

Genetics of Childhood Disorders: XLV. Autism, Part 4: Serotonin in Autism

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Early experiments on the isolation and identification of serotonin (5-hydroxytryptamine, 5-HT) were carried out from the late 1930s through the early 1950s. These studies demonstrated the presence of 5-HT in blood and in enterochromaffin cells of the gut, and they established the indole structure of the molecule. In 1953, it was shown that the mammalian brain contained appreciable ($\mu\text{g/g}$) quantities of 5-HT. A consideration of 5-HT's actions as a vasoconstrictor and cardiostimulant, the parallels between 5-HT and the then-nascent neurotransmitters norepinephrine and acetylcholine, and commonalities with the molecular structure of lysergic acid led rapidly to suggestions that 5-HT might play a role in mental disorders. In 1961, Shain and Freedman reported finding elevated levels of platelet 5-HT in individuals with autism. Serious consideration of the role of 5-HT in autism dates from this time.

Although platelet hyperserotonemia has continued to provide an impetus for the study of 5-HT in autism, a wide range of neurobiological, pharmacological, and genetic data has contributed to the continuing interest in this area. As background, the central serotonergic system is depicted in Figure 1. As shown, nearly all cell bodies of central 5-HT neurons are located in the dorsal midbrain and brainstem and project in a pervasive fashion throughout the brain. 5-HT is produced from the dietary amino acid precursor, tryptophan, and metabolized predominantly to 5-hydroxyindoleacetic acid (5-HIAA). As might be expected from its phylogenetically ancient role in neural transmission and its extensive CNS projections, 5-HT has been shown to play a key role in a variety of behaviors and processes including sensory gating, behavioral inhibition, appetite, aggression, sleep, mood, affiliation, and neuroendocrine secretion.

Theoretical considerations underlying the rationale for the study of 5-HT in autism include 5-HT's role in neurodevelopment, its especially rich innervation of limbic areas critical for emotional expression and social behavior, and the involvement of 5-HT in a wide range of behaviors often observed to be affected in individuals with autism. Providing a more empirical basis are studies showing therapeutic benefit of serotonergic agents in autism, reports of 5-HT-related neuroendocrine abnormalities, the well-characterized platelet hyperserotonemia, and recently reported associations between autism and 5-HT-related genes.

The critical involvement of 5-HT in guiding neurodevelopment and the extended ontogeny of the central serotonergic

system provide theoretical bases for positing a role for 5-HT in the etiology and pathophysiology of autism and related pervasive developmental disorders. Serotonin and its associated transporter and receptors are found very early in development (embryonic day 11–12 in the rat, by 4 months of gestation in humans). Much of the early expression of 5-HT appears to be related to its role as a growth factor and regulator of neuronal development. Thus, in addition to functioning as a modulator of neural transmission, 5-HT appears to have critical effects on neurogenesis, morphogenesis, and synaptogenesis in the developing brain. Serotonin genetics and neurodevelopment intersect in the recent observation of an effect of transporter gene variants (*HTT* intron 2 alleles) on patterns of 5-HT transporter gene expression in the developing mammalian brainstem. Accumulating evidence indicates that 5-HT projections continue to undergo age-related change through early adulthood and that the serotonergic system is particularly plastic.

Consideration of the fundamental social deficit in autism and of the behavioral sequelae of amygdalar lesions, as well as the results of cytological analysis of postmortem brain tissue, have made the amygdala and associated areas of limbic cortex of particular interest. The core social relatedness deficits in autism focus research attention on the rostral limbic system, including the amygdala, septum, medial orbitofrontal cortex, anterior insular cortex, anterior cingulate cortex, accumbens, and hippocampus. The various limbic areas are richly enervated with serotonergic projections. The cerebellum has also received intensive study in autism, with cerebellar alterations suggested due to its role in attention regulation and motor control and to the results of postmortem (cytological) and imaging studies. Although 5-HT innervation of the cerebellum is less prominent, 5-HT projections are critical to cerebellar function. Early transient dense expression of 5-HT receptors (5-HT_{1A}) appears important in the formation of the cerebellar cortex.

In adult animals, 5-HT plays important roles mediating the diverse autism-relevant behaviors of sleep, mood, arousal, aggression, impulsivity, and affiliation. Reduced serotonergic function has been associated with worsened sleep, depressed mood, altered arousal, increased aggression, greater impulsivity, and reduced social behavior. Although 5-HT tends to play an inhibitory role in the CNS, its actions are complex and depend greatly upon the specific location and class of receptor stimulated. For instance, markedly increasing extracellular 5-HT release can reduce appetite and aggression but also can lead to

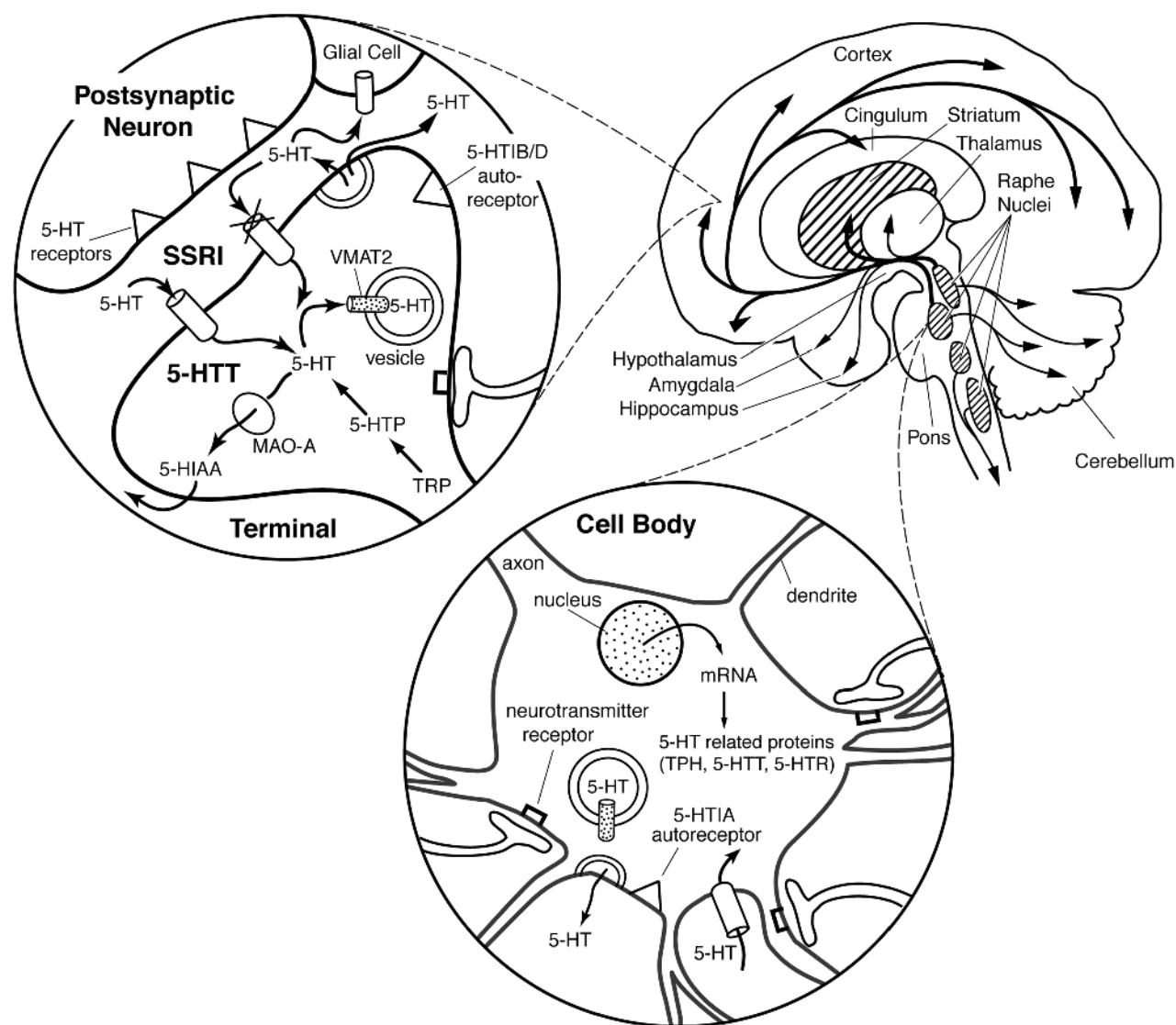


Fig. 1 Raphe nuclei of the brainstem contain the cell bodies of serotonergic neurons. Projecting rostrally to the brain and caudally to the spinal cord, serotonin (5-HT) is pervasive in the brain. Especially rich innervation is present in the basal ganglia, amygdala, hippocampus, and hypothalamus. Serotonin-related proteins are produced in the cell body after transcription of appropriate genes. The membrane 5-HT transporter (5-HTT), the less specific vesicular transporter (VMAT2; used for loading 5-HT into synaptic vesicles), the 5-HT_{1A} autoreceptor, and the synthetic enzyme tryptophan hydroxylase (TPH) are found in the cell body. These proteins (with the exception of the 5-HT_{1A} receptor) are also found in the terminal region along with the catabolic enzyme monoamine oxidase A (MAO-A) and the 5-HT_{1B/D} terminal autoreceptor. 5-HT is synthesized after hydroxylation of tryptophan (TRP) and decarboxylation of 5-hydroxytryptophan (5-HTP). Eventually most of the 5-HT produced is metabolized to 5-hydroxyindoleacetic acid (5-HIAA); however, extracellularly released 5-HT is mainly cleared by uptake through the 5-HTT. Blockade of the 5-HTT by selective serotonin reuptake inhibitors (SSRIs) leads to increased extracellular and synaptic levels of 5-HT and increased stimulation of autoreceptors and postsynaptic receptors. Receptors for other neurotransmitters (heteroreceptors) and autoreceptors on the cell body and terminal region control neuronal firing rate and release of 5-HT.

a syndrome of distinctive repetitive behaviors. Genetic data have connected 5-HT-related genes to disorders defined by symptoms in these areas of behavior (e.g., mood, social phobia, obsessive-compulsive, and anxiety disorders).

Discussion of “autism-relevant” behaviors raises central issues regarding the nature of autism and its underlying genetic factors. Family and twin studies clearly show that autistic behav-

ior is largely genetically determined and suggest a heterogeneous and polygenetic basis. Molecular genetic studies suggest that in most individuals a large number (>10) of genetic variants are contributing to the altered behavior. It also appears that the variants involved are common polymorphisms. It is natural to suggest that different groups of variants are involved in affecting different components of altered behavior. It also seems likely

that certain genes and their variants may play a role across behavioral domains. Serotonin-related genes are good candidates for exerting such epistatic (multiple interacting genes affecting a particular behavior) and pleiotropic (a specific gene affecting more than one behavior) effects.

It is unclear whether the same variants confer risk to disordered behavior across syndromes, whether the behaviors are continuous with normal behaviors, and whether genetic and behavioral interactions across domains are critical for the expression of full-blown autism.

Genes encoding a number of the components involved in 5-HT neural transmission (Fig. 1) have been examined as possible contributors to the potentially relevant behaviors and disorders mentioned. Research in autism has focused on the influence of 5-HT transporter gene (*HTT*) variants on risk to autism. Although taken together the studies do not convincingly support a role for *HTT* variants in determining risk, one of the latter studies did observe an (yet to be replicated) allelic association with severity of communication and social interaction impairment. Reported effects of 5-HT-related alleles on therapeutic response to serotonergic antidepressants and atypical neuroleptics (in mood disorders and psychosis, respectively) also tend to link 5-HT and autism.

Drug treatment studies have demonstrated that agents affecting the 5-HT system can be useful for improving symptoms in individuals with autism. Drugs targeting the 5-HT transporter, including the 5-HT reuptake inhibitors fluoxetine, fluvoxamine, and clomipramine, are now widely used in autism. The reuptake inhibitors appear to affect most aspects of autistic behavior, including social relatedness. Several studies have found poor response rates in younger subjects, with activation an especially common adverse effect of the reuptake inhibitors. Risperidone, another frequently used medication, also acts predominantly through a serotonergic target as it is a potent antagonist at the 5-HT_{2A} receptor. Paralleling the drug treatment studies are neuroendocrine and behavioral challenge paradigms using serotonergic agents. These studies have found abnormal responses to the 5-HT releaser fenfluramine, the 5-HT precursor 5-hydroxytryptophan, and the 5-HT_{1B/D} receptor agonist sumatriptan. Depletion of the 5-HT precursor tryptophan was reported to result in a significant worsening of autistic behaviors.

The platelet hyperserotonemia of autism has been especially well studied and is generally considered to be one of the more robust and well-replicated findings in biological psychiatry. Most studies have reported group mean elevations of 25% to 50% in platelet serotonin in persons with autism. Group differences appear to be more marked before puberty. Racial differences in mean platelet 5-HT levels may have confounded some of the prior studies. It appears that the elevation is not related to intelligence, and other behavioral correlates have not become apparent. The mechanism of the alteration and its pos-

sible relationship to brain abnormalities remain unknown. The platelet does not appear to be exposed to greater amounts of 5-HT, given normal urinary excretion of 5-HT and 5-HIAA and normal levels of plasma 5-HT. Thus attention had focused on the platelet's handling of 5-HT. To date, no clear alteration in the platelet has been identified, although there is some suggestion that uptake may be increased in some subjects with increased platelet levels.

Although continued advances in the genetics of autism are expected, the major revelation of the past 10 years has been the daunting complexity of the genetics of autism. While improved drug treatment is likely using more specific agents and with the application of pharmacogenetics, inferences regarding etiopathophysiology based on drug effects will be tenuous. Early screening and the application of neuropsychology to the identification of quantitative behavioral phenotypes (e.g., eye tracking studies) will offer new perspectives for dissecting and understanding autism-related behavior.

At present, the areas of neuroimaging and postmortem brain research seem to offer the greatest potential for rapidly advancing the field. The recent availability of postmortem brain tissue, made possible through the efforts of Dr. Margaret Bauman and colleagues (The Autism Research Foundation) and now others (The Autism Tissue Program) has opened a wide window of opportunity. Neurochemical and cytological investigations of the autistic brain should no longer lag behind those in other areas of neuropsychiatry. The analysis of pre- and post-synaptic serotonergic measures across a range of cortical and subcortical regions should be particularly informative. A number of structural imaging studies, initial functional magnetic resonance imaging (fMRI) studies, as well as the limited imaging research examining central 5-HT functioning, suggest that continued work in this area will prove fruitful. Reciprocal interchange between imaging, neuropsychological, and postmortem research should be especially useful and illuminating. Finally, work on the mechanism of the platelet hyperserotonemia may provide critically important information regarding possible central 5-HT dysfunction; the advantages of having identified a specific biochemical alteration in a delineated cell type might be best exploited by applying gene array or expression technology to this question.

The autism phenotype is gradually becoming less mysterious and the problems and research issues are becoming better defined. However, the complex and enigmatic nature of autism-related behaviors and their underlying determinants present an exciting and difficult challenge to neuroscience.

WEB SITES OF INTEREST

<http://www.nami.org/youth/autism.htm>
<http://psy-svr1.bsd.uchicago.edu/ldn/5htrev.html>
<http://www.vh.org/Providers/Conferences/CPS/41.html>

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