Myelin as the possible connection between antidepressant use and Autism spectrum disorder

What is the effect of using antidepressant during pregnancy on the fetal neurodevelopment regarding gene expression?

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Abstract

This paper examined the influence of selective serotonin re-uptake inhibitor (SSRI) use by the mother and its specific influence on the neurodevelopmental outcome of the fetus, including its relation to autism spectrum disorder (ASD). In humans, males show more significant changes in social behaviour when exposed to SSRIs during early development than females, which could be in line with males being more likely to develop ASD in general. Unfortunately, underlying mechanisms contributing to this vulnerability in males remain elusive. Some plausible leads have been brought up for discussion, like for instance the role of SSRI in altering the extra cellular matrix (ECM). The ECM, subsequently, plays an important role in the regulation and coordination of myelin. It is, however, unclear how and if there is a link between the ECM and ASD. This essay will therefor further explore this link. Although there is evidence on how perinatal SSRI exposure changes the ECM, which focusses on myelin-related gene expression, no overlap is found regarding specific components of the ECM that directly link the ECM to ASD.

Inhoud

Introduction

Depression is one of the most prevalent mental disorders globally. The risk of depressive symptoms is also widely affecting women during their pregnancy. Estimates of women experiencing depressive symptoms range from 10-20% (Woody et al., 2017), of which around 5% of women deal with a major depressive disorder (Melville et al., 2010). With these increases, we also see a worldwide increase in antidepressant use during pregnancy, with selective serotonin reuptake inhibitors (SSRIs) being the most prescribed antidepressant. In Europe, SSRI use during pregnancy is prevalent in 2-4% of women (Zoega et al., 2015), whereas in North America, according to Cooper et al, an increase in antidepressant use went from 5.7% in 1999 to 13.4% in 2003 (Cooper et al., 2007).

Due to both increases in depression rates and the use of SSRIs during pregnancy, there is an increased interest in both benefits and adverse effects of these two on the development of the child. Previous studies have shown that the use of SSRI is considered safe for both mother and child (Fischer Fumeaux et al., 2019). Furthermore, receiving no treatment for major depressive disorder during pregnancy may even be more harmful(Sandman et al., 1994; Wisner et al., 2000). Depression during pregnancy may have harmful consequences for the child, for example due to persistent behaviour patterns, like continued smoking by the mother (Edvinsson et al., 2019). There may be cognitive, emotional and behavioral consequences for both mother and child due to lack of treatment (Ryan et al., 2005).

On the other hand, there are also risks in the use of SSRIs during pregnancy. Research by Loughhead et al., 2006 states that '*the pattern of antidepressants concentrations in amniotic fluid is similar to data for placental passage, meaning that maternal antidepressants are accessible to the fetus'.* With SSRIs causing serotonin levels to increase, this is cause for concern because serotonin plays an important role in brain development and a disruption in its balance can potentially increase the risks of developing mental and behavioural disorders (Halvorsen et al., 2019).

Not much is known about the underlying mechanisms in behavioural change induced by SSRIs. A recent study by Ramsteijn et al 2022 investigated the effect of perinatal SSRI exposure and maternal adversity on gene expression levels in the offspring brain. For this study the authors used a rodent model that expressed behaviours of peripartum depression, similar to that observed in woman with depression. Ramsteijn et al. found that, compared to the vehicle, the SSRI fluoxetine upregulated myelin related gene expression in the prefrontal cortex (PFC) of males while downregulating these genes in the basal lateral area (BLA). Females only showed downregulation of myelin related genes in the BLA. Ramsteijn and colleagues showed that fluoxetine-induced changes in myelination could be facilitated by epigenetics (Anouschka S. Ramsteijn et al., 2022). With altered gene expression regarding myelination there is a link with the extra cellular matrix (ECM), as the ECM plays a role in the regulation of myelination (Buttery & ffrench-Constant, 1999; Marangon et al., 2020; Su et al., 2021). This raises the question what further implications antidepressant use may have on the development of the fetus and mainly in the PFC of males (Anouschka S. Ramsteijn et al., 2022).

The indirect influence of SSRI usage on gene expression in the fetus is cause for concern. Both serotonin and myelin have been implicated in neurodevelopmental disorders like autism spectrum disorder (ASD). In addition, several papers proposed a link between the ECM and neurodevelopmental disease like ASD (Loohuis et al., 2018; Rosenfeld, 2021). The paper by Staal et al., 2021 concluded that placentas nourishing male fetuses had 638 genes differentially expressed after prenatal exposure to the SSRI fluoxetine, compared to only 38 differentially expressed genes in placentas nourishing female fetuses. From these gene sets the most prominent changes were found for the ECM organization (Staal et al., 2021). This coincides with Ramsteijns finding of the ECM being

involved in altered gene expression regarding myelination (Ramsteijn et al., 2022b). Together with the research provided by Staal et al., about the link between SSRI and ECM it would be of great interest to elucidate the link between antidepressant use during pregnancy and how this effects the ECM, with the ECM subsequently being involved in the development of ASD. Grivas et al showed there is a 40% risk increase in developing ASD when using antidepressants during pregnancy (Grivas et al., 2021), however untreated depression during pregnancy also increases the risk of ASD in the offspring (Kaplan et al., 2017). Hence this thesis will address and evaluate the following topics: What is the effect of using antidepressant during pregnancy, on gene expression in the brain, for the fetal neurodevelopment? How is the extra cellular matrix affected? In what way are changes in the ECM and altered brain gene expression in the offspring linked? And finally, can we link the ECM alterations due to perinatal SSRI use to ASD in the offspring?

The role of serotonin in the placenta

The placenta is an important and diverse organ in the mammalian kingdom, playing a central part in the development of the embryo. During the gestational period it facilitates and protects the fetus. It helps in maintaining homeostatic balance, passing of nutrients and hormones from maternal side, and safeguarding the pregnancy overall (Burton & Fowden, 2015). During gestation the brain of the fetus is highly vulnerable to many neurobehavioral disorders when disruptive changes occur in the placenta (Mueller & Bale, 2008). Disruptive changes can come in all sorts of varying factors, ranging from certain toxins in the maternal bloodstream to high levels of maternal stress. These factors can then influence the homeostatic balance in the placenta, like that of serotonin levels on the fetal side of the placenta (Mueller & Bale, 2008; Ryan et al., 2005).

With increasing numbers of woman dealing with depression during pregnancy an increase in SSRI usage during pregnancy is observed (Cooper et al., 2007; Woody et al., 2017; Zoega et al., 2015). SSRIs have been found to not only impact the maternal brain, but also affect 5-HT levels in the fetal brain as maternal antidepressants are transferred across the placenta increasing extracellular 5-HT which then also circulates to the fetal brain (Loughhead et al., 2006; Rosenfeld, 2021). The role of 5-HT is to stimulate cell division, neuronal migration, cell differentiation and synaptogenesis (Yang et al., 2014).

Serotonin, which functions as a neurotrophic factor (Ansorge et al., 2007), plays a major role in the neurological development of the fetal brain (Kiryanova et al., 2013). The placenta being a hormone producing organ it also produces serotonin that may influence the brain development of the fetus and disturbances may be linked to neurobehavioral disorder like ASD (Rosenfeld, 2021). Serotonin may also be passed on to the fetus through the mothers plasma, as some evidence argues it can cross the placental barrier (Côté et al., 2007). However, other research rules out this possibility (Ganapathy et al., 1993; Koren et al., 1966). Fetal serotonin is said to originate from the placenta(Bonnin et al., 2011; Hudon Thibeault et al., 2017), although it is suggested that the placenta is reliant on 5-HT from the maternal side (Kliman et al., 2018). Maintaining adequate levels of serotonin is important and offsets can disrupt early neural programming, such as during placental hyperserotonemia or hyposerotonemia (Rosenfeld, 2021). Interestingly, changes in placental 5-HT production are linked to an increase in the risk of autism spectrum disorder (ASD) (Sato, 2013; Yang et al., 2014). As such, low levels of 5-HT, leading to hyposerotonemia, can impair sensory, motor, and cognitive abilities, which may lead to ASD (Yang et al., 2014). Elevated levels of serotonin, or hyperserotonemia, can result in a negative feedback loop inhibiting the signalling of 5-HT by supressing the expression of corresponding receptors in the 5-HT subfamilies (Rosenfeld, 2021; Yang et al., 2014). This results in elevated levels of 5-HT in the placenta (Rosenfeld, 2021), which can

hinder the production of oxytocin by the paraventricular nucleus of the hypothalamus and increase calcitonin gene related peptide (CGRP) in the central nucleus of the amygdala (Rosenfeld, 2021). Both factors are important in promoting social behaviour, something that is impaired in ASD (Rosenfeld, 2021). Another way through which 5-HT levels influences the brain development is by elevated extracellular 5-HT levels adversely affecting oligodendrocytes (OL) survival, development and myelination (Fan et al., 2016*).* OL play a key role in the metabolic support of neurons, and myelin in supporting and speeding up the signal transduction in these neurons (Daubert & Condron, 2010*).* The changes in 5-HT levels may contribute to altered neural connectivity due to abnormal outgrow and reduced expression of myelination protein, causing a reduced myelination of internodes in the brain (Fan et al., 2016). This elucidates the importance for the placenta to keep a right balance in the amount of 5-HT. As this balance is susceptible to the disruptive effects of SSRI, treatment with SSRIs could indirectly affect the OL survival and myelination.

A paper by Staal et al., 2021 describes how gene expression in the placenta is altered in woman treated with the SSRI fluoxetine (FLX). Their objective was to study the impact of gene expression alterations in the maternal serotonergic system on the placenta, by analysing the complete transcriptomes of the placenta obtained from pregnant woman who had normal pregnancies and those who were treated with the SSRI FLX. FLX exposure during prenatal development showed a significant difference in gene expression in male nourishing placentas compared to controls. A total of 638 differently expressed genes (DEGs) where identified. This in stark contrast to only 31 DEGs that were found in the female nourishing placentas exposed to FLX prenatally. In the male placentas, around one-third of the DEGs switched from a high expression level in control placentas to a lower expression in the SSRI treated group. The other two-thirds of the DEGs were strongly upregulated after SSRI treatment. In the female nourishing placentas there was no strong effect in the expression of these genes (Staal et al., 2021).

Many of the DEGs in the Staal et al. study affect processes of the ECM. They found that in male nourishing placentas there was an upregulation of three integrins; Integrin Alpha 2, Integrin Alpha 5, and Integrin Alpha 11. Alpha 11 integrin is exclusively associated with the β1 subunit at the cell surface, to form the α11β1 integrin (Zeltz & Gullberg, 2012). This integrin plays a role in collagen recognition and promotes proliferation of myelinating cells. However, for the integrin with the strongest correlation to ASD, ITGB3, which is listed in the Simon Foundation Autism Research Initiative (SFARI), no effect on gene expression by FLX was found. There are two other genes listed in the SFARI that were differently expressed due to FLX, kcnb1 and tcf7L2, but these seem to have no association with either the ECM or myelin.

Maternal adversity and SSRI use cause alterations in offspring brain gene expression

Maternal depression and prenatal SSRI exposure both affect the developing brain (Rosenfeld, 2021; Rotem-Kohavi et al., 2019). Particularly the corticolimbic structures are affected as they rely most on serotonin during early fetal development (Duan et al., 2019; Soe et al., 2018; Wen et al., 2017). A study by Ramsteijn et al., (2020) investigated the transcriptomic alterations in the corticolimbic circuitry of male and female juvenile rats after exposure to maternal adversity and/or perinatal SSRI exposure. They used female Wistar rats with a heterozygous serotonin transporter (SERT) knockout background as model for maternal vulnerability (MV) as they were shown to be susceptible to early life stress (Houwing et al., 2019; Smits et al., 2006). These female rats where either exposed to stress

(sMV) or control handled (cMV) early in life. During pregnancy and lactation, they were given either fluoxetine (FLX) or the vehicle methylcellulose (Veh).

The authors found that in the group of FLX-exposed males several gene sets were upregulated in the PFC, namely: OL differentiation, OL development, myelin sheath and myelination (see figure 1). On

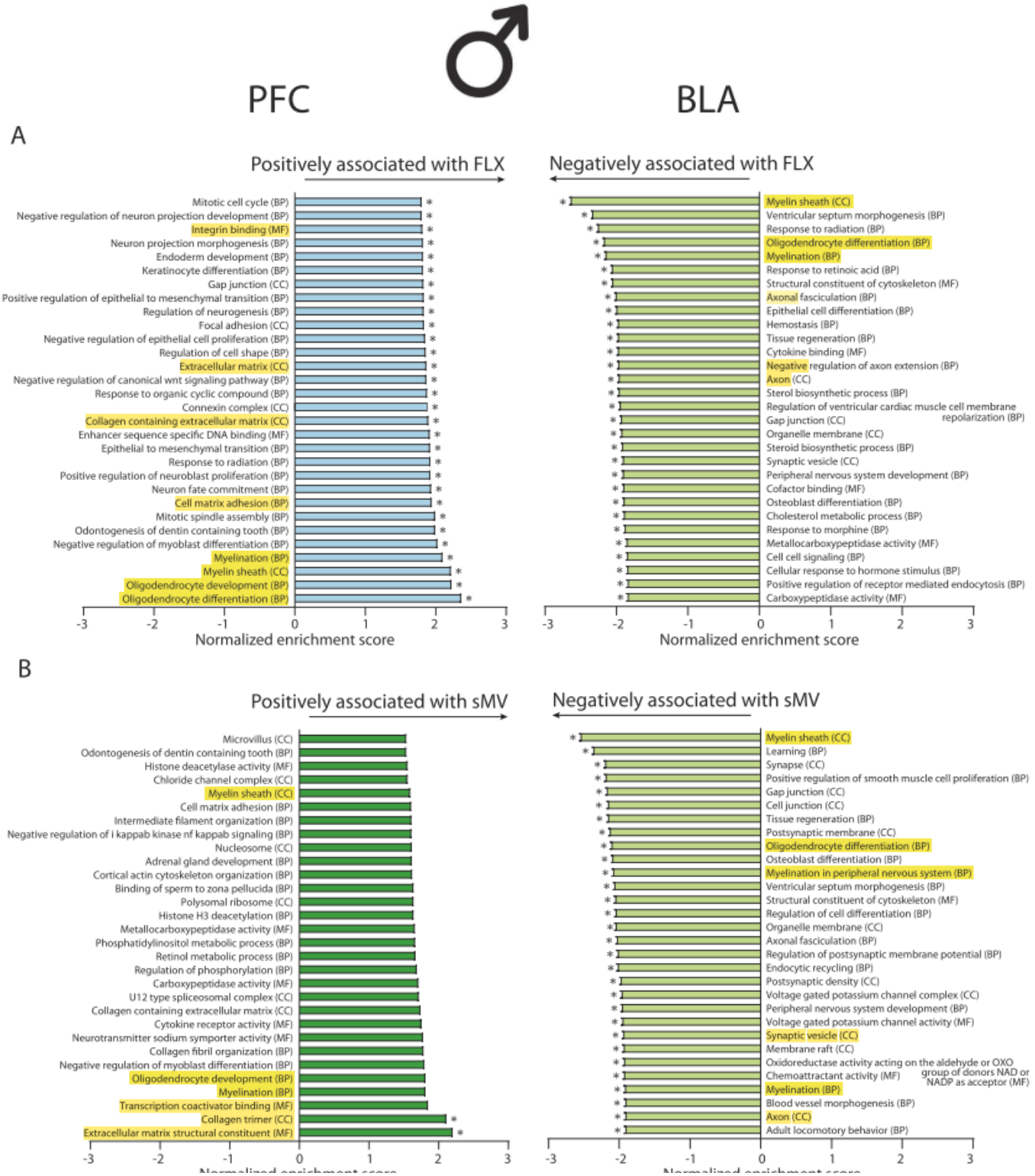

Figure 1 Brain region- and sex-specific effects of perinatal fluoxetine and maternal adversity on gene expression. A The effect of fluoxetine exposure (cMV-FLX vs. cMV-Veh) in males. B The effect of maternal adversity (sMV-Veh vs. cMV-Veh) in males. ECM and Myelin-related gene sets are highlighted in yellow. Asterisk (*) indicates FDR <0.25. (Ramsteijn et al., 2022a)

the other hand, a downregulation of the gene sets Myelin sheath, OL differentiation and Myelination was observed in the BLA. A similar effect was observed in the group of sMV-exposed males. For the female groups FLX caused downregulation of gene sets related to cell maintenance and proliferation in the PFC. In the BLA only a significant upregulation of Cellular oxidant detoxification was observed. The sMV-exposed females showed more significant changes in both PFC and BLA (Ramsteijn et al., 2022). The most profound changes were found in the male group exposed to FLX, with a downregulation in the BLA relating to myelin. The sMV female group showed the most significant changes in gene expression in the PFC. Although the female FLX group showed no significant changes in myelin related genes in the BLA it did show a similar response compared to the effect in the BLA of the male FLX group, but missed significance. Besides changes in myelin related gene sets the results also show significant changes in males exposed to FLX relating to the ECM. Collagen containing ECM, integrin binding and cell matrix adhesion are upregulated in the PFC. (Ramsteijn et al., 2022)

Most changes in offspring brain gene expression due to the SSRI FLX seem to relate directly to myelin or indirectly by changes in OL and ECM. OL plays an important role in the forming of myelin sheath around axons to ensure fast signal transduction and providing support to neurons in the central nervous system (CNS) (Stadelmann et al., 2019). This is in line with other research that also showed a correlation between SSRI exposure and myelin related gene expression (Kroeze et al., 2015). The research by Ramsteijn et al. showed a clear difference between sexes with males being more susceptible to altered gene expression due to SSRI exposure (Ramsteijn et al., 2022). This could hint at an interesting correlation with the fact that males generally are more likely to develop ASD, with four times increased chances of that compared to females (Werling et al., 2016). Furthermore, the results of the Ramsteijn et al. study showed an increase in myelin-related gene expression in the PFC of males. By measuring the neural activity in oligodendrogenisis, the research by Teissier et al. states that an increase in myelination related genes at PND15 cause a decrease in expression later in life, due to oligodendrocytes differentiating in the male PFC at PND15 resulting in depletion of oligodendrocytes later in life (Bordner et al., 2011; Teissier et al., 2017). This decrease could cause hypomyelination in the mPFC which is associated with decreased social behaviour, which is a symptom of ASD (Graciarena et al., 2019). A paper by Phan et al., stated that implications in OL and myelination are a common pathophysiology across the ASD spectrum (Phan et al., 2020). Evidence suggests that both hyper and hypo myelination can be present in individuals with ASD, suggesting that the effects are different for the specific brain areas. This coincides with the results in Ramsteijns research showing increased expression in PFC and decreased expression in BLA. These data indicate that pathologies are rather due to balance disturbance than specific up or down regulation of genes related to the ECM and myelin. To unravel the path between SSRI use and fetal neurodevelopment, we will look into the role of ECM in myelin development next.

Effect of ECM on myelin development and ASD

The ECM is a complex network of proteins and macromolecules outside the cells. It plays an important role in processes like cell adhesion, migration and differentiation which are crucial for regulating development and functions of the cell. Through cellular connections it gives physical support to cell structures. The main macromolecules present in the ECM are collagen, glycosaminoglycans (GAGs), non-collagen glycoproteins and elastin (Su et al., 2021). The interaction between cells and the ECM is mainly through the cell-surface proteins called integrins. Integrins play a role in the development of the nervous system by regulating processes that are associated with neural connectivity. Like neurite outgrowth and guidance, formation and maintenance of dendritic spines, and synaptic plasticity (Lilja & Ivaska, 2018). The integrin family are transmembrane

heterodimer receptors, consisting of an alpha and beta unit, and act as the bidirectional link between the ECM and the intracellular protein skeleton (Moreno-Layseca et al., 2019).

Growth and the regeneration of myelin is regulated by the ECM and with the ECM taking up 1/5th of the space in the brain it plays an important role, ECM disfunction has been linked to neurodevelopmental diseases (Reinhard et al., 2015; Rogers et al., 2018). Several studies showed a strong correlation between demyelinating disease in the CNS and changes in the ECM (Chudakova et al., 2008; Marangon et al., 2020).

In the CNS, oligodendrocytes express several integrins with various functions, such as αvβ1, α6β1, αvβ3, αvβ5, αvβ8 (Milner & ffrench-Constant, 1994). These integrins are crucial in regulating the development of the oligodendrocytes; promoting migration, adhesion, proliferation, differentiation myelination and more, which is further shown in Table 1 (Su et al., 2021).

Table 1 The regulatory role of several integrins in the development of oligodendrocytes (Su et al., 2021).

Integrin	Role in the regulation of oligodendrocytes	References
αvβ1	OPC migration, adhesion, proliferation and differentiation	(Milner et al., 1996; Milner and Ffrench-Constant, 1994; Blaschuk et al., 2000; Gudz et al., 2006)
α6β1	Oligodendrocyte survival and myelin membrane formation	(Buttery and Ffrench-Constant, 1999)
αvβ3	OPC proliferation and differentiation	(Blaschuk et al., 2000; Gudz et al., 2006)
αvβ5	OPC differentiation and myelination	(Milner et al., 1996; Milner and Ffrench-Constant, 1994)
αvβ8	Oligodendrocyte differentiation	(Milner et al., 1997; Baron et al., 2005)

The alterations in the extracellular matrix during the growth and repair of myelin indicate that the extracellular matrix has diverse roles during different stages of development and disease. These different roles are roughly summarized in table 2 (Su et al., 2021).

Collagen, one of the ECM components, in the CNS plays a role in the proliferation of oligodendrocyte precurser cells (OPC) (Mehta & Piao, 2017). During its differentiation, OPC undergoes a continuous migration towards its axonal target, and ultimately mature OLs wrap the axon at the appropriate location to create the myelin sheath (Su et al., 2021). Research by Su et al., indicates that the migration of OPC is significantly influenced by integrin αvβ1 together with the recognition of other

Table 2 ECM and Integrin receptors associated with myelin development and regeneration in the CNS (Su et al., 2021).

ECM component	Role in myelinating cells	Integrin receptor
Collagen	Promotes proliferation and inhibit migration	$\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_{10}\beta_1$, $\alpha_{11}\beta_1$, $\alpha_v\beta_8$
Fibronectin (FN)	Promote proliferation; Inhibit differentiation and remyelination	$\alpha_3\beta_1$, $\alpha_4\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$, $\alpha_v\beta_1$, $\alpha_M\beta_2$, $\alpha_X\beta_2$, $\alpha_D\beta_2$, $\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_4\beta_7$, $\alpha_v\beta_8$
Vitronectin (VN)	Promotes differentiation	$\alpha_8\beta_1$, $\alpha_v\beta_1$, $\alpha_D\beta_2$, $\alpha_1\beta_3$, $\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$ $\alpha_v\beta_5$, $\alpha_v\beta_8$
Laminin 2 (LN-2)	Promotes survival and myelination	$\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_3\beta_1$, $\alpha_4\beta_1$, $\alpha_6\beta_1$, $\alpha_7\beta_1$, $\alpha_6\beta_4$, $\alpha_v\beta_8$
Hyaluronic acid (HA)	Inhibits differentiation and remyelination	$\alpha_5\beta_1$
Tenascin C (TN-C)	Inhibits differentiation and myelination	$\alpha_2\beta_1$, $\alpha_8\beta_1$, $\alpha_9\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_6$
Tenascin R (TN-R)	Complex roles	

ECM components such as laminin (LN), fibronectin (FN) and vitronectin (VN). These integrins present on OPCs facilitates their movement, whereas unrecognizable collagen impedes their migration and thus hinders healthy axonal growth (Milner et al., 1996). In the research by Ramsteijn we see a positive association with FLX in the male rat PFC regarding Integrin binding and ECM containing collagen. This could mean that OL development would also be enhanced, which is also shown in Ramsteijns results. This in turn correlates with findings that show that children with ASD show excessive neuronal overgrowth in the PFC, with estimates showing an increase of 67% compared to children with healthy neurodevelopment (Courchesne et al., 2011). This neuronal overgrowth would thus require an increase in OPC proliferation and subsequent myelination to have taken place.

Research by Sloan Warren et al. (2012) focused on the importance of β1 integrin and its subsequent signalling in hippocampal neurons. In these neurons, it has been discovered that β1 integrin signals through the non-receptor tyrosine kinase Arg to regulate dendritic branching, synapse plasticity, and behaviour in the postnatal mouse hippocampus (see figure 2) (Sloan Warren et al., 2012). Furthermore, it has been demonstrated that β1 integrins have a regulatory function in long-term potentiation (LTP) in the hippocampus (Babayan et al., 2012; Kerrisk et al., 2014; Staubli et al., 1990). LTP in the hippocampus has shown deficits in several ASD mouse models (Hansel, 2019; Yin et al., 2012). Together, these results imply that a possible dysregulation of β1 integrins can cause the impaired LTP formation in the brain of ASD, linking the ECM to ASD.

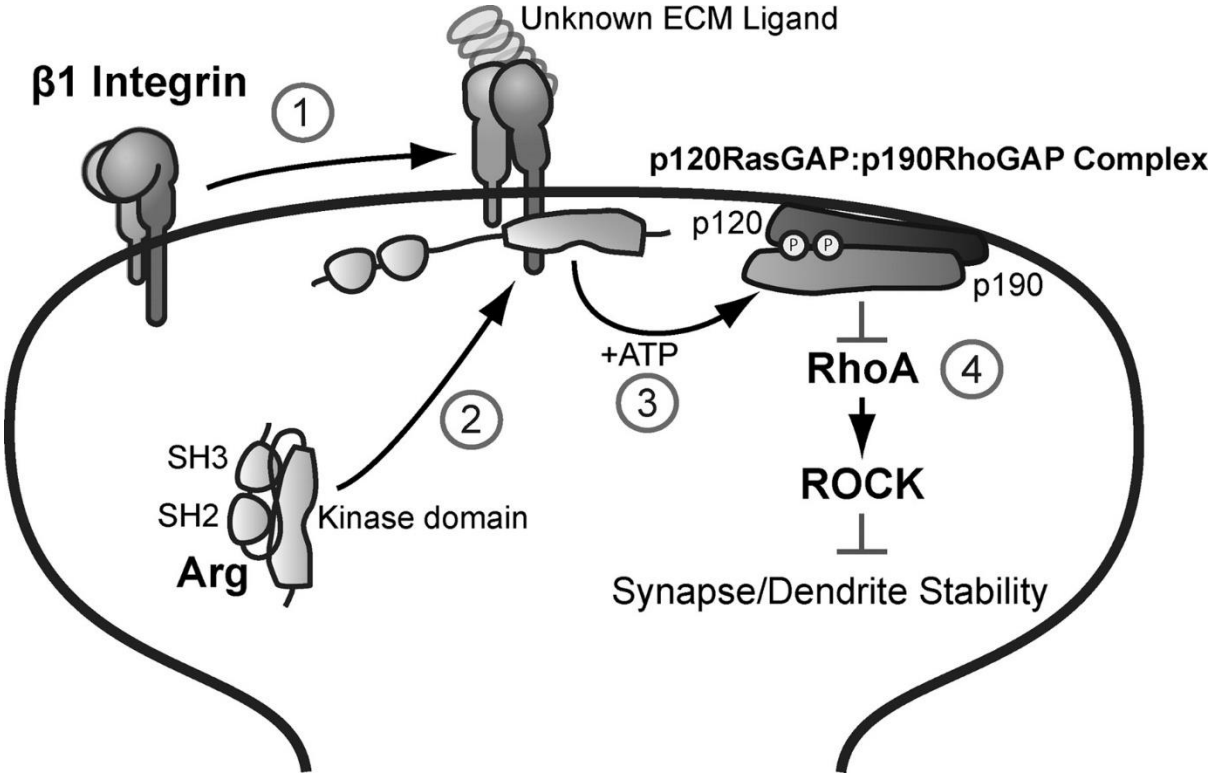

Figure 2. Model for integrin β1–Arg signaling in dendritic spines. (1) Integrin β1 is activated by binding to an unknown ligand. (2) The Arg kinase domain binds to the now exposed integrin β1 tail, stimulating Arg kinase activity by relieving autoinhibitory contacts between the SH3–SH2 domains and the kinase domain. (3) Arg phosphorylates p190RhoGAP, promoting its association with p120RasGAP at the membrane. (4) The p120RasGAP:p190RhoGAP complex inhibits RhoA, stabilizing synapses and dendrites. Sloan Warren et al. (2012)

Furthermore, a genetic-linkage study also identified an association between the gene encoding for the integrin β3-subunit, ITGB3, and ASD (Carter et al., 2011; Dohn et al., 2017; Lilja & Ivaska, 2018; Napolioni et al., 2011; Schuch et al., 2014). Besides playing a role in OPC proliferation and differentiation, β3 integrin expression regulates the brain 5-HT system (Weiss et al., 2004, 2006). Enhanced integrin signalling to the focal adhesion kinase, a significant non-receptor tyrosine kinase,

and an increase in the expression or active β3 integrin variants are responsible for modulating the function of the serotonin 5-HT transporter (SERT) leading to increased whole-blood serotonin levels. Interestingly elevated 5-HT levels have been associated with developmental abnormalities of ASD (Cook & Leventhal, 1996; Dohn et al., 2017; Jaiswal et al., 2015). Thus, β3 integrin is of interest as it links the ECM and altered brain serotonin levels, which have been associated with ASD.

Discussion

The relevance of this thesis is based on the increased number of woman experiencing depression during pregnancy, resulting in increased usage of antidepressants during pregnancy where percentages reach as high as 13.4% in certain continents (Cooper et al., 2007). The cause for concern mainly comes from evidence that SSRI do not only influence the maternal brain, but can also find their way into the amniotic fluid (Loughhead et al., 2006; Rosenfeld, 2021). This means that antidepressants can cross the placenta and thus can affect the foetus. This accessibility of SSRI on the fetal side influences serotonin levels, which balance is crucial for healthy neurodevelopment. A disbalance due to the effects of SSRI usage is hypothesised to influence the risk of the neurodevelopmental disease ASD (Rosenfeld, 2021). During the collecting and reviewing of the literature relevant to the effect of SSRI usage during pregnancy, the main focus is on how myelin is involved in the neurodevelopment of the foetus. And how myelin may serve as a linking factor between SRRI usage and changes in the ECM, and respectively how the ECM has a possible influence on the development of ASD.

The main findings in the literature are that there are multiple ways in which SSRI usage may be linked to ASD. One of which is the role of serotonin in the placenta and how this neurotransmitter plays a major role in neurological development of the fetal brain (Kiryanova et al., 2013). Initially the placenta is the main source of serotonin for the foetus (Rosenfeld, 2021). SSRIs can cause hyper serotonemia which impact oxytocin production in the paraventricular nucleus of the hypothalamus and CGRP in the amygdala, which both play a role in social behaviours and this impairment is a characteristic of ASD (Rosenfeld, 2021; Yang et al., 2014). Hyper serotonemia has also been shown to affect OL survival, development and myelination (Fan et al., 2016). The latter is experimentally validated in rat studies. The study by Ramsteijn et al., (2022) showed that in male rats the effects of the SSRI FLX is most profound compared to females. Here FLX caused site specific changes in gene sets directly related to the ECM and through gene sets influencing myelination. Myelination and the role of OL are of interest as disruptions have been linked to ASD (Phan et al., 2020). The ECM plays an important role in regulating processes of myelination and various aspects related to the role of OL. Genetic linkage studies have linked a specific integrin β3-subunit, which is part of the ECM, to ASD (Carter et al., 2011; Dohn et al., 2017; Lilja & Ivaska, 2018; Napolioni et al., 2011; Schuch et al., 2014). However Ramsteijn et al., (2022) looked into how SSRI affect gene regulation during fetal development and did not find changes in expression related to this specific integrin. They did however find other integrins to be upregulated, but these have so far not been linked to ASD.

The effect of antidepressant use during pregnancy on fetal development regarding brain gene expression, shows to impact the neurodevelopment of the foetus by altering the expression of myelin related gene sets. Studies by Ramsteijn et al., (2022) and Houwing et al., (2019) on rats showed that antidepressant use in the form of the SSRI FLX during pregnancy, male offspring are more susceptible than females concerning changes in gene expression. This correlates with the observation that male offspring showed a decrease in social interaction later in life, which can be taken as a symptom of ASD. Whereas female offspring showed no such effect on social behaviour (Houwing et al., 2019). Although no hard conclusions can be made on this basis it is interesting to

note that this finding is in line with the fact that males are up to four times more likely to develop ASD (Werling et al., 2016). Furthermore, the study by Ramsteijn et al., (2022) showed that the effects of FLX are site specific. In the male PFC significant upregulation of ECM and myelin related gene sets was observed where in the BLA these gene sets were downregulated. In the group exposed to stress but not given FLX, significant changes in expression of similar gene sets were found, although less compelling. This indicates that FLX causes a change in gene expression levels in the brain, where untreated depression can influence these levels similarly but show to be less significant. Future research could look further into the effect of SSRI during specific stages of pregnancy and see if it can limit the impact of SSRI during vulnerable stages.. As research has shown that an increase in myelin gene sets during PND15 can later in life cause hypomyelination in the PFC, being a symptom of ASD (Bordner et al., 2011; Teissier et al., 2017). Future research could look into site specific inhibition of myelin related gene sets in the PFC during PND15.

The ECM plays a role in myelin development, which is of interest as myelin deficits have been linked to ASD (Reinhard et al., 2015; Rogers et al., 2018). The complexity of the ECM is still widely studied due to the diverse role all throughout the body. The ECM to cell interaction is mediated by different integrin families. One of these, β3-subunit, has specifically been linked to ASD and is listed in the SFARI. It plays a role in regulating 5-HT levels in the brain. Increased expression causes an increase of 5-HT, which is often seen in ASD (Cook & Leventhal, 1996; Dohn et al., 2017; Jaiswal et al., 2015). Another integrin, β1, is not listed in the SFARI but has been shown to regulate LTP in the hippocampus which is partially impaired in ASD mouse models (Hansel, 2019; Yin et al., 2012). The studie by Staal et al., (2021) looking into the effect of SRRI did not find changes in these specific integrins. However, Staal et al., did find changes in the expression of Integrin Alpha 2, Integrin Alpha 5, and Integrin Alpha 11, which where upregulated in male placentas. These are involved in various aspects of myelination depending on which beta sub unit they are bound to, but have not been directly linked to ASD. But this does show that male placentas exposed to SSRI, significantly impacts the ECM related gene expression regarding myelination which is connected to ASD.

The research has some limitations and points to address. First regarding the question ‘what the effect is of using antidepressants during pregnancy on the fetal development regarding gene expression?’ It should be noted that the focus remained on SSRI usage and its impact, opposed to SSRI usage counteracting the impact of the depression itself. The importance of this is to elucidate the possible risk of misdiagnosing or wrong dosage of a SSRI. From the literature most significant changes have been found in males, which corresponds with ASD being most common in males. This does not mean that research in the field regarding females should be ignored. Furthermore, the findings that have been discussed are the products of research done on different animal models of which none exactly replicate the human placenta. This leads to the fact that the results are more indications and hypothesis on how SSRI usage might impact ASD in human pregnancies. Also, different forms of antidepressants are taken all over the world, the most common being SSRIs. And within the SSRI classification there are also different sorts, here the focus was mainly on the impact of FLX.

Future research could look more into the limitations that are addressed here. It can be interesting to see how different SSRIs impact gene expression differently, especially those related to myelin, as certain SSRIs have a higher or lower diffusion rates across the placenta (Ewing et al., 2015). Furthermore, there appears to be a link, in the form of myelin related gene sets, between SSRI use and changes in ECM and how ECM is involved in ASD. Mainly OL appear to play a major role in ASD and is also largely affected by SSRI use. The difficulty lies mainly in the diverse role OL play throughout the body, with increased myelination at on place and a decreased at another. By diving

into the molecular aspects of OL differentiation, migration and proliferation in specific areas of the brain it could help in making specific treatment counteracting the balance disturbances due to SSRI.

Conclusion

To conclude, using antidepressants while pregnant can influence the neurodevelopment of the fetus through altering gene expression levels. These alterations may increase the likelihood to develop neurodevelopmental diseases like ASD. Alterations in myelin-related gene sets could be a partial explanation to certain pathologies found in people with ASD. SSRIs also appear to influence the ECM, the ECM has been linked to the development of ASD. However the direct link between how SSRIs influence aspects, like expression changes of specific integrins, in the ECM which are also linked to ASD have thus far not been found. Further research is needed to investigate this link and see if the changes due to SSRI can be counteracted.

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