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“A Role for the Serotonin Reuptake “Transporter in the Brain and Intestinal Features of Autism Spectrum Disorders and Developmental Antidepressant Exposure”

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Abstract

Many disease conditions considered CNS-predominant harbor significant intestinal comorbidities. Serotonin (5-HT) and the serotonin reuptake transporter (SERT) have increasingly been shown to play important roles in both brain and intestinal development and long-term function. 5-HT and SERT may thus modulate critical functions in the development and perpetuation of brain-gut axis disease. We discuss the potential roles of 5-HT and SERT in the brain and intestinal manifestations of autism spectrum disorders and developmental antidepressant exposure. The potential therapeutic value of 5-HT₄ modulation in the subsequent treatment of these conditions is also addressed.

Keywords

serotonin; serotonin reuptake transporter; autism spectrum disorders; antidepressants; selective serotonin reuptake inhibitors; brain-gut axis; 5-HT₄ receptor

Researchers and clinicians have increasingly recognized that medical conditions that affect the brain may also impact the intestine. This recognition has led to a surge in research focusing on the links between gastrointestinal (GI) pathology and psychiatric conditions such as anxiety and depression¹⁻³. The bidirectional relationship that exists between the brain and the gut, termed the “brain-gut axis”, seems to play a critical role in these conditions and recent studies in this field have largely focused on the role of the intestinal microbiome^{2,4,5}. Although the evidence for the existence of the gut-brain-microbiota axis is strong, many of these studies provide associations rather than a causal nexus⁴. Another factor critical to further understanding brain-gut diseases should therefore include the determination of specific shared modulators of brain and gut development. Exploration of the role of serotonin (5-hydroxytryptamine; 5-HT) and the 5-HT reuptake transporter (SERT) in brain-gut disease is in its infancy but the information available thus far is intriguing and supports important roles for 5-HT and SERT in the development and long-

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term function of both organ systems⁶⁻¹⁰. Prior studies support the idea that 5-HT and SERT play key roles in the brain manifestations of individuals with autism spectrum disorders (ASD)^{11,12} or those exposed to the antidepressants, selective serotonin reuptake inhibitors (SSRIs), during neurodevelopment^{13,14}. Recent research, however, endorses the notion that SERT regulation of 5-HT may also be critical in the intestinal manifestations of both of these conditions⁶

5-HT and SERT are located in both the brain and the intestine. The vast majority of 5-HT research has been in the brain where it has been demonstrated to be a key modulator of both central nervous system (CNS) development and behavior¹⁵. 95% of the body's 5-HT, however, is actually found in the intestine where it plays critical roles in enteric nervous system (ENS) development and the GI functions that the ENS modulates, including enteric neurogenesis and GI motility^{6,15-18}. Intestinal SERT is present on both enteric neurons and intestinal epithelial cells¹⁵. As in the brain, SERT is the primary intracellular transporter of intestinal 5-HT, and this transport leads to the inactivation of 5-HT by monoamine oxidase¹⁹⁻²¹. Changes in SERT-mediated 5-HT clearance could thus affect all 5-HT-mediated ENS functions.

One major difference in 5-HT synthesis between the brain and the intestine is in the isoforms of tryptophan hydroxylase (TPH), the key 5-HT biosynthetic enzyme, that each contains. One TPH isoform (TPH2) exists in the CNS while two (TPH1 and TPH2) exist in the intestine, each with its own distinct location; TPH1, located in enterochromaffin (EC) cells and in mast cells in mice and rats, synthesizes the largest pool (90%) of intestinal 5-HT. The remaining 10% is generated by TPH2, which resides in serotonergic neurons of the ENS¹⁵. TPH1 and TPH2-derived 5-HT play important, differing roles in intestinal development and function^{8,16,22}. EC-cell-derived 5-HT stimulates extrinsic sensory nerves that transmit signals of discomfort to the CNS while the neuronal pool of 5-HT, partially through binding to the 5-HT₄ receptor, can stimulate a variety of GI functions including enteric neurogenesis, motility and intestinal epithelial cell proliferation. In GI motility, TPH1- and TPH2-derived 5-HT may be complementary; although TPH2-derived 5-HT is the major modulator of GI motility, there may be a subtle, yet distinct role for TPH1-derived 5-HT in the coordination of GI peristalsis²³⁻²⁵. Abnormalities in SERT availability or efficacy may also affect 5-HT mediated GI function through alteration of TPH1 and/or TPH2 levels²⁶.

Recent data has highlighted the potential importance of SERT in the brain-gut manifestations of ASD and developmental SSRI exposure²⁶. ASD is a condition characterized by deficits in social interaction, deficient communication and repetitive behaviors²⁷. ASD prevalence has increased substantially over the past several decades with the most recent studies suggesting a prevalence rate of 1 in 68²⁸. Despite the commonality of the diagnosis, the etiologies underlying the condition are complex and largely unknown. This lack of understanding has delayed the creation of novel therapeutics to treat the condition. Although ASD is characterized behaviorally, it is often accompanied by GI problems. GI issues are over 4-fold more common in individuals with ASD and constipation is the most frequent complaint²⁹. Further, the resulting discomfort that is generated by the GI problems is often accompanied by severe behavioral problems including self-injury and

aggression^{29,30}. It is not yet known why the GI, brain and behavioral manifestations simultaneously occur in this subset of individuals with ASD though there may be a connection to underlying abnormalities in SERT and 5-HT signaling.

Multiple SERT coding variants, that all confer SERT hyperactivity, are overexpressed in individuals with ASD^{11,31}. Interestingly, platelet 5-HT, which is almost entirely derived from the GI tract, is increased in about one-third of individuals with ASD and has been shown to correlate with lower GI symptoms, such as constipation^{7,11}. Knock-in mice containing the most common hyperactive SERT variant overexpressed in children with ASD, SERT Ala56, display hyperserotonemia, CNS- and ENS-based abnormalities, suggesting that constitutively increased SERT activity interferes with the 5-HT signaling required for normal brain and gut development and long-term function^{26,32}. In the brain, these mice demonstrate high levels of 5-HT clearance, hypersensitivity of 5-HT_{1A} and 5-HT_{2A} receptors, and behavioral abnormalities reminiscent of ASD. ENS development is also markedly abnormal³². The myenteric and submucosal plexuses of the ENS are hypoplastic with abnormalities in neuronal subtypes specifically generated after serotonergic neurons during development. These include those subsets expressing tyrosine hydroxylase, calcitonin gene related peptide and gamma-aminobutyric acid²⁶. These observations are consistent with the idea that the increased 5-HT clearance of SERT Ala56 mice interferes with enteric neurogenesis. A similar ENS phenotype is observed in TPH2KO mice, further supporting the notion that enteric neuronal 5-HT is an ENS growth factor and that factors that decrease neuronal 5-HT signaling cause decreases in enteric neuronal growth³³.

The abnormalities in ENS development in the SERT Ala56 mice result in defective motility. GI motility measured both in vivo (GI transit time and colonic transit) and in vitro (velocity, frequency, and length of conduction of contracting migrating motor complexes [CMMCs]) are decreased in the SERT Ala56 mice²⁶. Because CMMCs are exclusively ENS-dependent³⁴, it is evident that the GI motor abnormality in the SERT Ala56 mice is directly related to the abnormal development of the ENS.

The SERT Ala56 hyperactive variant led to increased GI expression of both of the 5-HT biosynthetic enzymes TPH1 and TPH2, suggesting that the decrease in 5-HT signaling caused by SERT Ala56 may trigger a positive feedback response in both TPH1 and TPH2 – producing cells²⁶. EC cells, which express TPH1, were increased in the SERT Ala56 intestine and may account for the increased abundance of TPH1²⁶.

When ENS anatomy and GI motility were examined in mice exposed to the SERT antagonist, fluoxetine during development, the intestinal abnormalities contrasted, in an almost mirror-image fashion, to those present in the SERT Ala56 mice. The ENS of the fluoxetine-treated mice was hyperplastic, with the neuronal subsets that were deficient in SERT Ala56 mice being particularly abundant²⁶. CMMCs, measured in vitro, were increased in fluoxetine-exposed mice, demonstrating an ENS-centric abnormality that opposed the slower CMMCs demonstrated by the SERT Ala56 mice²⁶. Further, in contrast to the SERT Ala56 mice, TPH1 was significantly greater in the WT mice compared to those that were fluoxetine-exposed. Central effects were also revealed in the fluoxetine-exposed mice; the inhibition of SERT during development resulted in an enhancement of central

sympathetic activity, which slowed GI motility in vivo²⁶. Prior studies support the idea that fluoxetine-exposed mice exhibit additional defects in brain development as well as behavioral anomalies including increased anxiety, depression and aggression³⁵⁻³⁹. Further, similar observations in enteric neurogenesis and GI motility were made in SERTKO mice, indicating that these abnormalities were the result of SERT dysfunction, rather than off-target effects of fluoxetine⁶.

In clinical studies, the impact of SERT antagonism on CNS and ENS development and function is best represented in studies of children exposed to SSRIs antenatally. SSRIs cross the placenta and are also present in breastmilk⁴⁰. Consequently, the embryo and the breast-feeding baby are directly exposed to SSRIs⁴⁰. In these studies, the gut and behavioral anomalies noted in these children overlap with those shown in mice; Antenatal SSRI exposure has been associated with significant impairments in behavior and language⁴¹⁻⁴⁶ as well as gastrointestinal (GI) dysfunction (constipation), all of which can persist long-term^{47,48}.

There are several major points highlighted by these findings. First, the contrast in ENS development and GI motility between the SERT Ala56 and fluoxetine-exposed mice illustrates that SERT efficiency is directly related to ENS development and the long-term regulation of GI motility. Further, the fluoxetine-treated animals were exposed to the drug exclusively through gestation and breastfeeding and were evaluated for differences in neurogenesis and motility at 6-10 weeks of age, allowing substantial time for drug washout. This finding suggests that it is the period of active neurodevelopment that is critical for the long-term effects of SERT function in enteric neurogenesis and motility. Finally, given the brain and intestinal abnormalities demonstrated in both humans and experimental models with SERT dysfunction, we can conclude that an abnormality in systemic SERT function can influence both brain and gut development and long-term functions in both the GI tract and in behavior.

Given that SERT dysfunction causes abnormalities in both brain and intestinal development, it is plausible that by circumventing SERT, we may be able to prevent SERT-modulated abnormalities in disorders that affect the brain and the intestine. This idea was tested by exposing SERT Ala56 mice to a 5-HT₄ receptor agonist, prucalopride, during gestation and breastfeeding, which are the most active times of neurodevelopment²⁶. The 5-HT₄ receptor was targeted because of its established link to 5-HT-promoted enteric neurogenesis and GI motility^{49,50}. Administration of prucalopride to the SERT Ala56 mice during gestation and weaning prevented the ENS hypoplasia, deficiencies of late-developing neurons, and the slowing of in vivo and in vitro GI transit²⁶.

Overall, these studies reveal that enteric neurogenesis and GI motility are critically dependent on SERT activity during neurodevelopment and that SERT does this by modulating 5-HT signaling; More specifically, defective 5-HT signaling due to the increased 5-HT clearance, in SERT Ala56 mice, decreases enteric neurogenesis, whereas increased signaling due to genetic ablation (SERTKO) or its inhibition during development, with fluoxetine, enhances neurogenesis⁶. These findings also suggest that a global defect in SERT affects the CNS and well as the ENS in ASD and developmental SSRI exposure.

ASD is increasing in prevalence at a rapid rate and its impact on society is substantial. The extreme complexity and heterogeneity of the underlying etiologies of ASD^{51,52} makes the identification of biomarkers, such as hyperserotonemia, highly desirable. Biomarkers can assist in both the identification of sets of specific connecting traits and also in the effort to discover new pathways to account for disease pathophysiology. The SERT Ala56 mouse is the first experimental model that mimics the brain-gut-hyperserotonemia phenotype found in individuals with ASD⁶. Because gut-brain-behavior relationships cannot easily be disentangled in humans, this model is advantageous for the studies required to help elucidate these interactions. Further, while the data is supportive of the concept that abnormal serotonergic signaling pathways could be a common feature underlying the brain-gut connection ASD, a prospective human study will be needed for confirmation.

Our data supports the idea that fluoxetine exposure during neurodevelopment has a long-lasting impact on brain and gut function. Depression during pregnancy affects approximately 10% of women nationally. Untreated depression in pregnancy is associated with long-lasting developmental outcomes in children, including an increased risk of anxiety and depression, and a decrease in cognitive and social functioning⁶³⁻⁶⁶. These potential outcomes thus necessitate the consideration of treatment with antidepressants. SSRIs are prescribed to as many as 8% of all pregnant women nationally⁶⁷. SSRIs are used as first line treatment for depression during pregnancy because they are thought to be safe compared to other antidepressants. SSRI exposure during pregnancy, however, has been linked to a 2-fold increase in congenital defects and long-term effects in language, behavior and GI dysmotility⁴⁸. Given the importance of 5-HT signaling to ENS development and the long-lasting effects of fluoxetine treatment on gut function and sympathetic output, additional investigation may be warranted on the administration of antidepressants that affect SERT or 5-HT function to pregnant or lactating women. These risks must be considered while also accounting for the risks posed by untreated depression during pregnancy.

The potential effects of 5-HT and SERT in other conditions known to affect the brain and the gut also merit more study. Further investigation in this area may provide a greater understanding of the link between the anxiety, depression and irritable bowel syndrome (IBS)⁵⁴⁻⁵⁷ as well as the pathophysiological connection between the stress and “flares”, or increased intestinal inflammation, in inflammatory bowel disease (IBD)⁵⁸. Both IBD and IBS have been linked to changes in 5-HT signaling or SERT in both experimental models and clinical studies^{18,59}.

A greater understanding of 5-HT signaling and SERT in brain-gut disease is likely to facilitate the creation of novel therapeutics to treat these intractable conditions. The ability of prucalopride to prevent SERT Ala56-associated defects in ENS development and GI motility supports the idea that SERT and 5-HT₄ receptors play important roles in enteric neurogenesis and ENS-mediated functions. Interestingly, although 5-HT₄ agonists were developed for treating chronic constipation and constipation-predominant irritable bowel syndrome⁶⁰, 5-HT₄ has also been shown to affect neurogenesis in the CNS⁶¹ and may actually promote the hippocampal neurogenesis that underlies the neurogenesis induced by SSRIs⁶². Future studies should determine whether 5-HT₄ receptor modulators are beneficial

in treating ASD and the consequences of antenatal SSRI exposure and/or other brain-gut diseases.

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Highlights

- Diseases with brain and intestinal anomalies may share a common etiology.
- Such conditions include autism (ASD) or those exposed to SSRIs pre- and postnatally.
- Serotonin and SERT play critical roles in brain and gut development and function.
- Novel data demonstrate connections between serotonin and SERT and the brain-gut axis in ASD and developmental SSRI exposure.