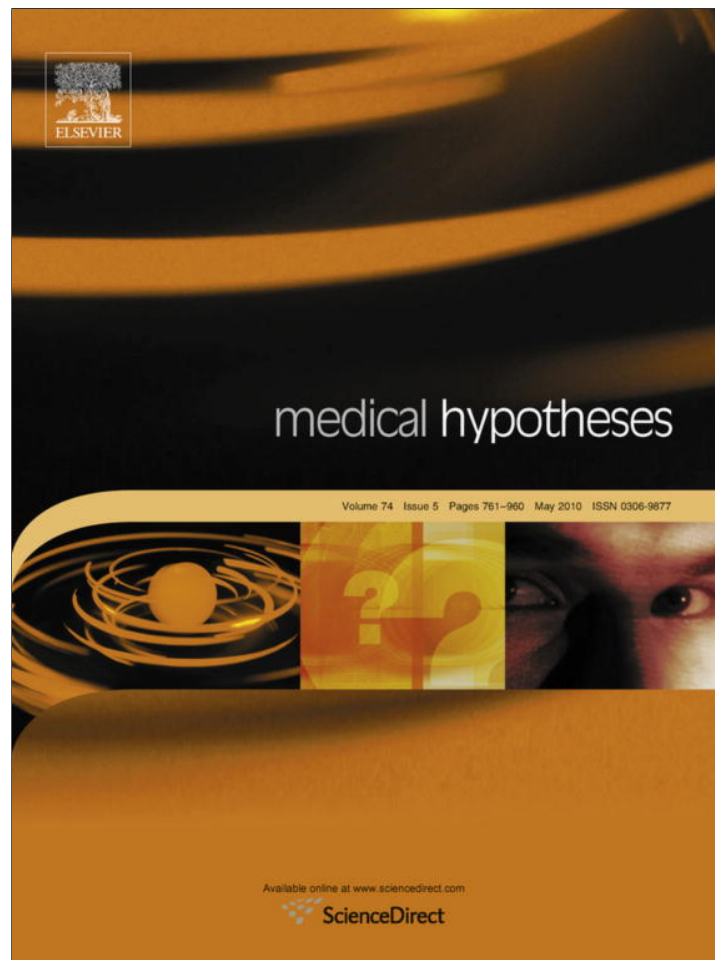


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# Medical Hypotheses

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## Serotonin, pregnancy and increased autism prevalence: Is there a link?

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### SUMMARY

The prevalence of autism, a neurodevelopmental condition resulting from genetic and environmental causes, has increased dramatically during the last decade. Among the potential environmental factors, hyperserotonemia during pregnancy and its effect on brain development could be playing a role in this prevalence raise. In the rodent model developed by Whitaker-Azmitia and colleagues, hyperserotonemia during fetal development results in a dysfunction of the hypothalamo–pituitary axis, affecting the amygdala as well as pro-social hormone oxytocin regulation.

Dysfunction of the amygdala and abnormal oxytocin levels may underlie many clinical features of ASD.

Selective serotonin reuptake inhibitors (SSRI) are the most widely used class of antidepressants drugs, and they are not contraindicated during pregnancy. In this paper, we hypothesize that increased serotoninemia during pregnancy, including due to SSRI intake, could be one of the causes of the raising prevalence in autism. If our hypothesis is confirmed, it will not only shed light on one of the possible reason for autism prevalence, but also offer new preventive and treatment options.

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### Introduction

Autism spectrum disorder (ASD) is a behaviorally defined neurodevelopmental disorder affecting as many as 1 in 150 children prevention [1], or even 1:91 according to the latest report of National Survey of Children's Health [2]. Its defining features include mild to severe impairments in communication and reciprocal social interaction, as well as repetitive and stereotyped behaviors.

Reports of autism prevalence have increased dramatically during the past decade. This may be partly due to increased awareness of ASD resulting in more diagnoses being made, but also to environmental factors [3,4]. Not much is known yet on the possible effect of certain drugs, food or environmental conditions on ASD progression.

### DHS model of autism

There is evidence that *otr* (coding for oxytocin, OT) and *avpr* (coding for vasopressin) genes may be abnormal in some ASD individuals (for review, see [5]). However, decreased levels of OT could also be the consequence of abnormal levels of serotonin (5HT) during brain development.

The developmental hyperserotonemia (DHS) model of autism was first hypothesized by Patricia Whitaker-Azmitia (reviewed in

[6]), who based her theory on the observation that high levels of serotonin is seen in the blood of a third of ASD children.

Hyperserotonemia is indeed the most consistent neurochemical change in autism [7–11]. Hyperserotonemia is also found in first-degree relatives [12] and is associated with recurrence risk of autism within families [13–15].

It is important to keep in mind that in the mature brain, blood levels of serotonin are not an indicator of brain serotonin, because (1) serotonin does not cross the mature blood brain barrier (BBB) and (2) the synthetic enzyme tryptophan hydroxylase is different in the brain and in the periphery [16]. However, the immature BBB allows the passage of 5HT and in infants, the BBB becomes impermeable to serotonin at only 2 years of age.

The DHS model states that at early stages of development, when the BBB is not fully formed, high levels of maternal blood serotonin could enter the brain of the developing fetus and cause loss of 5HT terminals through negative feedback (Fig. 1).

Developmental hyperserotonemia was mimicked in the rat from gestational day 12 to postnatal day 20 [6]. Changes were observed: (1) in columnar development in cortex (also seen in humans with ASD [17]), (2) in 5HT receptors and (3) in the behavior of rats, that exhibited 'autistic-like' traits. In addition, changes were found (4) in the amygdala, with an increase of CGRP (also seen in ASD [18]), and (5) in the paraventricular nucleus of the hypothalamus (PVN), with as a consequence decreased OT levels (also seen in ASD [19,20]). Both changes in the amygdala and the PVN could result from loss of 5HT innervation. Recently more evidence has been produced supporting the DHS model, showing

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that pups, similarly to ASD children, exhibit increased tendency to seizures, are less social, and show fewer olfactory-based social interactions [21].

In the human brain, serotonergic neurons appear at five weeks of gestation [22]. Serotonin fibers grow continuously prenatally, and brain serotonin levels increase until a peak is reached at about 2 years of age, after which they decline until adult levels are reached, which represent 50% of the peak values (reviewed in [6]).

Serotonin exerts a negative feedback on the development of serotonin neurons, mediated by 5HT1A receptors [23]. Serotonin terminals innervate both the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus, and the release of CGRP and OT is mediated by 5HT1a and 5HT2 receptors [24].

### Increased serotonin during pregnancy

In humans, increased levels of serotonin during pregnancy could have several distinct etiologies, including increased internal release, increased intake and decreased metabolism. As mentioned above, it is known that first-degree relative hyperserotonemia increases the risk of autism [13–15].

Drugs that release 5HT, such as cocaine, have been shown to dramatically increase the prevalence of autism, with 11.4% of children exposed in utero being affected [25]. However, in the light of recent prevalence increases, can we think of another substance that was newly introduced and could be playing a role?

### SSRIs and autism – is there a link?

Prozac was introduced in the USA in 1987. SSRIs are the third most prescribed antidepressant [26], with over 22.2 million prescriptions in the US in 2007. SSRIs are not contraindicated during pregnancy, and as high as 2.3% of mothers report using SSRIs from one month before to 3 months after conception [27–29].

Several studies have examined the teratogenic effects of SSRIs [30,31], and some have concluded to an association with slightly increased risks of cardiac abnormalities. Those studies examined the potential effects of SSRI exposure in utero on the presence of fetal malformation, and the effect of withdrawal syndrome after birth. However, they did not address the long-term effect of SSRI exposure on cognition and, to our knowledge, no study has so far explored the presence of a correlation between SSRI intake and autism prevalence. SSRIs remain the treatment of choice of depression during pregnancy.

Borue et al. [32], recently reviewed the possible effects of SSRIs on cognitive development in rodents, and have shown that administration of SSRIs during a key developmental window creates changes in brain circuitry and maladaptive behaviors that persist into adulthood, including increased anxiety, aggression and depression.

Epidemiological data may shed some light on a putative connection between SSRIs and autism. In 2007, Utah was the state with the highest rate of depression in the USA [33], and Utah is number one in prescription for depression. In 2009, a study published by the US Center for Disease Control and Prevention revealed that Utah has the third highest rate among 14 states examined, with prevalence rates 12% higher than national averages, and that increased twentyfold in 20 years. While no causality can be drawn from these epidemiological observations, and while we are lacking specific data on the prevalence of SSRI intake by pregnant women in Utah, the coincidence of highest SSRI intake and top ten autism rates in the same state, given what we have learned from the rodent model, certainly warrants further investigation.

Other factors can be suspected, including high tryptophan containing food intake. Tryptophan is present in dietary supplements, but also in many different foods like soybeans, turkey and chocolate.

### Evidence supporting the DHS model of autism

In line with the DHS model, decreased levels/activity of serotonin have been described in ASD brains: PET studies have revealed decreased activity of radiolabeled serotonin in the frontal cortex and thalamus [34] and decreased serotonin synthesis [35] in autistic children, and a recent SPECT study has shown lowered serotonin binding potential in several brain areas in Asperger individuals, including the superior temporal cortex [36].

In addition, it is known that drugs that increase serotonin availability in the brain can be therapeutically helpful in ASD [37], and that tryptophan depletion worsens autistic symptomatology [38]. Tryptophan depletion has also recently been shown to disrupt emotion processing in healthy controls [39].

Noteworthy, both thalidomide and valproic acid exposure, commonly used in animal models of autism, produce hyperserotonemia [40] and alter serotonergic neurons [41].

### Effects of hyperserotonemia on oxytocin

Oxytocin (OT) is a neuropeptide produced in the magnocellular neurosecretory cells in the supraoptic nucleus and the paraventricular nucleus (PVN) of the hypothalamus. It is released into the blood from the posterior lobe of the hypophysis, as well as directly from the perikarya, dendrites or axon collaterals of magnocellular neurons. OT fibers have endings in a variety of different brain areas, including the thalamus, the hippocampus, the amygdala, the pineal gland and the cerebellum [42].

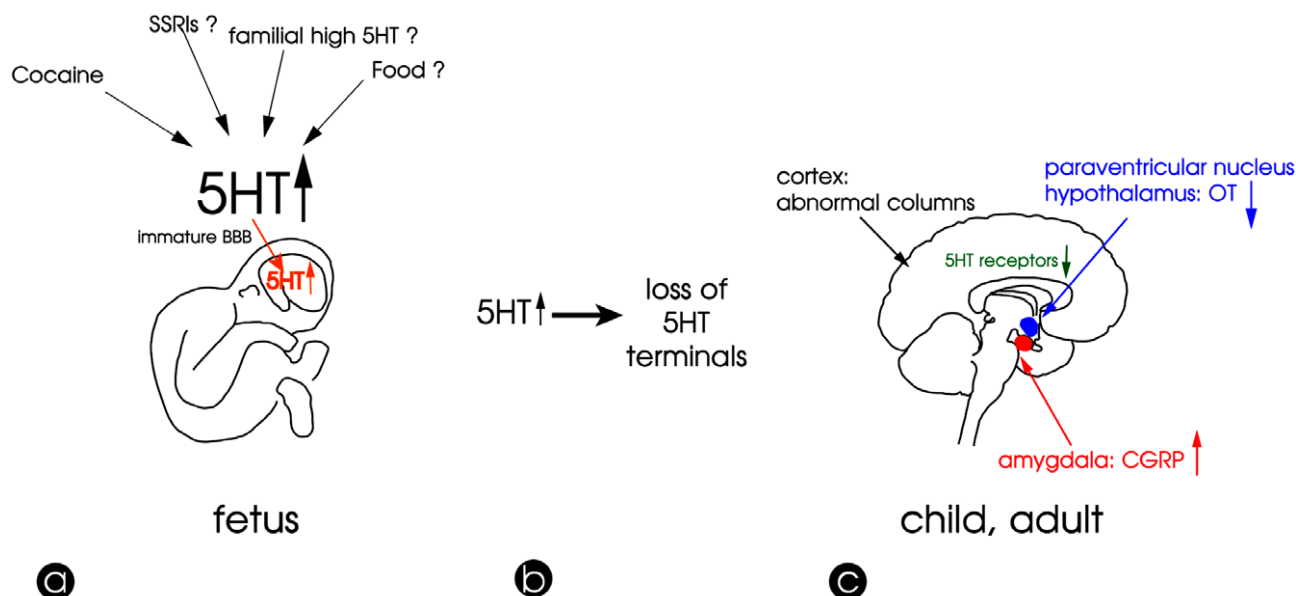
OT is involved in many aspects of mammalian social behavior, including social recognition and anxiety [43]. OT KO mice have reduced social recognition, and central OT administration into the amygdala restores social cognition [44]. Rodents with abnormal OT have been proposed as potential animal models for autism [45–47].

In the DHS model, a loss of OT-containing cells in the hypothalamus as well as a loss of OT projections towards the amygdala is associated with an abnormal social behavior [6].

In humans, OT regulates social interactions, social cognition, social behavior and fear [5,48–51]. In particular, in healthy controls OT increases gaze to the eye region of the face [52], and attenuates amygdala response to emotional faces regardless of valence [53]. Intranasal administration of OT specifically improves recognition memory for faces, but not for non-social stimuli in healthy humans [54]. Studies done in ASD children have shown decreased plasma OT [19,20].

### Effects of hyperserotonemia on the amygdala

The amygdala plays an important role in the perception of emotion, and there are indications from several neuropathology, lesion and neuroimaging studies that it plays a role in the social cognition deficits in autism. Altered connections between the amygdala and other components of the emotional processing network could lead to an aberrant emotional response. Several anatomical studies have found abnormalities in the amygdala of autistic subjects, although their results do not allow any conclusion regarding an increase or a decrease of amygdala volume in autism [55–61]. Cell packing density has been described as abnormal [55]. In addition, a number of functional studies have reported abnormal amygdala



**Fig. 1.** Developmental hyperserotonemia model of autism [6]. Panel A: during gestation, the blood brain barrier is still permeable to 5HT. An increase in the maternal blood of 5HT could be caused by several factors: Cocaine [25]; constitutive high HT level [12]; food-related 5HT intake, SSRIs intake [32]. Increased maternal plasma 5HT results in increased 5HT in the fetal brain. Panel B: Increased 5HT in the fetal brain provokes a loss of 5HT terminals through a negative feedback mechanism. Panel C: As a consequence, in the developed brain we can observe an abnormal cortical columnar architecture, decreased oxytocin production from the hypothalamus, and increased production of calcitonin-gene related peptide (CGRP) in the amygdala.

activation (e.g. [62,63] and some have proposed that the amygdala may play a pivotal role in autism [64].

Calcitonin-gene related peptide (CGRP) projections to the amygdala are involved in conditioned response to acoustic and somatosensory stimuli and play a role in fear conditioning [65], and an increase in CGRP increases fear responding (Fig. 1).

**Significance**

The dramatic rise in autism prevalence may not only be due to an increased awareness and broader definition, but also to some factors in the environment. Among these factors, an elevated level of serotonin during pregnancy could play an adverse role in brain development. Elevated serotonin could be caused by intake of drugs elevating serotonin levels, and by the consumption of foods rich in serotonin. If our hypotheses are confirmed, our data would have consequences not only in our understanding of the pathophysiology of autism, but also in the development of preventive actions meant to limit the amount of serotonin intake during pregnancy. In addition, if further studies are consistent with a dysfunctional oxytocin production in the brain of ASD individuals, they will open the way for new therapeutical approaches based on oxytocin administration.

**Conflicts of interest statement**

None declared.

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