Genetic and Neurobiological Aspects of Attention Deficit Hyperactive Disorder: A Review*

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This paper reviews key studies that have addressed genetic and neurobiological aspects in attention deficit hyperactive disorder. Genetic studies can be divided into three distinct types: twin, adoption, and family studies. Evidence for a particular mode of inheritance and the possible specific genetic abnormalities are also explored. There is strong evidence of genetic involvement in this condition, although a clear-cut mode of inheritance and specific genetic abnormalities are yet to be determined. Neurobiological aspects such as the neuroanatomical and neurochemical evidence of various neurotransmitter system involvement is explored. Frontal lobe and dopamine and norepinephrine neurotransmitter systems appear to be involved in attention deficit hyperactive disorder.

Key Words: Attention Deficit Hyperactive Disorder, genetic, neurobiological

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a common condition which affects three percent to five percent of the school-aged population. It is characterized by problems with sustained attention, hyperactivity and impulsivity. Children with ADHD are often comorbid for a number of other conditions such as conduct disorder, oppositional defiant disorder and learning disability. The importance of genetic factors in this condition has been suggested by Cantwell (1972) and Morrison and Stewart (1974). Since then, other studies have lent support to the important role of genetics in this condition. These studies can be divided into three types: twin, adoption and family studies. It should be pointed out that comorbidity is an important issue in family studies and it will be discussed under that section.

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Twin studies

Generally, genetically based disorders should be concordant in twins and more so in monozygotic (MZ) than in dizygotic (DZ) twins. Recently, there have been a number of twin studies which have looked at the concordance of ADHD in twins.

An early study by Lopez (1965) compared four pairs of MZ males with six pairs of DZ twins. However, four of the DZ twins were opposite sex pairs in which the male was hyperactive. This limits the validity of the study. Another small study by Heffron et al (1984) reported on three pairs of MZ twins, all concordant for attention deficit disorder.

More recently, Goodman and Stevenson (1989) studied 570 13-year-old twins. These authors focused particular attention on 29 MZ and 45 DZ same sex twin pairs in which at least one twin met criteria for pervasive hyperactivity. MZ twins were more alike than same sex DZ pairs on objective measures of attentiveness and on parent and teacher ratings of hyperactivity (59% *versus* 33%). In their careful study, the authors also explored the possible effects of stereotyping (i.e., the tendency to rate identical twins similarly), adverse family factors (for example, marital discord, parental criticism and malaise) and perinatal adversity (for example, low

birth weight). They concluded that genetic effects accounted for approximately one-half of the explainable variance of hyperactivity and inattentiveness.

In their extensive study of reading-disabled twins in the Colorado Reading Project, Gillis et al (1992) and Gilger et al (1992) attempted to diagnose ADHD in the twins by parental responses on the Diagnostic Interview of Children and Adolescents (DICA - Herjanic et al 1982). They thus examined 81 MZ and 52 same sex DZ pairs of a reading disabled sample of twins. They found that for reading disability, the concordance rate was 84% for MZ twins and 66% for DZ twins. For ADHD, the concordance rate was 81% for MZ twins and 29% for DZ twins. The concordance rate for both reading disability and ADHD was 44% for MZ twins and 30% for DZ twins. The data suggests that both reading disability and ADHD may have strong though independent genetic components (Gilger et al 1992).

Gillis et al (1992) examined the same group of subjects but focused particularly on 37 MZ and 37 DZ same sex twin pairs of whom one twin had been diagnosed with ADHD *via* the DICA. The authors used a basic regression model for analysis and found that 79% of MZ twins and 32% of DZ twins were concordant for ADHD ($p < 0.001$). Furthermore, adjustment for IQ or reading performance differences did not substantially change their results. The authors thus conclude that the results of this analysis suggest that ADHD is highly heritable.

One of the largest twin studies is currently being carried out by Levy and Hay (1992) in Australia. They plan to screen 3400 four- to 12-year-old twin pairs and their siblings and determine the perinatal and developmental history as well as the incidence and concordance of ADHD, conduct disorder (CD) and separation anxiety (SA). The study is ongoing and current data is still very preliminary.

Various studies have suggested that different symptoms of the ADHD syndrome are heritable. In an early study, Rutter et al (1963) reported that monozygotic twin pairs were more similar to one another than dizygotic twins in psychomotor activity. Similarly, Willerman (1973) reported heritability of activity scores to be 0.77 based on data collected from 54 monozygotic and dizygotic twin pairs. Torgensen and Kringlen (1978) also found evidence for a genetic component in both activity levels and distractibility.

Stevenson (1992), using multiple regression analysis on data obtained from 91 pairs of MZ twins and 105 pairs of same sex DZ twins, concluded that results were consistent with a significant genetic contribution to individual differences in activity level and attention abilities.

Recently, Edelbrock et al (personal communication) evaluated 99 MZ and 82 same sex DZ pairs of twins aged four to 15 years *via* the Child Behavior Checklist (CBCL) completed by parents. They found correlation of 0.68 (MZ) and 0.29 (DZ) for attentional problems. Generally, using multiple regression analysis, they found significant genetic influences on competence in school and on all areas of problem behavior. Significant shared environmental influences were detected for participation in activities, quality of social relationship, performance in school, anxiety/depression, and delinquent behavior.

Thus, these twin studies also indicate a greater concordance in monozygotic than dizygotic twins for different components of the syndrome. This supports the hypothesis that there is a genetic component in this condition.

Siblings and half siblings

Welner et al (1977) evaluated 53 hyperactive children and their siblings and compared them to 38 nonhyperactive controls and their siblings. The authors found that the hyperactive child syndrome was more common among the brothers of the hyperactive children than among the brothers of controls (26% *versus* nine percent). Furthermore, the hyperactive children and their brothers presented with more symptoms of anxiety and depression than did the controls (16% *versus* six percent). The probands, but not their siblings, also presented with more antisocial symptoms than controls. This lends support to a family-genetic risk in this condition and suggests that hyperactive children may also show comorbid conditions of depression and anxiety.

In another early study, Safer (1973) compared the incidence of ADHD in 19 full and 22 half sibling pairs. Each pair had been raised together by a common mother. One member of this pair was known to have minimal brain dysfunction (MBD), now known as ADHD. Nearly one-half (ten) of the full sibling pairs were concordant for ADHD compared to only two of the 22 half sibling pairs. This significant difference between full and half siblings further supports a genetic component of hyperactivity.

Adoption studies

Early studies by Morrison and Stewart (1973) showed that adoptive relatives of ADHD children are less likely to have ADHD or associated disorders than are biological relatives of such children. In addition, biological relatives of ADHD children perform worse on standardized measures of attention than do adoptive relatives of ADHD children (Albert-Corush et al 1986).

In a recent adoption study, Cadoret and Stewart (1991) studied 283 adoptees aged 18 to 40. The adoptees were divided into two groups based on whether or not biological parents showed evidence (from adoption agency records) of psychiatric problems or behavioral disturbances. In addition to these evaluations, direct evaluations of adoptees and adoptive parents were performed. The authors concluded that adult adoptees with childhood histories of hyperactivity had to have both a biological parent with a history of criminality/delinquency and a placement in a lower SES adoptive home to have an increased likelihood of developing an antisocial personality disorder. This suggests that while in general adoptive studies support a genetic component in

hyperactivity, there is always an important interplay between genetic and environmental factors.

Thus, in general, adoptive studies also support a genetic component in this condition.

Family studies and comorbidity

Family studies of hyperactive children have been based on the assumption that a genetic component of hyperactivity will be reflected in a higher familial rate of the disorder for probands.

Thus in an early study, Morrison and Stewart (1971) found that 20% of hyperactive children had a parent who was (retrospectively) diagnosed as hyperactive compared to five percent of their medical controls. Similarly, Cantwell (1972) reported that 20% of hyperactive boys in his sample had a parent who could be classified as being hyperactive/antisocial in childhood *versus* two percent of the pediatric clinic controls.

However, in addition to an increased rate of hyperactivity in families of hyperactive children, these authors (Morrison and Stewart, as well as Cantwell) found that biological parents of hyperactive children had higher rates of "sociopathy, hysteria and alcoholism compared to parents of normal controls." Morrison (1980) also found a higher incidence of unipolar but not bipolar affective disorder in the combined second degree blood relatives of hyperactive children.

These may have been the first signs of the importance of other comorbid conditions in this disorder. The importance of particular comorbid conditions and their association with specific parental pathology has later been illustrated in studies by Lahey et al (1988) and more recently by Barkley et al (1991).

Lahey et al (1988) compared parental pathology in six- to 13-year-old children with conduct disorder (N = 37), with ADHD (N = 18) and with both disorders. Parents of children with conduct disorder were more likely to abuse substances. In addition, mothers of conduct disordered children were more often depressed and more frequently had the triad of antisocial personality disorder, substance abuse and somatization disorder. In contrast, parents of children with ADHD only did not have any significant disorders. However, fathers of children with both conduct disorder and ADHD were more likely to have a history of aggression, arrest and imprisonment.

Barkley et al (1991), in their eight-year follow-up of hyperactive children, also collected information on the biological fathers of these children. They found that fathers of hyperactive children, compared to fathers of normal controls, had a history of significantly more antisocial acts, alcohol abuse, police contacts and arrests. Their job histories were less stable and they were generally less financially responsible. The authors concluded that 11% of fathers of hyperactive children met the DSM-III-R criteria for antisocial personality disorder as opposed to 1.6% of fathers of normal control children ($p < 0.05$). When the authors examined the antisocial acts of fathers of children with hyperactivity, with and without associated conduct disorder, they found that the fathers of children with hyperactivity and conduct disorder had more antisocial acts than those with hyperactivity alone. However, fathers of children who were only hyperactive still had more antisocial acts than fathers of normal controls.

These studies clearly suggest that the combination of ADHD and conduct disorder is associated with significant parental pathology. As shown by Cadoret and Stewart (1991) in their adoption study described above, genetic and environmental factors may in fact act synergistically to influence antisocial outcome of this condition.

The most extensive family studies to date have been carried out by Biederman et al (1990, 1992). In the first of these studies, 73 male ADHD probands and 264 of their first degree relatives were compared to 26 psychiatrically referred but not ADHD children, and 101 of their first degree relatives and 26 normal pediatric clinic controls and 92 of their first degree relatives. The authors used blinded interviewers, structured psychiatric interviews and controlled for gender, generation of relative, age of proband, social class and the intactness of the family. Relatives of ADHD probands had higher morbidity risks for ADHD (25.1% *versus* 5.3% *versus* 4.6%, $p < 0.00001$), antisocial disorders (24.3% *versus* 6.9% *versus* 4.2%, $p < 0.00001$) and mood disorders (27.1% *versus* 13.9% *versus* 3.6%) than did relatives of psychiatric patients and normal subjects. These findings indicated the importance of family-genetic risk factors in ADHD. In a more recent, similar, expanded study (Biederman et al, 1992) of 140 probands, 120 normal controls and 822 first degree relatives, Biederman showed nearly one-half (49%) of the ADHD subjects had no comorbidity with conduct disorder, major depressive or multiple anxiety disorder. However, compared to controls, ADHD probands were more likely to have these conditions. Similarly, relatives of ADHD probands had a higher risk for ADHD (25% *versus* eight percent), antisocial disorders, major depressive disorders (26% *versus* nine percent), substance dependence and anxiety disorders. Biederman suggests ADHD and major depressive disorders may show common familial vulnerabilities, that ADHD and conduct disorder may be a distinct subtype and that ADHD and anxiety disorders are transmitted independently in families. He concludes that these results extend previous findings indicating family-genetic influences.

Mode of inheritance

Given the strong evidence of genetic influence in attention deficit hyperactive disorder, there have been several hypotheses presented as to the possible mode of genetic transmission. Omenn (1973) examined the possibility of sex-linked transmission given the preponderance of males with the condition. However, the author concluded that this was unlikely because of the high frequency of father-to-son trans-

missions. Morrison and Stewart (1974) suggested a polygenic mode of transmission, but could not substantiate it because of limitations of their sample size. Deutsch et al (1990), studying dysmorphic children with ADHD, stated that the dysmorphic changes were consistent with a single genetic autosomal dominant inheritance. Tests of this model would require larger samples and more definitive diagnoses of both ADHD and dysmorphic phenotypes.

Faraone et al (personal communication) used the data obtained from subjects and relatives studied by Biederman et al (personal communication) and applied segregation analysis to this data. Specifically, they analyzed the family data with a mixed model as implemented in the computer program POINTER and a Class A regressive logistic model as implemented in the computer program REGTL. They then concluded that their results regarding the familial distribution of DSM-III-R attention deficit hyperactivity disorder are consistent with a single major locus gene affect and polygenic transmission and that nonfamilial environmental transmission and cultural transmission could be rejected.

A definitive mode of inheritance for this disorder has not yet been established but work in this area is proceeding. However, Pauls (1991) points out that diagnostic uncertainty impedes progress in developing genetic models that address the type of genetic transmission that is involved. He argues for the importance of longitudinal studies of prospectively identified subjects and careful observation of their children as the best way to resolve some of the thorny methodological difficulties of family and genetic studies.

Specific genetic abnormality

Recently, Hauser et al (1992) at the National Institute of Health have been studying generalized resistance to thyroid hormone (GRTH) which is a rare dominant disorder. Eighteen kindreds comprising 49 affected and 55 unaffected family members have been studied. Blind interviews using structured questionnaires found that 61% of GRTH patients had ADHD compared to 13% of unaffected family members. The mutations have been pinpointed in 13 kindreds. The authors suggest that this is the first molecular model of ADHD and may open the door to pinpointing the specific genetic abnormalities in this condition.

An exciting and potentially important genetic finding has been reported by Comings et al (1991). They discovered that a genetic variant of the dopamine D_2 receptor gene (D_2A1 allele) was significantly increased in patients with Tourette's Syndrome (44%, N = 147), attention deficit hyperactive disorder (46.2%, N = 104), autism (54.5%, N = 33), alcoholism (42.3%, N = 104) and post-traumatic stress disorder (45.7%, N = 33) compared to normal controls (24.5%, N = 77). However, the prevalence of this A1 allele was not significantly increased in patients with depression, panic attacks, Parkinson's disease or obesity. However, since the D_2A1 variant is present in less than one-half of the individuals affected, the gene is not thought to be the primary cause of these disorders. The authors suggest that the D_2 receptor gene acts as a modifying gene which can modify the expression (making the symptoms better or worse) of the major gene (yet to be discovered) which causes the condition. This data is still preliminary and controversial and has been negated by other investigators. It thus needs replication. However, it does suggest that in some cases of ADHD more than one gene may be involved.

We can thus see that the genetic contribution to attention deficit hyperactive disorder may be complex to unravel but important clues are being discovered and followed. It is important to place the role of genetics in proper perspective. If the complete genetic make-up of an individual could be determined and our diagnostic assessments were certain, only a portion of an individual's future children's ADHD can be predicted genetically. The remainder may be accounted for by "environmental" factors such as events during pregnancy, delivery, diet, toxins (for example, lead), temperament and parenting styles. Thus, even though new genetic developments are relevant and interesting, they do not provide all the answers in this important condition.

Neurobiological developments

Generally, the neurobiology of ADHD has not been comprehensively worked out. Several excellent recent reviews on the subject (Jensen and Garfinkel 1988; Mirsky 1987; Zametkin and Rapoport 1986, 1987; Voeller 1991) clearly illustrate the complexity of the area, the divergent findings and the many questions yet to be resolved. The condition is not unidimensional and its symptoms involve various interrelated neuroanatomical and neurochemical systems. Thus, it is unlikely that any one area or neurochemical system will be found to be solely or primarily involved in the condition. The summary which follows is a brief overview of neuroanatomical and neurochemical systems which may be involved.

Neuroanatomic system

Mirsky (1987), in his excellent review entitled "Behavioral and psychophysiological markers of disordered attention," makes the case that attention has various distinct and separate aspects such as focusing, executing, sustaining and shifting attention. Each of these different attentional functions involve different brain regions that are interconnected and organized into a system. This attentional system is very widespread and thus vulnerable to damage and dysfunction. Depending upon where the damage or dysfunction occurs, different aspects of attention may be affected (see Figure 1). Specifically, Mirsky outlined that:

> ... the functions of focusing on environmental events are shared by superior temporal and inferior parietal cortices, as well as by structures that comprise the corpus striatum, including caudate, putamen and globus pallidus. The infe-

rior parietal and corpus striatal regions have strong motor execute function. Considerable amounts of encoding of stimuli are accomplished by the hippocampus, and essential mnemonic function that seems to be required for some aspects of attention. The capacity to shift from one salient aspect of the environment to another is supported by the prefrontal cortex. Sustaining a focus on some environmental event is the major responsibility of rostra structures, including the tectum, mesopontine reticular formation and midline, and reticular thalamic nuclei.

Thus, it is understandable that over the years a wide variety of brain areas have been implicated in this condition as shown by Zametkin in his review of the literature (Zametkin and Rapoport 1987) (see Table 1).

In recent years, the development of sophisticated neuro--imaging technology has opened up new ways for investigating neural substrates of behavior and psychopathological conditions.

Few neuro-imaging studies involving individuals with attention deficit disorder exist. Shaywitz et al (1983) performed CT scans on 35 children with ADD aged four to 19. Twenty-seven children, matched for age, sex and IQ, who had scans for other reasons, were used as a contrast group. Using quantitative techniques and "blind" analyses of the CT scans, the authors found no differences in the two groups.

Lou et al (1984) measured cerebral blood flow in 13 subjects aged 6 1/2 to 15 years with developmental dysphasia and/or ADD. The normal comparison group consisted of nine children, aged seven to 15 years, who were siblings of the dysphasic ADD children. Lou found no CT differences in the two groups. However, the dysphasic/ADD children showed hypoperfusion in both hemispheres compared to normal controls. Areas of hypoperfusion included periventricular white matter, border zones between major arterial territories and, in dysphasic subjects, perisylvian regions. All ADD subjects showed hypoperfusion in white matter of frontal lobes and some caudate nuclear regions. Object-naming tasks did not show any increased blood flow. However, methylphenidate increased perfusion in central regions (for example, mesencephalon basal ganglia) and decreased perfusion of motor and primary sensory cortical areas. These results need to be evaluated in light of the fact that subject numbers were relatively small and age ranges relatively wide, which reflects varied stages of development and the sample included subjects with developmental dysphasia and mental retardation. Thus, the subjects were not truly representative of most ADD children. Furthermore, the method used did not allow precise localization of the group differences in cerebral blood flow (CBF). In addition, the authors were limited in their analysis to one (middle) slice only.

More recently, Lou et al (1989) used similar xenon inhalation techniques to show hypoperfusion in the striatal regions of children with symptoms of hyperactivity, impulsivity and inattention. The primary sensory and sensorimotor cortical regions were highly perfused. Methylphenidate increased flow to striatal and posterior periventricular regions and tended to decrease flow to primary sensory regions. Thus, low striatal activity may be involved in these symptoms.

Nasrallah et al (1986) studied 24 young adults (mean age 23) with a history of hyperactivity in childhood and reported that the hyperactive subjects had increased cortical atrophy compared to 27 male matched normal controls. All subjects with hyperactive symptoms had received stimulant medication in childhood. However, a large proportion of the hyperactive patients also had a history of significant substance abuse. Therefore, it is unclear if the cortical atrophy found was associated with the hyperactivity, stimulant medication or was secondary to chronic drug use.

Most recently, Zametkin et al (1990) evaluated glucose metabolism *via* positron emission tomography in 25 biological parents of hyperactive children. These parents had retrospective histories of childhood hyperactivity and met Utah criteria for adult ADHD, but had not received any stimulant medication in childhood. The control group consisted of 50 subjects of similar age, sex and IQ. Glucose metabolism tests were carried out while subjects were performing an auditory attention task (selection of lowest of three tones). The task lasted for 35 minutes. Analyses were performed by computer assisted measurements and two "blinded" research assistants. Zametkin et al (1990) reported that global glucose metabolism was decreased by 8.1% in the hyperactive adults *versus* the controls. Specifically in the hyperactive subjects, absolute rates of glucose metabolism were significantly low in 30 out of 60 brain regions examined, including lateral, frontal and parietal cortex (bilaterally), medial frontal cortex (including the cingulate) and some subcortical structures (the striatum and the thalamus). When the rates of glucose metabolism were normalized (i.e. regional rate of glucose metabolism was divided by global glucose metabolism rate, to minimize the effect of individual variation in global glucose metabolism on regional metabolism), the only regions with significantly reduced metabolism were the premotor and prefrontal cortex in the left hemisphere. However, since the diagnosis of the patients in this study was based on retrospective reports, its validity is obviously somewhat compromised.

Additional evidence for possible frontal lobe involvement in ADHD has also come from Chelune et al (1986), who pointed out that the prefrontal regions of the frontal lobes have reciprocal pathways with the reticular formation and the diencephalic structures, which regulate arousal and the ability to suppress responses to task-irrelevant stimuli. Lesions in this area decrease goal-directed activity and the modulation of impulsive behavior. Thus, frontal lobe lesions result in hyperactivity and disturbed higher-level cortical inhibition with the resulting failure to inhibit inappropriate responses. The authors found partial support for this frontal lobe dysfunction hypothesis by comparing normal controls and children with symptoms of hyperactivity, impulsivity and

inattention on a comprehensive neuropsychological test battery designed to asses the above functions.

Since then, Gorenstein et al (1989), Tannock et al (1989) and Everett et al (1991) have also shown deficits in children with ADHD which are compatible with frontal lobe dysfunction. Recent reviews by Heilman et al (1991) and Benson (1991), which explore a number of syndromes of abnormal mental awareness associated with prefrontal frontal and striatal dysfunction, suggest that abnormalities seen in these patients resemble deficits documented in children with ADHD. They thus suggest that these areas, prefrontal and right frontal-striatal systems, may be affected in children with ADHD.

We thus see that a number of different areas of the brain have been implicated in this condition. Recently, there has been particular emphasis on the frontal lobes. It is likely that different areas may be associated with different aspects of the syndrome and that the various areas mentioned may be interconnected into a reciprocal modulating system. Unravelling which areas may be affected and how these interconnections function is being explored with new neuro-imaging tools such as CT scans, Magnetic Resonance Imaging (MRI) and Positive Emission Tomography (PET scans).

Neurochemical aspects

The hypotheses of the possible neurochemical systems which may be involved in ADHD come from three general types of studies: neuroanatomical studies, nonpharmacological biochemical studies of neurotransmitters and their metabolites and psychopharmacological studies of neurotransmitters. These studies are well summarized and reviewed by Zametkin and Rapoport (1986, 1987) and Hechtman (1991) .

Neuroanatomic studies of neurotransmitters

Even though some areas of the brain have been clearly associated with certain neurotransmitters, neuroanatomic studies of neurotransmitters have proven to be very complex. The complexity comes from the fact that any particular area can be involved with several different neurotransmitters or receive projections from various neurotransmitter pathways or nuclei. Thus, there is not a one-to-one correspondence between a particular area and a single neurotransmitter exerting exclusive influence on this area.

Nonpharmacological studies of neurotransmitters and their metabolites

These types of studies have compared patients with ADHD and normal subjects with regard to monoamines and their metabolites in urine, plasma, platelets, and rarely, cerebrospinal fluid. The limitations of such peripheral measures in reflecting an accurate central nervous system neurotransmitter picture are clear. Generally, no consistent differences in any of the peripheral measures of monoamines and their metabolites were found between children with ADHD and normal subjects.

Psychopharmacological studies of neurotransmitters

These types of studies look at a particular psychopharmacological agent, its possible relationship to one or more neurotransmitters and its clinical effect. From such analysis, it is then postulated how the drug may work and what the possible underlying problem in the neurotransmitter systems may be. The three types of studies outlined above have given rise to various neurotransmitter hypotheses.

Dopamine hypothesis

The dopamine hypothesis was first proposed by Shaywitz et al (1977) following the examination of cerebral spinal fluid dopamine levels in ADHD children and their work with an animal model of hyperactivity in rats whose brains were depleted of dopamine by injection of hydroxydopamine (6-OHDA).

More recently, Schneider and Kovelowski (1990) and Roeltgen and Schneider (1991) showed that chronic low dose N-methyl-4phenyl-1,2,3,6- tetrahydropyridine (MPTP) administered to monkeys caused caudate-frontal dysfunction and cognitive difficulties that were consistent with those seen in children with attention deficit disorder. Pilot neurochemical studies on these monkeys have suggested abnormalities in dopamine and norepinephrine metabolism. Moreover, stimulants affect both the dopamine and norepinephrine system and are very effective in ameliorating this condition. Lou et al (1989) has suggested that methylphenidate activates the dopamine neurons by decreasing the reuptake of dopamine. However, stimulants are also known to have dopamine releasing effects. These studies clearly suggest dopamine involvement in this condition.

Noradrenergic hypothesis

The noradrenergic system has been implicated in a number of ways. Stimulants, particularly dextroamphetamine, have been shown to release epinephrine in the hypothalamus and clinical studies have noted that dextroamphetamine and methylphenidate elevate urinary epinephrine excretion by as much as 200% (Elia et al 1990). A norepinephrine agonist, clonidine (an adrenergic agonist) has been somewhat effective in treating ADHD (Hunt et al 1984). Hunt et al have suggested that the effectiveness of clonidine is mediated by direct stimulation of presynaptic sites to decrease production or release of norepinephrine and a corresponding increase in postsynaptic noradrenergic sensitivity.

Furthermore, the moderate effectiveness of some antidepressants (for example, desipramine, Donnelley et al 1986) and some monoamine oxidase inhibitors also suggests drug-induced changes in the noradrenergic system.

McCraken (1991) has thus proposed a "two part model of stimulant action in attention deficit hyperactivity disorder in children." He suggests that stimulant medication increases dopamine release and increases adrenergic mediated inhibition of the noradrenergic locus coeruleus. Thus, he involves both the dopamine and norepinephrine systems.

Serotonergic hypothesis

There is weak evidence for involvement of this neurotransmitter system in ADHD. Serotonic depleted animals show increased aggression and hyperactivity. Tricyclic antidepressants and MAOI are moderately effective in ADHD and are known to affect serotonin metabolism. However, hyperactive subjects have shown inconsistent changes in platelet and blood 5-hydroxy-tryptophan. Furthermore, pharmacological studies involving L-tryptophan, a serotonin precursor (Nemzer et al 1986), and fenfluramine, which acutely increases and then depletes brain serotonin, showed no consistent results.

Nonspecific catecholamine hypothesis

It thus becomes clear that not one but several neurotransmitter systems are involved (for example, dopamine, norepinephrine and serotonin). Stimulants, which are the most effective treatment for most ADHD children, promote catecholamine utilization in the synapse by facilitating synthesis and release of catecholamines and by blocking their reuptake. Furthermore, stimulants appear to inhibit the catabolic enzyme monoamine oxidase. A summary of various neurotransmitter systems and how they may be affected by various drugs was presented by Zametkin and Rapoport (1986) as shown in Figure 2.

The interrelationship of the various neurotransmitter systems further undermines the likelihood of the single-neurotransmitter hypotheses being correct.

Enzymatic regulation of neurotransmitter production and metabolism have also been investigated. Children with ADHD and normal children have shown no significant differences in levels of dopamine B-hydroxylase (DBH), monoamine oxidase (MAO) and catechol-o-methyltranferase (COMT) (Brown et al 1985).

Other neurotransmitters

One should consider other neurotransmitters that have not been studied in relation to ADHD but may be implicated in the future such as gama-aminobutyric acid (GABA) which is thought to be predominantly an inhibiting neurotransmitter in the central nervous system and histamine which acts centrally and peripherally.

Summary of neurobiological aspects

Generally, there has been some progress in the understanding of the neurological basis of attention deficit hyperactive disorder. Neuroanatomically, it is clear that the frontal lobes, particularly the prefrontal and striatal areas, play an important role in this condition. Neurotransmitters such as norepinephrine, dopamine and, to a lesser degree, serotonin are clearly important. However, it is also clear that no one area or neurotransmitter will adequately explain the neuropathology or neurophysiology of this condition. It is much more likely that the condition results from an interaction of various areas of the brain and possibly a number of different neurotransmitters. The variation in the condition with regard to variability of particular symptoms (for example, ADHD, ADD, and their severity and the association of particular comorbid conditions), may reflect the various areas and neurotransmitter systems involved. Recent technological advances in neuro-imaging (for example, CT scans, magnetic resonance imaging (MRI) and positron emission tomography (PET) scans) including measures of cerebral blood flow, glucose utilization and positron-emitting liquids that can quantitate and label specific neurotransmitter receptors will, it is hoped, enable researchers to unravel the complex puzzle of what underlies attention deficit hyperactive disorder.

REFERENCES

Alberts-Corush J, Firestone P, Goodman JT (1986) Attention and impulsivity characteristics of the biological and adoptive parents of hyperactive and normal control children. Am J Orthopsychiatry 56:413-423.

Barkley RA, Fischer M, Edelbrock CS, et al (1991) The adolescent outcome of hyperactive children diagnosed by research criteria III: mother-child interactions, family conflicts and maternal psychopathology. J Child Psychol Psychiatry 32:233-255.

Benson F (1991) Role of frontal dysfunction in attention deficit hyperactivity disorder. J Child Neurology (Supplement) 6:S9-S12.

Biederman J, Faraone S, Keinan K, et al (1990) Family genetic and psychosocial risk factors in DSM-III attention deficit disorder. J Am Acad Child Adolesc Psychiatry 29:526-533.

Biederman J, Faraone SV, Keinan K, et al (1992) Further evidence for family-genetic risk factors in attention deficit hyperactivity disorders: Patterns of comorbidity in probands and relatives in psychiatrically and pediatrically referred samples. Arch Gen Psychiatry 79(9) 728-738.

Brown GL, Ebert MH, Minichiello MD (1985) Biochemical and pharmacological aspects of attention deficit disorder. In: Attention Deficit Disorder: Identification, Course and Treatment Rationale. Bloomingdale LM (ed). New York: Spectrum, pp 93-130.

Cadoret RJ, Stewart MA (1991) An adoption study of attention deficit hyperactivity/aggression and their relationship to adult antisocial personality. Comp Psychiatry 32:73-82.

Cantwell D (1972) Psychiatric illness in families of hyperactive children. Arch Gen Psychiatry 27:414-423.

Chelune GJ, Ferguson W, Koon R, Dickey TO (1986) Frontal lobe disinhibition in attention deficit disorder. Child Psych Hum Development 16:221-234.

Comings DE, Comings BG, Mitleman D, et al (1991) The dopamine D_2 receptor locus as a modifying gene in neuropsychiatric disorders. J Am Med Association 266:1793-1800.

Deutsch CK, Matthysse S, Swanson JM, Farkas LG (1990) Genetic latent structure analysis of dysmorphology in attention deficit disorder. J Am Acad Child Adolesc Psychiatry 29:189-194.

Donnelly M, Zametkin AJ, Rapoport JL, et al (1986) Treatment of hyperactivity with desipramine: Plasma drug concentration, cardiovascular effects, plasma and urinary catecholamine levels and clinical response. Clin Pharmaco Therapy 39:72-81.

Edelbrock C, Rende R, Plomin R, Thompson LA (in press) Genetic and environmental effects on competence and problem behavior in childhood and early adolescence.

Elia J, Borcherding BG, Potter WZ, et al (1990) Stimulant drug treatment of hyperactivity: Biochemical correlates. Clin Pharmaco Therapy 48:57-66.

Everett J, Thomas J, Cote F, et al (1991) Cognitive effects of psychostimulant medication in hyperactive children. Child Psych Hum Development 22:79-87.

Faraone SV, Biederman J, Chen WJ, et al (in press) Segregation analysis of attention deficit hyperactivity disorder: Evidence for single gene transmission.

Gillis JJ, Gilger JW, Pennington BF, DeFries JC (1992) Attention deficit disorder in reading-disabled twins: Evidence for a genetic etiology. J Abnorm Child Psychology 20:3:303-315.

Gilger JW, Pennington BF, DeFries JC (1992) A twin study of the etiology of comorbidity. Attention deficit hyperactivity disorder and dyslexia. J Am Acad Child Adolesc Psychiatry 31:2:343-348.

Goodman R, Stevenson J (1989) A twin study of hyperactivity II: The aetiological role of genes, family relationship and perinatal adversity. J Child Psychol Psychiatry 30:691-709.

Gorenstein EE, Mammato CA, Sandy JM (1989) Performance of inattentive-overactive children on selected measures of prefrontal-type function. J Clin Psychology 45:619-632.

Hauser P, Zametkin AJ, Vitiello B, et al (1992) Attention deficit hyperactivity disorder in 18 kindreds with generalized resistance to thyroid hormone (abstract). American Society of Clinical Investigation Proceedings.

Hechtman L (1991). Developmental neurobiological and psychosocial aspects of hyperactivity, impulsivity and attention. In: Child and Adolescent Psychiatry: A Comprehensive Textbook. Lewis M (ed). Baltimore: Williams & Wilkins, pp 318-331.

Heilman KM, Voeller KS, Nadeau SE (1991) A possible pathophysiologic substrate of attention deficit hyperactivity disorder. J Child Neurology (Supplement) 6:S76-S81.

Heffron WA, Martin CA, Welsh RJ (1984) Attention deficit disorders in three pairs of monozygotic twins: A case report. J Am Acad Child Psychiatry 23:299-301.

Herjanic B, Campbell J, Reich W (1982) Development of a structural psychiatric interview for children: Agreement between child and parent on individual symptoms. J Abnorm Child Psychology 10:307-324.

Hunt RD, Cohen DJ, Anderson G, et al (1984) Possible changes in noradrenergic receptor sensitivity following methylphenidate treatment. Growth hormone and MHIG response to clonidine challenge in children with attention deficit disorder and hyperactivity. Life Science 35:885-879.

Jensen JB, Garfinkel BD (1988) Neuroendocrine aspects of attention deficit hyperactivity disorder. Endocrinol Metab Can North Am 17:111-129.

Lahey B, Piacentini J, McBurnett M, et al (1988) Psychopathology in the parents of children with conduct disorder and hyperactivity. J Am Acad Child Adolesc Psychiatry 27:163-170.

Levy F, Hoy D (1992) ADHD in twins and their siblings. Presented at the Society for Research in Child and Adolescent Psychopathology, Sarasota, Florida, February.

Lopez RE (1965) Hyperactivity in twins. Can Psych Assoc Journal 10:421-426.

Lou HC, Henricksen L, Bruhn P, et al (1984) Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. Arch Neurology 41:825-829.

Lou HC, Henriksen L, Bruhn P, et al (1989) Striatal dysfunction in attention deficit and hyperkinetic disorder. Arch Neurology 46:48-52.

McCraken J (1991) A two part model of stimulant action on attention deficit hyperactivity disorder in children. J Neuropsychiatry 3:201-209.

Mirsky A (1987) Behavioral and psychophysiological markers of disordered attention. Environmental Health Perspectives 74:191-199.

Morrison JL (1980) Adult psychiatric disorders in parents of hyperactive children. Am J Psychiatry 137:825-827.

Morrison JL, Stewart M (1971) A family study of the hyperactive child syndrome. Bio Psychiatry 3:189-195.

Morrison JL, Stewart M (1973) The psychiatric status of legal families of adopted hyperactives. Arch Gen Psychiatry 28:888-891.

Morrison JL, Stewart M (1974) Bilateral inheritance as evidence of polygenicity in the hyperactive child syndrome. J Nerv Ment Disease 158:226-228.

Nasrallah HA, Loney J, Olsen SC, et al (1986) Cortical atrophy in young adults. Psych Research 17:2241-243.

Nemzer ED, Arnold LE, Votolato NA, et al (1986) Amino acid supplementation as therapy for attention deficit disorder. J Am Acad Child Adolesc Psychiatry 25:509-513.

Omenn GS (1973) Genetic issues in the syndrome of minimal brain dysfunctions. Sem Psychiatry 5:5-17.

Pauls DL (1991) Genetic factors in the expression of attention-deficit hyperactivity disorder. J Child Adolesc Psychopharmacology 1:353-360.

Roeltgen D, Schneider JS (1991) Chronic low-dose MPTP in non-human primates: A possible model for attention deficit disorder. J Child Neurology (Supplement) 6:S82-S89.

Rutter M, Korn S, Birch HG (1963) Genetic and environmental factors in the development of "primary reaction patterns". Br J Soc Clin Psychology 2:162-173.

Safer DJ (1973) A familial factor in minimal brain dysfunction. Behav Genetics 3:175-186.

Schneider JS, Kovelowski CJ (1990) Chronic exposure to low doses of MPTP. Cognitive deficits in motor asymptomatic monkeys. Brain Research 519:122-128.

Shaywitz BA, Cohen DJ, Bower MB (1977) CSF monoamine metabolites in children with minimal brain dysfunction: Evidence for alteration of brain dopamine, a preliminary report. J Pediatrics 90:671-677.

Shaywitz BA, Shaywitz SE, Bryne T, et al (1983) Attention deficit disorder: quantitative analysis of CT. Neurology 33:1500-1503.

Stevenson J (1992) Evidence for a genetic etiology in hyperactivity in children. Behav Genetics 22:3:337-343.

Tannock R, Schachar RJ, Carr RP, et al (1989) Effects of methylphenidate on inhibitory control in hyperactive children. J Abnorm Child Psychology 17:473-491.

Torgensen AM, Kringlen E (1978) Genetic aspects of temperamental differences in infants. J Am Acad Child Psychiatry 17:433-444.

Voeller KS (1991) Toward a neurobiologic nosology of attention deficit hyperactive disorder. J Child Neurology (Supplement) 6:S2-S8.

Welner Z, Welner H, Stewart M, et al (1977) A controlled study of siblings of hyperactive children. J Nerv Ment Disorders 165:110-117.

Willerman L (1973) Activity level and hyperactivity in twins. Child Development 44:286-293.

Zametkin AJ, Nordahl TE, Gross M, et al (1990) Cerebral glucose metabolism in adults with hyperactivity of childhood onset. N Eng J Medicine 323:1361-1366.

Zametkin AJ, Rapoport JL (1987) Neurobiology of attention deficit disorder with hyperactivity: Where have we come in 50 years? J Am Acad Child Adolesc Psychiatry 26:676-686.

Zametkin AJ, Rapoport JL (1986) The pathophysiology of attention deficit disorder with hyperactivity: a review. Adv Clin Child Psychology 9:177-216.