

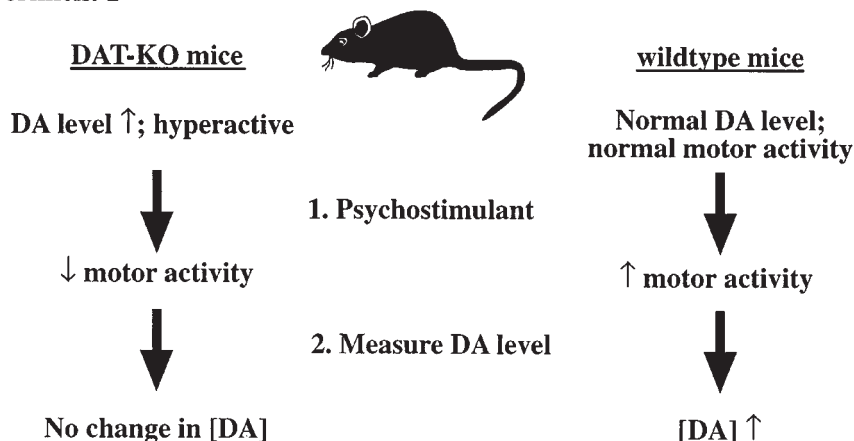
Genetics of Childhood Disorders: XXIII. ADHD, Part 7: The Serotonin System

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A central premise in the “catecholamine hypothesis” of attention-deficit/hyperactivity disorder (ADHD) is that dopamine (DA) dysfunction leads to clinical symptoms. The hypothesis arises, in part, from the clinical efficacy of methylphenidate, as well as evidence from brain imaging studies that suggest reduced activity in frontal-striatal regions. The theory, however, overlooks the phenotypic complexity of the disorder and the possible interactions between the dopamine and serotonin (5-HT) neurotransmitter systems.

ADHD is a heterogeneous disorder manifesting itself in various behavioral dimensions including inattention, hyperactivity, and impulsivity often co-occurring with other child behavioral disorders including comorbid oppositional defiant disorder and conduct disorder. It is likely that different neurotransmitter systems and the relative balance between them have varying degrees of influence over these behavioral dimensions. Variation in genes involved in these neurotransmitter systems are likely to mediate this delicate balance and have an effect on the function of these

Experiment 1



Experiment 2

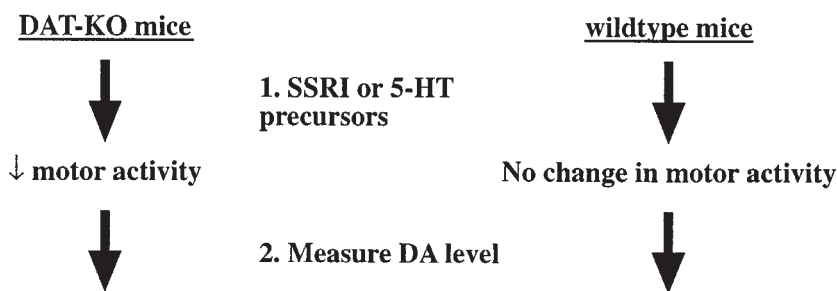


Fig. 1 Mice that lack a functional copy of the dopamine transporter show hyperactive behavior. Both psychostimulants and serotonergic medications decrease the motor activity of these mice (Gainetdinov et al., 1999). One of the conclusions the authors arrived at from these two sets of experiments is that 5-HT modulates hyperactivity without changing extracellular DA levels. DAT-KO = dopamine transporter knockout; [DA] = concentration of dopamine; SSRI = selective serotonin reuptake inhibitor; 5-HT, 5-hydroxytryptamine. Adapted with permission from Gainetdinov et al. (1999), *Science* 283:397–401. Copyright 1999, American Association for the Advancement of Science.

chemicals in the brain. The purpose of this review is to discuss the neurobiology of ADHD in light of a serotonin hypothesis. A review of human and animal studies in support of a role for serotonin in ADHD and related behaviors is presented. A discussion is included of the interaction between the serotonin and dopamine neurotransmitter systems in the context of dopamine-mediated behaviors and possible implications for ADHD.

Although serotonin has been studied less thoroughly in the neurobiology of ADHD, its role in the pathophysiology of this disorder has become an area of intense investigation recently. Considerable evidence suggests a role for this neurotransmitter in the etiology of behavioral disorders characterized by disinhibition including alcohol abuse, suicide, bulimia, antisocial personality disorder, conduct disorder, and aggression. As ADHD is a behavioral disorder largely characterized by deficits in inhibition and is a well-known precursor for many adult disorders of impulse control, a role for 5-HT in ADHD has been hypothesized. Indeed, there is mounting evidence from both human and animal studies that serotonergic neurotransmission is necessary for mediating several of the behaviors present in ADHD.

Both direct and indirect measures of central serotonergic function have been assessed in children with disruptive behavior disorders. Cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid or responses in pharmacological challenge tests indicate abnormal serotonergic function. Results from such studies, however, have been inconsistent. Some show reduced central 5-HT function, whereas others indicate higher 5-HT function (Kruesi et al., 1990; Pine et al., 1997). Peripheral measures of blood serotonin have been reported as reduced in children with ADHD (Spivak et al., 1999). Although psychostimulant medications appear to be most effective in the treatment of ADHD, there is some evidence that certain serotonin-enhancing agents including tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) are also effective in reducing symptoms in these children. Often these may be used as second-line agents for patients who do not respond adequately to stimulants.

A growing number of animal studies suggest the involvement of serotonin in mediating behaviors such as attention, impulsivity, and hyperactivity. Rodents that had a greater degree of serotonin utilization in the frontal cortex performed worse on a task measuring attention and impulsivity (Puumala and Sirvio, 1998). A recent study of a mouse model of ADHD provided evidence linking serotonin to the control of hyperactive behavior (Gainetdinov et al., 1999). In this study, the researchers developed a strain of hyperactive mice by knocking out the gene responsible for the dopamine transporter (DAT-KO).

In the absence of the dopamine transporter, there is an increase in extracellular levels of dopamine which is thought to lead to the increased locomotion seen in the knockout mice. Treatment of the mice with psychostimulant drugs produced a calming effect not seen in wildtype mice. Furthermore, this

reduction in hyperactivity was not associated with changes in extracellular levels of dopamine in the striatum (Fig. 1, experiment 1). The results suggest that the response to these drugs is through a mechanism other than blockade of the DAT, as the transporter is not present in the knockout mice.

The researchers then treated the same mice with several serotonergic drugs. These included both SSRIs and serotonin precursors, and both produced a calming effect in the mice that was independent of any changes in dopamine levels (Fig. 1, experiment 2). The authors suggest that serotonin neurotransmission plays a role in mediating the hyperactive behavior in these mice.

Additional animal studies have suggested that specific serotonin receptors may be involved in impulsive and hyperactive behaviors. Investigations with knockout mice that lack the 5-HT_{1B} receptor show increased cocaine acquisition and alcohol intake, as well as hyperactivity and aggressive behavior (Brunner et al., 1999). This receptor is expressed in a variety of brain regions including areas involved in motor control such as the striatum and cerebellum. In an earlier study, Saudou and colleagues (Saudou et al., 1994) developed homozygous knockout mice also lacking the 5-HT_{1B} receptor gene and assessed for various behaviors. When wildtype and knockout mice were treated with the 5-HT_{1B} agonist RU 24969, stimulation of locomotor activity was observed in the wildtype mice that was absent in the mutant mice, suggesting that the hyperlocomotor effect of this agonist was mediated by 5-HT_{1B} receptors. Rats treated with the same 5-HT_{1B} agonist in another report showed a dose-dependent increase in locomotor hyperactivity (Rempel et al., 1993).

There is a considerable amount of interaction between the dopaminergic and serotonergic neurotransmitter systems (Kelland and Chiodo, 1996). One hypothesis for the involvement of 5-HT in the development of ADHD is the regulatory control of 5-HT over DA neurotransmission. Disruption of the 5-HT system will disrupt the DA system and affect DA-mediated behaviors.

5-HT neurons send projections to DA cell bodies located in the midbrain regions including the substantia nigra and ventral tegmental area. In addition, they project to DA terminals present in the striatum, nucleus accumbens, and prefrontal cortex. The 5-HT innervation of dopaminergic cell bodies and terminals allows for the functional regulation by 5-HT of both DA neuronal firing and DA release. Results from electrophysiological and neurochemical studies on rodents have generally shown that 5-HT exerts an inhibitory influence on midbrain dopamine cell bodies. 5-HT influence over DA release in terminal regions, however, is less clear as both inhibitory and excitatory effects have been observed (Kelland and Chiodo, 1996).

Different 5-HT receptor subtypes mediate the regulation of 5-HT over DA neurotransmission and include the 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} receptors. Certain 5-HT_{1B} and 5-HT_{1A} agonists have been shown to increase striatal DA release whereas

the 5-HT_{1B} antagonist, GR 127935, inhibits 5-HT-induced dopamine release. These results provide some evidence for a facilitatory role for 5-HT over DA in the striatum. Alternatively, the 5-HT_{2A} receptors that are located on DA neurons inhibit DA firing while antagonism of 5-HT_{2A} releases DA from this inhibition (Kapur and Remington, 1996).

As a consequence of the complex interaction between these two neurotransmitter systems, 5-HT is likely to influence DA-mediated behaviors. The experiments on DAT-KO mice suggest that the calming effects observed after psychostimulant and SSRI treatments occur by increasing 5-HT levels. These higher levels of serotonin then balance the high DA levels that result from the absence of DAT.

Although the 5-HT system is likely to be involved in motor activity, it remains unclear which specific 5-HT receptors are involved in motor control. Evidence from pharmacological studies has suggested that striatal 5-HT_{2A} receptors regulate stimulant-induced dopamine release and hyperactivity (O'Neill et al., 1999). Treatment of rodents with selective 5-HT_{2A} antagonists attenuates the locomotor stimulating effects of amphetamine and cocaine by preventing the increase in dopamine release that causes hyperactivity (O'Neill et al., 1999). The 5-HT_{2A} receptor, therefore, must be activated in order to mediate the effects of dopaminergic agents. Similarly, several studies have demonstrated the hyperlocomotor effects of 5-HT_{1A/1B} agonists (Kelland and Chiodo, 1996), which are most likely mediated via 5-HT_{1B} receptors. Results such as these provide evidence for a facilitatory role for 5-HT in DA function and DA-mediated behaviors. This appears to be inconsistent with the hypothesis that 5-HT is inhibitory to DA function and DA-induced behavior.

The ability of 5-HT to exert both facilitatory and inhibitory influences over DA neurotransmission, thus varying the degree of influence over DA-mediated behaviors, is a complex issue and may be a function of both the brain region studied, the drugs used, and the 5-HT receptor subtypes involved. Needless to say, there is an abundance of evidence demonstrating that dopaminergic neurotransmission is functionally regulated by serotonin, which has important implications for 5-HT in controlling the behavior commonly exhibited in ADHD.

To date, there have been no molecular genetic studies demonstrating specific serotonin genes as risk factors for ADHD, yet future research in this area is warranted. Although the mode of inheritance of ADHD is unknown, it is likely to be polygenic based on its modest relative risks and high population prevalence. The individual risk contribution per gene, therefore, may be quite small. This has been one of the greatest challenges in ADHD genetics research. Furthermore, identifying a gene as a risk factor for ADHD does not help clarify the aspect of the disorder to which that gene contributes. Do defects in dopamine genes contribute to the inattention component of ADHD while serotonin genes determine the impulsive compo-

nent? Are dopamine and serotonin both contributing factors in the hyperactivity displayed by children with ADHD? What genes in these systems account for the high proportion of children who exhibit comorbid disruptive behaviors disorders and aggression? There are no definitive answers to these complicated questions, but it is probable that a delicate balance exists between these two neurotransmitter systems and that this balance is necessary to maintain normal behavior in childhood.

The future of dissecting the genetics of ADHD lies in a shift from searching for risk-enhancing genes for ADHD as a disorder per se toward searching for genes contributing to the symptoms of the disorder in a quantitative approach. A notion such as this would lead to the hypothesis that a higher genetic load would lead to greater symptom severity. This approach could help identify which genes contribute to particular symptoms of ADHD. For example, examination of a group of children with high levels of impulsive symptoms might identify a serotonin gene as a risk factor, whereas that gene may not be detected if inattention was measured. Waldman and colleagues (1998) adopted this kind of approach, showing that the hyperactive-impulsive symptoms rather than the inattention symptoms of ADHD were associated with a greater loading of the DAT1 high-risk allele and that this association increased with symptom severity.

In conclusion, there is accumulating neurobiological evidence pointing toward a role for the serotonin system in ADHD. The strongest support from existing data suggests that serotonin is responsible, at least in part, for mediating the hyperactive and impulsive components of ADHD behavior. Genes involved in serotonin receptor function, metabolism/biosynthesis, and reuptake are good candidates for future molecular genetic studies of ADHD. Thus the existing view of ADHD as a "dopaminergic disorder" will broaden toward the inclusion of serotonin as a contributing factor in its etiology.

WEB SITES OF INTEREST

To view hyperactive knockout mice:
For modems at 56k:
<http://media.med.yale.edu:8080/ramgen/mouse/mouse-lw.rm>
For faster connections:
<http://media.med.yale.edu:8080/ramgen/mouse/mouse-hi2.rm>
<http://www.nimh.nih.gov/publicat/adhd.cfm>
<http://www.add.org/content/kids1.htm>

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