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REVIEW

Applications of pharmacogenetics in children with attention-deficit/hyperactivity disorder

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Abstract: This review examines molecular genetic studies shown to be of importance in the etiology of attention-deficit/hyperactivity disorder (ADHD) and contrasts prefrontal versus subcortical mechanisms. Although these mechanisms are not completely dissociated, an understanding of prefrontal dopaminergic/noradrenergic versus subcortical D1/D2 receptor mechanisms is useful for studies of diagnosis versus potential adverse effects. Dopamine physiology, dopamine receptor studies, alpha-2 agonist studies, and dopamine transporter and potential new therapies are reviewed. Further understandings of molecular mechanisms involved in etiology versus treatment and adverse effects should help personalize the treatment of ADHD.

Keywords: ADHD, dopamine transporter, dopamine receptors, alpha-2 agonists, COMT, stimulant side effects

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common, highly heritable condition affecting 8%–12% of school-aged children (Faraone et al[1]), including subtypes. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,*[2] describes a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning and consists of predominantly hyperactive/impulsive, predominantly inattentive, and combined presentations. These presentations may have differing implications for psychogenomic studies. Most clinical studies report on the combined subtype, which manifests with poor impulse control, locomotor hyperactivity, and impaired working memory.

According to Arnsten,[3] numerous neuroimaging and neuropsychological studies have implicated the prefrontal cortex (PFC) as the region of the brain most affected in ADHD (in regulating behavior and attention) via dopamine transmission. Researchers have consistently found associations between genes that encode the D1, D4, and D5 receptors, and PFC functions, but effects have been small, whereas genes encoding norepinephrine, including the alpha-2A adrenoreceptor, have also been associated with ADHD.[4] Levy[5,6] has drawn attention to the fact that although dopamine at subcortical levels is metabolized by the dopamine transporter (DAT), dopamine in the PFC is metabolized by catechol-O-methyltransferase (COMT). To date, animal and human studies have provided suggestive indications that the D1 receptor is the specific site at which dopamine is metabolized by the COMT enzyme, giving rise to inverted-U effects of stimulant medications.[7,8] However, a clear demonstration of this effect, in which the same dose may produce an improvement in one child but cognitive rigidity in another, has been limited by the availability of systematic adverse effect data.

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Stimulant effects may be subclassified in relation to functions controlled via the PFC and both subcortical motor effects and emotional effects. This review will distinguish cognitive effects such as working memory thought to be mediated via the D1/noradrenaline (NA) receptors in the PFC from motor effects believed mediated via the D2 receptor at subcortical levels. These differences in dopamine modulation are believed to have implications for both therapeutic responses and adverse effects.

Dopamine physiology

Carboni et al postulated a top-down theory of behavior control in which the lateral PFC controls different domains of behavior, the content of which may vary depending on the subcortical area involved.[9] According to the authors, dopamine innervations in the PFC are localized to the prelimbic and infralimbic cortex, whereas acetylcholine and serotonin have wide contacts in the PFC. Dopamine innervation is via the ventral tegmental area, which projects to cortical deep layers. Dopamine innervation of the PFC is thought to be functionally inhibitory either by direct action on PFC cells or via gamma aminobutyric acid (GABA) interneurons, resulting in reduced glutamic excitatory output to the nucleus accumbens or ventral tegmental area. As the density of the D1/D5-type receptors is considerably greater than that of the D2 receptors in the PFC, the former are thought to be crucial in suppressing sustained neuronal firing that takes place during working memory activity.[10] Carboni et al[9] discussed the implications of differences in activity of the COMT gene, where the less active *COMT met*^{158} allele is associated with approximately 75% reduction in dopamine methylation and increased dopamine function, linked with improved working memory, executive functioning, and attention control, but also a higher risk for anxiety, whereas the *COMT val*^{158} allele is associated with decreased dopamine availability.[9]

Bilder et al[11] suggested that synaptic levels of dopamine in the PFC are modulated by COMT, in contrast to subcortical dopamine metabolism by DAT. Low "tonic" dopamine levels are sufficient to stimulate D2 inhibitory autoreceptors in the PFC, but when high "phasic" levels of dopamine are released, in response to external stimuli, dopamine modulation in the PFC is via COMT. As discussed earlier, the *COMT met*^{158} allele is associated with low COMT enzyme activity, resulting in increased levels of PFC dopamine with increased D1 and relatively decreased D2 transmission, increasing the stability of working memory representations. In contrast, the high-activity *COMT val*^{158} allele decreases dopamine concentrations cortically, allowing a release of phasic dopamine transmission from tonic autoreceptor modulation, with consequent higher phasic responses. Thus, COMT met effects are thought to result in increased stability, but decreased flexibility, of neural networks via the D1 receptor, whereas COMT val effects result in greater flexibility but also distractibility.

Dopamine receptor studies

Keeler et al have contrasted functions at the level of PFC that are important for cognitive functions such as working memory and attention, with striatal functions that are important for response selection, including sequencing, and instrumental responding.[12] The authors have discussed functional implications of D1 versus D2 receptors. Their model (based on animal studies using agonists and antagonists specific to the different dopamine receptors) suggests that the basal ganglia function as a stimulus–response interface, in which sensory information is channeled to the basal ganglia from the cortex (and thalamus) in the form of excitatory (glutamatergic) inputs, from which medium spiny neurons (MSNs) send inhibitory (GABAergic) projections to targets. According to the authors, there is a "race" between D1 and D2 pathways, in which D1 prepares and D2 selects a particular response, and where the D2 pathway is more complex and functions as a feedback and feed-forward center for response selection.

The model differs from previous "Go" and "No-Go" formulations but more clearly relates D1 and D2 to motor response selection at subcortical levels. In contrast, the authors point out that D1 and D2 receptors may also have important and contrasting functions at the PFC level for cognitive functions such as working memory and attention. In pharmacogenomic terms, there may thus be differences between variations in "risk" genes acting subcortically and between cognitive functions at cortical levels.

According to Surmeier et al,[13] the "classical" model of how dopamine shapes striatal activity posits that D1 receptors excite MSNs of the "direct" striatonigral pathway, whereas D2 receptors inhibit MSNs of the "indirect" pathway.[13,14] Dopamine activation of G-protein receptors is thought to excite or inhibit MSNs by modulating voltage-dependent and ligand-gated ion channels by changing the way MSNs respond to glutamatergic signals. According to the authors, D1 receptors appear to depress weak asynchronous synaptic signals but augment strong coordinated glutamatergic input, whereas D2 receptors reduce glutamate release as well as postsynaptic responsiveness of striatopallidal MSNs. Thus, modulation of cortically driven action selection appears to be a balance of D1 versus D2 receptor activity, and striatonigral

D1-responsive MSNs served to promote "action" in response to environmental cues in coordination with postsynaptic D2 receptors, which prevents incompatible action programs.

Trantham-Davidson et al[15] investigated differences in cortical induced pluripotent stem cell (IPSC) amplitude after low and high doses of dopamine bath application. They found that at low applications of dopamine (10–100 nM), a dose-dependent increase in the amplitude of the IPSC was observed, whereas at higher doses (1–20 μM), an initial decrease in amplitude was most significant, at 20 μM.[15] The investigators hypothesized that a low-concentration dopamine-mediated increase in GABA currents was a result of D1 stimulation and was found to be prevented by coapplication of the D1 antagonist SCH 23390. In contrast, the high dopamine-mediated decrease in GABA currents was attributed to D2 receptors because coapplication of dopamine and SCH 23390 did not block this effect, whereas the presence of a D2 antagonist increased the IPSC. The authors argued that dopamine exerts concentration-specific effects on cortical inhibition: lower concentrations are believed to preferentially activate D1 receptors, whereas higher concentrations were found to activate D2 receptors via separate signaling pathways. The authors suggest that during a working memory task, cortical dopamine levels reach nanomolar concentrations, with moderate activation of the mesocortical dopamine system, allowing working memory buffers to robustly hold information. In contrast, synaptically located D2 receptors might respond to high phasic dopamine to transiently allow new information to have access to working memory.

Dopamine transporter

The gene for DAT, known as *DAT1*, is located on chromosome 5p15. The protein-encoding region of the gene is more than 64 kb long and includes 15 coding segments or exons. This gene has a variable number tandem repeat (VNTR) at the 3′ end (rs28363170) and another in the intron 8 region. Differences in the VNTR have been shown to affect the basal level of expression of the transporter; as a consequence, researchers have looked for associations with dopamine-related disorders. Hill et al[16] investigated the relative activity of VNTR alleles of SLC6A (dopamine transporter) under basal and stimulated cellular conditions, as well as in the presence of a pharmacologic blockade of the dopamine transporter. They reported that the intron 8 VNTR 5-repeat allele was more active than the 6-repeat allele and concluded that the intron 8 VNTR is a functional variant ADHD susceptibility allele with reduced activity. An association between *DAT1* and ADHD has been reported by a number of investigators.[17–19]

Bellgrove et al[20] investigated sustained attention response variability and attentional bias in 27 right-handed children and adolescents diagnosed with ADHD and 20 right-handed controls.[20] They used a Landmark grayscales task, shaded from pure black to pure white, to assess perceptual bias, and a fixed-sequence sustained attention task[21] to investigate response variability. *DAT1* genotyping indicated that only 9% of ADHD probands did not possess a 10-repeat allele, 45% were heterozygous, and 45% were homozygous.[21] The investigators grouped the ADHD cohort as high risk (two 10-repeat alleles) and low risk (one or no copies of 10-repeat alleles). ADHD symptomatology measured dimensionally was correlated with a Landmark Asymmetry index, showing that left-sided inattention was correlated with inattentive symptoms. A significant effect of the *DAT1* genotype group was found for right spatial bias/left-sided inattention. The Landmark Asymmetry index significantly predicted biased parental transmission of high-risk versus low-risk parental alleles. Finally, an analysis of methylphenidate (MPH) medication response showed that the high-risk *DAT1*/very good response group displayed left-sided inattention, although the low-risk *DAT1*/mediocre response group also showed a small leftward bias. The investigators proposed that increased transporter activity would result in reduced extracellular dopamine within right hemisphere attentional networks. Treatment with MPH was thought to inhibit the transporter and restore dopaminergic balance in spatial attentional systems.

Bellgrove et al[22] investigated the relationship between spatial inattention measured on the Landmark Task and the *DAT1 3′* variable number of tandem repeat polymorphism in 43 ADHD children and their parents. Children who were rated by their parents as showing a good response to MPH displayed left-sided inattention, whereas children with a poor response did not, replicating the above smaller study. In addition, left-sided inattention predicted transmission of the 10-repeat *DAT* allele from parents to probands.

Tomasi et al[23] investigated the relationship between dopamine transporters in the striatum and the default mode network (DMN) during visuospatial attention. They used positron emission tomography scans with a cocaine radiotracer to estimate DAT availability and functional magnetic resonance imaging (fMRI) during a parametric visual attention task. The investigators hypothesized that higher DAT levels would result in a lower concentration of extracellular dopamine, reducing the availability to deactivate the DMN during the visual attention task. Higher DAT was

thought to result in activation, rather than deactivation, of DMN and greater activation of compensatory dorsal network regions. Fourteen healthy nonsmoking adult men were investigated. The results indicated that DAT availability in the caudate showed positive correlations with blood-oxygen-level-dependent signals in right postcentral gyrus, bilateral superior parietal lobe, left ventral precuneus, and left thalamus, and negative correlations with signals in right perigenual anterior cingulated gyrus (although thalamus correlations were not significant after the removal of an outlier). According to the investigators, the study showed that most of the correlations with DAT occurred in areas deactivated by the task, implying that greater DAT levels were associated with less deactivation. The study is important in suggesting that the beneficial effects of stimulant medications (one of the actions of which is to block DAT) might be manifested through deactivation of the DMN. A longer-lasting presence of dopamine in patients with low DAT might ensure longer-lasting interest and attention to relevant stimuli.

Kambeitz et al[24] reported results of a meta-analysis that investigated the moderating effect of *SLC6A3 VNTR* on response to methylphenidate treatment in 16 studies including 1,572 subjects. They found no significant summary effect, although 10R homozygotes showed less improvement than non-10/10 carriers. The authors questioned whether other genetic polymorphisms or nongenetic factors might be important. Braet et al[25] showed that possession of a "high-risk" 10-repeat *DAT1* allele was associated with decreased activation in parietal and prefrontal brain regions during response inhibition and in frontal and medial brain regions on error trials in a go-no-go task.

Cummins et al[26] investigated the association of allelic variation in polymorphisms of the dopamine transporter gene (*SLC6A3*: rs37020: rs 46000). They used a stop-signal task that measured inhibition of response by stop-signal delay. Delay times were set relative to individuals' mean response time to ensure approximately 50% of delay times. fMRI was carried out to assess brain activity during response inhibition and correlated with the genetic polymorphisms mentioned earlier. The author found evidence of association among SLC6A3 variants, rs 37020b and rs 460000, and measures of response speed and reaction time variability.

Cummins et al[26] also conducted an fMRI analysis on "successful inhibition-go" trials to assess the effect of genotype on brain activity associated with inhibition (longer stop-signal response times [SSRTs]). An association between *SLC6A3 rs 37020* and SSRT was demonstrated at the corrected level. The T allele was coded as 0, 1, and 2 (GG, GT, and TT), respectively. The fMRI results showed that activity in the caudate nucleus and frontal regions increased additively for the TT to GT to GG genotype of *rs 37020*, with patients with the poorest inhibitory ability (TT genotype) showing the least inhibitory activity in inhibition networks. The authors concluded that the influence of genetic variation in *SLC6A3* might represent a key risk mechanism for disorders of behavioral inhibition. Thus, many studies point to the *10R DAT* allele as a risk allele for diagnosis.

Alpha-2 agonist studies

The noradrenergic system is thought to be modulatory in exciting or inhibiting target cells. Moderate levels of NA are thought to act on alpha-2A adrenoreceptors coupled with Gi proteins to inhibit cyclic adenosine monophosphate signaling, whereas higher levels released during stress activate lower-affinity β1 adrenoreceptors.[3] According to Arnsten,[3] NA is crucial for many PFC functions such as working memory, attention, planning, and behavioral inhibition. A useful study in relation to inverted-U effects was reported by Gamo et al.[8] The study examined the effects of both MPH and atomoxetine (ATM) on PFC function in monkeys and explored the receptor mechanisms underlying enhancement of PFC function at the behavioral and cellular levels. Monkeys performed a working memory task after administration of a wide range of MPH or ATM doses, and optimal doses were challenged with the alpha-2 adrenoreceptor antagonist, indoxan, or the D1 dopamine receptor antagonist, SCH 23390. Also, in a parallel physiological study, neurons were recorded from the dorsolateral PFC of a monkey performing a working memory task, whereas ATM, SCH 23390, or the alpha-2 antagonist yohimbine was applied to the neurons by iontophoresis. The results indicated that both MPH and ATM generally produced inverted-U dose–response curves, with improvements at moderate doses, but not at higher doses, and that these effects were shown to be blocked by indoxan or SCH 23390, respectively.

Kim et al investigated the relationship between measures of attention (reaction time variability, visual and auditory selective attention tests, Flanker interference task, and an impulsivity task) and polymorphisms in the alpha-2A-adrenergic receptor and the norepinephrine receptor (*SLC6A2*) in children administered MPH osmotic release oral system (OROS) for 12 weeks.[27] The authors pointed out that although the primary mode of action of MPH in ADHD was thought to be blockade of the DAT, evidence from animal studies demonstrated that MPH might also inhibit the NA

transporter.[28] Kim et al[27] found that increasing amounts of an A-allele at the G1287A polymorphism of SLC6A2 was significantly related to greater response time variability at baseline in the sustained and auditory selective tests, whereas the response time variability at baseline increased additively with possession of the T allele at the DraI polymorphism of the *alpha-2A-adrenergic receptor* gene in the auditory selective task. The investigators found that increasing possession of a G-allele at the MspI polymorphism of the *alpha-2A-adrenergic receptor* gene after taking medication was associated with an increased MPH-related change in response time variability in the Flanker task. These results suggested an association between norepinephrine gene variants and response time variability at baseline and after MPH treatment in ADHD children. The authors pointed to growing evidence for central noradrenergic dysregulation in the pathophysiology of ADHD, suggesting that allelic variation in the alpha-2 adrenergic receptor gene located on chromosome *10q24-26* or the norepinephrine transporter gene (*SLC6A2*) located on chromosome *16q12.2* might confer genetic risk for ADHD. They also suggested that response time variability is a "viable endophenotype" for ADHD and treatment response.

According to Arnsten,[3] alpha 2A agonists enhance delay-related cell firing, whereas D1 receptor stimulation suppresses "noise," so these receptors act synchronously with each other at optimal catecholamine levels. Either excessive or insufficient catecholamine receptor stimulation can markedly impair PFC function.[3] The beneficial effects of alpha-2A versus D1 are thought to arise from opposing effects on cyclic adenosine monophosphate signaling, where alpha-2A stimulation inhibits and D1 activates cyclic adenosine monophosphate production. Moderate levels of D1 receptor stimulation are believed to lead to the opening of hyperpolarization-activated cyclic nucleotide-gated channels on spines receiving inputs from neurons with dissimilar spatial properties, reducing delay-related firing to nonpreferred directions, whereas alpha-2A adrenoreceptor stimulation is thought to result in the closure of hyperpolarization-activated cyclic nucleotide-gated channels on spines receiving inputs from neurons with similar spatial properties, possibly increasing firing during delay periods for preferred directions.[10] This selective process allows a particular spatial representation in the PFC that is important for working memory, as well as guidance of action. Importantly, the modulation of dopamine/NA functions involved in working memory at cortical levels depend on dopamine/NA synchronicity, as distinct from subcortical motor sequencing modulation by D1/D2 balance. It should be noted that although working memory effects at the PFC differ from subcortical motor effects, both are modulated via dopaminergic mechanisms, although the former modulation also requires noradrenergic effects. These differences may have implications for the phenomenology of stimulant versus noradrenergic therapies, as well as for adverse effect profiles.

Stimulant adverse effect studies

Little is known about what predicts the adverse effects of stimulant medication in the treatment of ADHD. Levy et al reviewed the literature on stimulant adverse effects and investigated whether "zombie-like" adverse effects of stimulant medication are predicted by variations in dopamine receptor genes.[29] A sample of 78 Caucasian children diagnosed and treated for ADHD at an outpatient clinic specializing in children with developmental and behavioral problems was investigated by a file review using a modified version of the Barkley adverse effect questionnaire. DNA assays were conducted for known polymorphisms of dopamine receptor genes and the *COMT* gene. Higher mean severity of nausea, zombie, and irritability symptoms were associated with the minor CC homozygote of the D1 receptor rs4532 single-nucleotide polymorphism. No effects were found for D2, D3, D4, or COMT. The significant effect of the D1 CC allele remained significant for zombie-like symptoms after adjustment for multiple testing and controlling for IQ, dosage/weight, age, and concurrent mediation use. Consistent with findings for medication effects in schizophrenia, variations in the D1 receptor gene predicted unwanted adverse effects to stimulant medication in ADHD children. In the present context, the study draws attention to the importance of the D1 receptor in predicting personalized responses to stimulant medication.

Stein et al[30] investigated variants of *DAT1* (*10/9*, *9/9*, *9/10*) in relation to the dose–response effects of long-acting dex-methylphenidate and mixed amphetamine salts in children with ADHD.[30] They reported a significant main effect for dose on total ADHD ratings and a significant curvilinear dose response for subjects with either the *10/10* or *10/9* genotype, but not for the *9/9* genotype. The latter subjects were shown to display higher ADHD symptoms at all dose levels and a lesser response to increasing doses of either D-MPH or mixed amphetamine salts. The authors also investigated the relationship among *DAT1* genotypes, long-acting dex-methylphenidate, and mixed amphetamine salts doses and empirically derived adverse effect factor scores. They reported that subjects with combined-type ADHD displayed higher emotionality scores than those with the inattentive

subtype. Patients with at least one 10-repeat allele were found to display higher scores on a "somatic" factor than patients with the 9/9 genotype. Interestingly, patients with the 9/9 genotype showed significantly higher ratings on an "overfocused" factor (stares, bites nails). The investigators commented that the 9/9 genotype of *DAT1* had previously been associated with increased dopamine transporter binding in the striatum,[31] giving rise to lower-baseline striatal DAT activity, and thus requiring higher stimulant doses to achieve symptom control, whereas 10/10 subjects might respond to lower stimulant dose levels.

Potential new therapies

According to Markowitz et al,[32] MPH is characterized by its low bioavailability and short half-life of 2–3 hours.[32] Thus, a wide range of MPH analogs directed at either DAT or a norepinephrine transporter as principal neuropharmacological targets have been investigated. The authors studied the metabolic profile and pharmacological activity of the isopropyl ester derivative of MPH dl-isopropylphenidate (IPH). Immediate-release MPH is thought to be metabolized by hepatic-carboxyl-esterase yielding inactive ritalinic acid. According to the investigators, MPH analogs that are similar in terms of pharmacological activity, yet resistant to carboxylesterase isoenzymes (CS1), are likely to extend the duration of action and provide more predictable and less interindividual variability.

Markowitz et al[32] synthesized the MPH analog IPH. They carried out monoamine transporter binding and cellular uptake experiments on racemic IPH compared with MPH and the ethyl ester congener dl ethylphenidate (EPH), as well as an assessment of metabolic hydrolysis of the three compounds by CS1. They also examined the IPH stimulant effects on locomotor activity in rats. Their results indicated that the binding of racemic IPH, MPH, and EPH showed similar significant binding affinities for DAT, with little interaction for serotonin transporter. However, IPH showed less binding capacity than MPH, and significantly less capacity than EPH, at a concentration of 10 μM. Uptake of norepinephrine was also found to be relatively lower for IPH than for MPH and EPH. The authors concluded that IPH is primarily a dopaminergic compound with significantly less noradrenergic activity than MPH or EPH at this concentration. It would thus be less likely to cause cardiovascular adverse effects such as increased heart rate or blood pressure. The study also indicated that IPH was more resistant to CS1 catalyzed hydrolysis and trans-esterification hydrolysis than MPH, offering a longer duration of action and less potential for drug–drug interactions, suggesting the importance of preclinical studies. The study draws attention to potential therapeutic and adverse effect differences between primarily dopaminergic and noradrenergic medications,[32] with possibly fewer cardiovascular adverse effects for the dopaminergic compound.

Cholinergic nicotinic mechanisms

Potter and Newhouse pointed out that adolescents with ADHD take up cigarette smoking at twice the rate of non-ADHD adolescents.[33] They hypothesized that nicotinic administration would improve cognitive/behavioral inhibition in adolescents with ADHD. The investigators used a stop signal reaction task and a Stroop task and transdermal nicotine patches in a small sample of ADHD adolescents. They found that the speed of inhibiting a response (SSRT) was significantly improved after both nicotine and methylphenidate, whereas nicotine but not methylphenidate significantly decreased the Stroop effect on cognitive inhibition. The authors suggested that nicotine potentiated "dopaminergic tone" in fronto-striatal systems.

Levin et al[34] reviewed the effects of nicotine and nicotine agonists on learning, memory, and attention. The authors pointed out that attention to receptor subtype specificity could improve clinical efficacy. For example, nicotinic α4β2 receptor agonists have been shown to improve working memory in rats,[35] whereas the nicotinic α7 receptor ARR1779 significantly improved learning and memory in rats.[36] Wilens et al[37] reported a double-blind placebo-controlled crossover trial comparing a transdermal patch of ABT-418 (selective agonist for α4β2 receptor) in adults diagnosed with ADHD, using a structured clinical interview. They reported significant improvement with the transdermal patch for a higher proportion of ADHD subjects compared with placebo, based on self-report. Adverse effects were dizziness, nausea, headaches, and dysphoria.[37] These effects may account for the relatively slow clinical application of animal and human studies of nicotine agonists.

Discussion

The present review raises questions in relation to both dopaminergic and noradrenergic circuit functions in ADHD, suggesting it may be useful to investigate predictors of cortical versus striatal functions. Consistent findings in relation to the modulation of dopamine effects in prefrontal/subcortical circuits appear to relate to comparative concentration levels at specific D1 versus D2 receptors required for optimal thresholds of neurotransmission. These effects are suggested

by the comparative findings of Trantham-Davidson et al[15] in relation to cortical pluripotent IPSCs and the dose effects demonstrated by Gamo et al.[8] At cortical levels, dopamine concentration is controlled via COMT, but noradrenergic effects via the alpha-2 adrenoreceptor are also important and are thought to act synchronously at D1/NA receptors. In contrast, motor inhibitory functions appear to be controlled at subcortical striatal levels via the D2 receptor, where dopamine metabolism is via DAT. It is of interest that dopamine metabolism by COMT variations is an enzymic reaction, whereas the subcortical dopamine transporter pumps dopamine out of the synapse into cytosol, from which other transporters sequester dopamine and NE into vesicles for later storage and release, suggesting differences in the rate of dopamine metabolism, which may be faster at prefrontal levels.

The modulation of cortical dopamine/NA functions involved in working memory appears to differ from subcortical dopamine modulation of motor sequencing. The former effects may help explain noradrenergic adverse effects, such as somnolence, fatigue, and headache, associated with alpha-2 adrenoreceptor agonist treatments, whereas the latter may provide insight into restrictive motor effects of high-dose stimulants in some children.

The adverse effect findings of Levy et al[29] and Stein et al[30] point to the importance of allelic variation for understanding adverse effects and differences in therapeutic responses. In all cases, differential dopamine concentrations at specific *D1* alleles versus therapeutic effects of a specific blockade of *DAT* alleles suggest that individualization of treatments might be directed to a better understanding of personalized treatments on the basis of *D1*, *DAT*, and *D2* alleles in ADHD subjects.

Interesting questions have been raised about the significance of *DAT1 10/10* versus *9/9* phenotypes. Although the *10/10* genotype has generally been considered a high-risk phenotype, Stein et al[30] draw attention to the *9/9* phenotype in relation to severe inattention and overfocused adverse effects. Further studies may indicate the mechanism of these effects. It also could be useful to separate etiological mechanisms related to subcortical DAT/D2 functions from therapeutic and adverse effect mechanisms related to COMT/D1/NA effects. For example, MPH analog IPH was thought to show more dopaminergic remediation and fewer noradrenergic adverse effects than MPH. Further understanding of dopamine versus NA mechanisms involved in etiology versus remediation and adverse effects should help personalize the treatment of ADHD. Head-to-head comparisons between primarily dopaminergic versus noradrenergic medications should help tease out the dissociations of the effects discussed earlier.

Disclosure

The author reports no conflicts of interest in this work.

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