, exposure to SSRIs (fluoxetine) in early development of mice decreased dendritic complexity of pyramidal neurons in the somatosensory cortex (Lee 2009). Furthermore, the high levels of 5-HT during development can decrease the migration speed of cortical pyramidal neurons in mice (Riccio et al. 2012). Therefore indicating that 5-HT homeostasis is important for normal neocortical circuit formation and dysregulation of this homeostasis may result in a increased risk to develop 5-HT associated disorders. Thus, increased 5-HT levels due to SSRI treatment may alter migration of pyramidal neurons. Interestingly, the effects of the SSRI fluoxetine on the development of cortical neurons were not present after inhibiting the 5-HT_{3a} receptor and in 5-HT_{3a} knockout mice (Smit-Rigter et al. 2012). Therefore, the effects of SSRIs on neurodevelopment in cortical neurons, specifically the SSRI fluoxetine, may be mediated by the 5-HT_{3a} receptor.

Postnatal exposure in rats (comparable to the third trimester in humans) to the SSRI fluoxetine reduced cell proliferation in the hippocampus compared to untreated controls (Rayen et al. 2011). However, in these experiments administration of fluoxetine seemed to reverse the decrease in cell proliferation in the hippocampus and neurogenesis seen in the offspring of rats subject to stress during late gestation. Therefore it seems that the SSRI fluoxetine is beneficial for the development of the offspring when depressive-like behaviour is present. In addition, selectively bred rats that were exposed to the SSRI paroxetine showed abnormal behaviour compared to vehicle treated controls, as they spend more time immobilized in the forced swim test which suggests that they show depression-like behaviour (Glover et al. 2015). These selectively bred rats already had a relatively low behavioural response to novelty (called low responders), but these selectively bred rats were more anxious and showed depression-like behaviour compared to other selectively bred rats (called high responders) to novelty. These findings suggest that the use of SSRIs may worsen the already present disposition to anxiety and depression-like behaviour in the offspring. Furthermore, rats exposed to the SSRI paroxetine showed different expression of multiple genes (involved in many processes that may be important for neurodevelopment, including neurogenesis for instance) in both the amygdala and the hippocampus compared to untreated controls, ranging from postnatal day 7 to 75 (Glover et al. 2015). Therefore, alteration in the gene expression in the hippocampus and amygdala due to SSRI treatment may be due to the 5-HTergic circuitry present from the raphe nuclei which developed in early gestation.

Conclusions

In conclusion, it seems that disruption of different processes during pregnancy can underlie behavioural abnormalities in the offspring. First, maternal 5-HT signalling in very early development, independent of fetal HT-5, seems to be important for normal neurodevelopment of the offspring in mice (Côté et al. 2007). Therefore, very early treatment of maternal depression during pregnancy with the use of SSRIs might indirectly alter morphogenesis in neurodevelopment of the offspring, as it has been shown that certain SSRIs can decrease serum 5-HT levels (Alvarez et al. 1999). Thus, it would be interesting to see if SSRIs could have an influence on these structural changes found in mice and if this can alter behaviour in the offspring. Secondly, placental 5-HT seems to play an important role in normal neurodevelopment as well (Bonnin et al. 2011). Placental 5-HT levels are found in both the fore- and hindbrain before fetal 5-HT is present and it has been shown that the SSRI fluoxetine can reduce 5-HT content in placental tissue of rats. In this period outgrowth of axons and their guidance, which are partly mediated by HT-5, is starting. Thus SSRIs might act on placental 5-HT which in turn might affect the role of 5-HT in these processes. This suggest another indirect pathway in which SSRIs may act and alter processes in the fetal brain which are mediated by 5-HT signalling. Therefore, placental 5-HT levels might also be of importance in later neurodevelopment, since these placental 5-HT levels were found in both early and late developmental stages.

Thirdly, the direct effect of SSRIs on 5-HT signalling in the neurodevelopment of the child is most likely the most important path of SSRI induced alterations in the offspring. In humans, the receptor on which SSRIs can act, the SERT, is present from approximately week 8 (compared to day 12.5 in mice) (Verney et al. 2002; Narboux-Nême et al. 2008). This receptor is not only expressed in different brain regions, it is also expressed in both non-5HTergic and 5-HTergic cells. Therefore, SSRIs might not only act on cells that express 5-HT, but also cells that respond to extracellular 5-HT levels. In addition, the SERT is necessary for normal thalamocortical axon segregation (Cases et al. 1996). Therefore, SSRIs might not only act on thalamocortical axons through placental 5-HT but also directly act on fetal 5-HT and its role in circuitry formation in the thalamus, possibly affecting sensory information processing and emotional and cognitive functions in the offspring. In addition, other brain regions might also be affected by exposure to SSRIs during early neurodevelopment. In rats, both the total amount of neurons and dendritic development in the hippocampus and cortex rely on the presence of 5-HT in early development (Lauder & Krebs 1976; Yan et al. 1997). In addition, proliferation of cells in the hippocampus can be reduced by exposure to the SSRI fluoxetine (Rayen et al. 2011). Furthermore, SSRIs can reduce the spine density of dendrites from hippocampal neurons in late development in mice (Zheng et al. 2011). This in turn results in anxiety and impaired locomotor activity in these mice later in life, thus indicating that late exposure to SSRIs might also affect the behaviour of the offspring. It seems that the development of neuronal circuitry towards and possibly from brain regions like the cortex, hippocampus and thalamus are prime candidates for SSRI induced alterations. Interestingly, this might not be limited to 5-HTergic circuitry but might also be affecting non-5-HTergic circuitry. Specifically axonal outgrowth, segregation and guidance of neural axons may be important for the effects of SSRI on neurodevelopment and disruption of these processes may possibly lead to behavioural disorders later in life.

Distinguishing between the effects on neurodevelopment by either depression or SSRIs is important in properly understanding the risks of SSRI treatment during pregnancy. Knowing

the periods of neurodevelopment in which the developing child is most likely to develop behavioural disorders due to SSRI treatment is important to minimize the possible effects of SSRI treatment thus having minimal consequences for both the depressed mother and developing child. It seems that the period of neurodevelopment in which SSRI treatment is given is important and early developmental stages are most vulnerable as they are more associated with behavioural abnormalities in the developing child later in life. Treatment of maternal depression using SSRIs does not come without risks for the developing child. However, since depression can have a more severe effect on both the mother and the developing child, antidepressant treatment can be necessary to reduce health risks for both.

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