ABSTRACT

This article defines and explores possible links between phenotypes and pathophysiologies associated with attention-deficit/hyperactivity disorder (ADHD). This article presents a selected overview of research linking phenotypes and pathophysiologies, and explores how they may impact ADHD treatments.

Modern biological psychiatry has long sought to subdivide patients with the same diagnosis according to different “phenotypes” with the goal of improving treatment. These phenotypes may best be viewed as groups of patients with similar psychiatric signs and symptoms that are hoped to be produced by the interaction of 1 or more genes and the environment, even though a relationship to specific genes has yet to be proven.

The pathophysiology of a psychiatric disorder may be considered the alteration in typical brain physiology that results from the interaction of 1 or more genes and the environment to produce psychiatric signs and symptoms associated with a specific mental illness. Psychotropic medications presumably decrease psychiatric signs and symptoms by correcting the alterations in brain physiology that are part of a specific pathophysiology. Thus, the importance of the link between phenotypes and pathophysiologies comes down to this: diagnosis drives treatment.

The definitions of phenotypes and pathophysiologies are connected by “the interaction of 1 or more genes and the environment.” Thus, phenotypes represent refinements of current psychiatric diagnoses (essentially, syndromes) that may become surrogate markers for specific pathophysiologies (diseases). The goal of much psychiatric research is to develop treatments that benefit patients with a specific phenotype, because those treatments target the specific pathophysiology—perhaps even the specific gene(s)—that underlie that phenotype.

Looking into the future, we might posit that in psychiatry, attention-deficit/hyperactivity disorder (ADHD) will be subdivided into phenotypes, much as Cushing’s syndrome is subdivided. Under this system, each ADHD phenotype would be associated with a specific pathophysiology and, thus, a specific treatment. This is the vision toward which ADHD research is heading, and we may not be far from making it a reality.

PROPOSED ADHD PATHOPHYSIOLOGIES

The precise etiology of ADHD has yet to be proven. Proposed pathophysiologies may be divided into psychosocial and biological factors, and combinations of or interactions between these factors. In recent years, research has focused on psychosocial theories of ADHD, and the possible biological etiologies of ADHD, including environmental injury, disruption of neu-
roanatomical pathways, differences in neurochemistry, and genetic variations.

**Psychosocial Theories of ADHD**

Family stressors (e.g., marital discord) and psychosocial adversity (e.g., poverty) have been proposed as a cause of ADHD, but these hypotheses have been examined via a number of studies with limited supporting data. Instead, this research suggests that although psychosocial factors may not necessarily cause ADHD, they can contribute to the severity of symptoms and to the likelihood of comorbidities.

**Environmental Injury and ADHD**

Pre- and perinatal insults have been associated with ADHD in maternal offspring. For example, investigators have found that mothers of ADHD children were more likely to have complicated and/or difficult labors and deliveries. Associations with various forms of ADHD have been reported in 20% of individuals suffering severe traumatic brain injury, but additional research in this area is needed. Infections, such as meningitis, can also damage the brain and produce symptoms of ADHD in some individuals. Other environmental factors implicated in ADHD include exposure to chemical toxins such as lead, exposure to nicotine and alcohol in utero, and even therapeutically administered medications.

Although numerous factors have been associated with ADHD, the exact cause and pathophysiology of ADHD continues to elude researchers. To achieve additional insights, some research has centered on identifying patterns of brain structure and activity within individuals with ADHD.

**Neuroanatomy and ADHD**

When comparing ADHD patients with controls in structural imaging studies, the most common findings are small decreases in the size of certain brain areas in ADHD patients, as well as a loss of normal brain asymmetry (areas in the right hemisphere are normally slightly larger than in the left hemisphere). Functional imaging studies have implicated the same brain regions: the prefrontal cortex, anterior cingulate, and the striatum. Considered as a whole, imaging studies and neuroanatomical work in animals suggest the presence of a circuit in the brain that extends from the prefrontal cortex to the basal ganglia (striatum) to the thalamus, and then back around to the prefrontal cortex (Figure 1). This hypothesized neuroanatomical pathway, the cortical-striatal-thalamic-cortical loop, is thought to be the primary circuit involved in the etiology of ADHD, as well as several other psychiatric disorders.

Much scientific research surrounding ADHD has also focused on the neurochemical pathways, especially the dopamine pathway. The cell bodies of dopamine-containing neurons are found in the midbrain (e.g., the substantia nigra pars compacta and the ventral tegmental area), and their projections extend throughout the brain, but most notably to the frontal cortex and basal ganglia. Because dopaminergic medications, methylphenidate and amphetamines in particular, have been useful in ADHD, the dopamine system has been the focus of many genetic studies of ADHD. Genetic variants of the dopamine transporter (DAT1), the D2 receptor (DRD2), and the D4 receptor (DRD4) have all been implicated in ADHD.

Scientific inquiry surrounding ADHD has also focused on the noradrenergic system because norepinephrine helps to regulate dopamine release, and because norepinephrine affects attention, alertness, vigilance, and other ADHD-related processes. Like the dopaminergic system, noradrenergic neurons are
located in the midbrain and project throughout the brain, especially to the frontal cortex. Measurements of urinary catecholamines and their metabolites over short periods of time in response to specific tasks do suggest that children with ADHD have higher levels of norepinephrine activity and lower levels of epinephrine activity than controls. Moreover, children with ADHD have lower plasma levels of 3-methoxy-4-hydroxyphenylglycol, a metabolite of norepinephrine, than those with ADHD and reading disability. Additional evidence suggesting a possible role for norepinephrine in the etiology of ADHD comes from studies of atomoxetine, an investigational drug that is a highly selective norepinephrine reuptake inhibitor and has been reported to reduce ADHD symptoms.

The last neurochemical system implicated in ADHD is the serotonergic system, which also has projections to the frontal cortex. Serotonin is also believed to help regulate the release of dopamine. However, the main data suggesting a role for serotonin in ADHD are preclinical. Much of the data come from studies of mice in which the genes for the DAT or serotonin 1B receptor have been “knocked out.” On the other hand, clinical data supporting the role of serotonin in ADHD is lacking; most notably, there is no published, double-blind, placebo-controlled trial of a selective serotonin reuptake inhibitor demonstrating the efficacy of these drugs for ADHD.

**Genetics and ADHD**

Studies of adopted children and twins with ADHD symptoms have shown that ADHD runs in families and is one of the most heritable of all medical conditions. One study suggests that a genetic child of an adult diagnosed with ADHD in childhood has a >50% chance of having ADHD. Family studies and linkage analyses have implicated variants of the genes for DRD2, DRD4, and DAT in ADHD. One line of research suggests that a specific variant of DRD4 is associated with risk taking and novelty seeking in some ADHD patients. Ongoing genetic research may help to further define the role of individual genes or possibly combined alleles of several genes in ADHD and its subtypes. At the same time, additional insights into the genetics of ADHD might be achieved by studying well-defined genetic syndromes that are often associated with ADHD, e.g., Down’s syndrome and Smith-Magenis syndrome. Such an approach was used in the field of dementia, where similar neurofibrillary tangles were observed in patients with Down’s syndrome and with Alzheimer’s dementia, a finding that helped in the identification of genes thought to be involved in Alzheimer’s disease.

**Proposed ADHD Phenotypes**

**Symptom Based**

The best example of symptom-based phenotypes is the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) classification of ADHD subtypes as predominantly inattentive, predominantly hyperactive/impulsive, and combined. DSM-III also used symptom-based phenotypes, but was limited to attention-deficit disorder (ADD) with or without hyperactivity.

The data linking symptom-based phenotypes to specific pathophysiologies is limited. Family studies have produced mixed, complex findings that provide some support. One genetic study suggests that a variant of the DAT1 gene may be associated with hyperactive-impulsive symptoms, while another genetic study suggests that a variant of the DRD4 gene is associated more often with inattentive symptoms. However, these data are by no means conclusive, so much research is needed before symptom-based phenotypes can be definitively linked to specific genes.

**Comorbidity Based**

A wide variety of conditions have been associated with ADHD, including conduct disorder, oppositional defiant disorder, affective disorders, anxiety disorders, tic disorders, learning disorders, and other developmental disorders. Data supporting specific pathophysiologies with comorbidity phenotypes suggest that when psychosocial stressors increase, a corresponding increase in ADHD severity, complexity, and comorbidity occurs. Results from the Multimodal Treatment Study (MTA), involving 579 children followed for a total of 14 months, suggest that there are 3 ADHD subtypes (phenotypes): pure ADHD, ADHD with comorbid oppositional defiant or conduct disorder, and ADHD with comorbid anxiety disorders. Some individuals have ADHD, oppositional defiant disorder or conduct disorder, and an anxiety disorder. The MTA also suggests that a combination of medication and psychosocial interventions is most effective for patients with ADHD, oppositional defiant disorder, and an anxiety disorder.

Family studies have provided support for ADHD phenotypes that incorporate comorbid conduct disorder/aggressive behavior, bipolar disorder, and generalized
anxiety disorder, which suggests there may be specific genes underlying these phenotypes. Family studies have also suggested that environmental factors may play a role in the pathophysiology of a phenotype involving ADHD and comorbid depression. Some data suggest that dopamine transporter gene variants are associated with adult bipolar disorder and childhood ADHD, which is interesting because of the hypothesized link between the 2 conditions.

Other Possibilities

Phenotypes have been described based on age (child, adolescent, or adult) and gender. Another approach is to describe phenotypes based on the environmental settings in which symptoms are most noticeable or problematic. For example, while a child might have difficulties with ADHD in several settings, the problems may be most severe at school, making that the focus of treatment. Yet, another child with ADHD might have problems that are more pervasive, affecting every aspect of his or her life. The pathophysiology associated with different age-based ADHD phenotypes is beginning to be elucidated. Recent research has demonstrated that the brain continues to develop through the mid 20s. Not surprisingly, the mid 20s is a period when characteristics associated with ADHD change significantly. Some research suggests that the variant of DRD4 is more common in adults with ADHD, suggesting a genotype that links with a more pervasive and continuous form of the disorder.

Conclusion

Phenotypes may be considered surrogate markers for specific pathophysiology that are associated with ADHD. In the future, treatment for ADHD may be based on the specific pathophysiology of a patient's phenotype. Unfortunately, the connections between ADHD phenotypes and pathophysiology are just beginning to be explored, so there is currently little value in attempting to base treatment selections on phenotypes. Nevertheless, existing research is encouraging regarding the link between phenotypes and pathophysiology, which gives us hope that some day this information may be used to drive treatment selection.

REFERENCES