CHAPTER FOURTEEN

Nutrition for ADHD and Autism

Jacques Duff

This chapter presents the rationale that may explain why the incidence of attention deficit hyperactivity disorder (ADHD), autism, depression and modern diseases is relentlessly increasing, despite the billions of dollars invested in research and medications each year. This rationale leads to the need to investigate and treat the underlying genetic predispositions and the nutritional causes, rather than indiscriminately medicating our young at a time of their life when their vulnerable brains are still developing. Throughout this chapter reference is made to genes, enzymes, nutrients and lifestyle factors that affect mental health, including ADHD, autism, depression, anxiety and schizophrenia. It is common sense and good science to address these potential causal factors, in addition to addressing the dysfunctional neurophysiology with neurotherapy.

NUTRIGENOMICS, EPIGENETICS, NUTRIENTS AND LIFESTYLE

Through the processes of meiosis and mitosis a single fertilized egg differentiates into an embryo, and eventually into a unique baby on account of the genetic instructions in the DNA interacting with nutrients to form proteins and enzymes that catalyze biochemical reactions. These nutrigenomic interactions are responsible for the composition of our body tissues and carry out a multitude of functions in the circulatory, respiratory digestive, cardiovascular, endocrine, central and peripheral nervous systems. Some of these proteins and enzymes enable brain functions that make us uniquely human, such as the ability to talk, think abstract thoughts, plan ahead and organize our environment into complex systems to serve our needs and promote our survival.

Nutrigenomics is the study of the interaction between genes and nutrition. Research in this field has taught us that the nutrients in food have complex interactions with our DNA, affecting our health outcomes

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and our disease risks. Everything we consume has some degree of impact on our DNA and has a consequence at a molecular level. Through the process of natural selection, our evolutionary ancestors adapted genetically to daily low-grade exercise, an organic diet and a clean environment. By the end of the Palaeolithic period, modern man had emerged as the result of an optimum balance between genes, environment, nutrition and the hunter–gatherer lifestyle. Today, we carry these genes and are genetically adapted to a Palaeolithic hunter–gatherer diet and lifestyle.[1,2]

Epigenetics is the study of changes in inherited gene expression or cellular phenotype caused by mechanisms other than changes in DNA nucleotide sequence. Epigenetics research has shown that our DNA is controlled by signals from outside the cell, and that environmental factors shape the development and function of cells. Recent scientific studies have revealed that we can influence our health outcomes through changes in lifestyle factors, nutrient uptake and the elimination of environmental and other toxins; even our thoughts and feelings can affect the expression of our genes.[3] Gene expression is altered by dietary transcription factors, such as low zinc status, or by exposure to toxic environmental substances, such as mercury or organophosphate pesticides. Studies have shown that gene expression patterns differ geographically between and within populations, suggesting that environmental factors are responsible. Such changes in gene expression can adversely affect neuronal plasticity, resulting in neurodevelopmental disorders such as ADHD, autism and mental retardation.[4]

Essential nutrients help maintain normal neuronal plasticity. Nutritional deficiencies, including deficiencies in the long-chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the amino acid methionine, zinc and selenium, have been shown to affect neuronal plasticity and function and produce behavioral deficits in children, including those with ADHD.[5]

In 1998, Dean Ornish and colleagues demonstrated that improved nutrition, moderate exercise, stress management techniques and increased social support were associated with the expression of over 500 epigenetic genes being changed in only 3 months. These include upregulating or turning on disease-preventing genes and downregulating or turning off genes that promote heart disease, cancer, inflammation and oxidative stress.[6] Genetic screening for selected epigenetic gene polymorphisms that affect health outcomes is commercially available, suggesting that the future of healthcare may well be determined by personalized nutrigenomics and

medicine. Some of these genes, when missing or mutated, can result in the complete absence of key enzymes responsible for liver detoxing, or in mild to dramatic reduction in the capacity of enzymes to carry out their functions. Hence, a one-size-fits-all diet and generic lifestyle recommendations no longer make sense in light of this emerging knowledge from epigenetics research.

Our highly processed modern diet, with its manmade *trans*-fatty acids, chemical additives, preservatives, colorings, added hormones and antibiotics, is affecting the delicate balance of nutrigenomic interactions and is affecting our genome. Genetic weaknesses, which previously did not seem to affect us, now interact with dietary nutritional deficiencies and environmental toxins to promote the modern diseases. It is not surprising that the rates of incidence of modern diseases, such as cancer, diabetes, heart disease, ADHD, autism, depression, anxiety, irritable bowel syndrome and inflammatory bowel disease, to name but a few, continue to rise despite the billions of dollars spent each year on research and pharmaceutical treatment, which for the most part are toxic to our genome and often carry unacceptable side effects.

A large part of my clinical practice consists of examining these genetic polymorphisms and recommending dietary and lifestyle changes and nutrient supplementation to modulate the expression of these genes, reduce toxicity and oxidative stress, modulate risk factors and promote optimum health. Throughout this chapter I shall be outlining the rationale for the need to test for genetic polymorphisms and nutrient levels, and for supplementing key nutrients to optimize the physical and mental health of patients, including children with ADHD and autism.

OMEGA-3 (n-3) AND OMEGA-6 (n-6) ESSENTIAL FATTY ACID (EFA) BALANCE

The body cannot manufacture EFAs; therefore they must be part of our diet. A number of studies have estimated that our modern diet provides around 20–40 times more n-6 and five to ten times less n-3 than the Palaeolithic hunter–gatherer diet.[1] Most of the n-6 in our diet comes from vegetable sources of linoleic acid (LA) such as nuts and vegetables; n-3 also comes from vegetable sources of alpha-linolenic acid (ALA), such as flaxseed oil and nuts such as walnuts. However, it is the consumption of polyunsaturated cooking oils and margarines in our modern diet that has caused the imbalance. These fatty acids are converted to longer-chain

EFAs by elongase and desaturase enzymes (Figure 14.1), and all play a crucial role in the body's composition and functions; human beings require the long-chain polyunsaturated fatty acids from fish for brain development and function.[1]

Polymorphisms in the desaturase encoding genes FADS1 and FADS2 have been associated with several n-6 and n-3 fatty acids. The relationship between FADS gene cluster polymorphisms and red blood cell (RBC) fatty acid levels in over 4000 pregnant women participating in the Avon Longitudinal Study of Parents and Children was analyzed. The study found that FADS polymorphisms influence maternal RBC n-3 DHA levels, which affected the baby's DHA supply during pregnancy.[7] Given the fundamental role of DHA in fetal neuronal development,[8] this finding is of particular concern. Animal studies have shown that an imbalance of high n-6:n-3 ratio early in life leads to irreversible changes in hypothalamic phospholipid composition, consistent with a dysfunction or down-regulation of the conversion of ALA to DHA by the delta-6 desaturase enzyme (Figure 14.1). These two findings[7,9] suggest that FADS polymorphisms may lead to irreversible structural changes in brain cells, affecting their function; and that for those people with FADS polymorphisms, a higher lifetime consumption of fish and fish oils may be necessary to prevent deficiencies that affect brain function.

Arachidonic acid (AA), an n-6 fatty acid, is essential for cell membrane stability and also starts a cascade of inflammatory processes (thromboxins, leukotrienes and prostaglandins) for the defense of cells against antigens. EPA, an n-3 fatty acid, produces anti-inflammatory processes, protecting cells against free radical damage and from inflammatory cytokines.[10] The ratio of AA to EPA is ideally around 1.5–3.0, and this is achieved when a person limits his or her meat intake (a good source of AA) and consumes deep-sea cold-water fish four or five times a week, or has an adequate intake of fish oils as supplements. Too much AA leads to a propensity for excessive inflammation; too little adversely affects cell membrane stability and necessary inflammatory responses.[10]

Trans-fatty acids are manmade (usually resulting from heating polyunsaturated oils) and can displace EPA and DHA from cell membranes. This has two detrimental effects: first, the cell membrane becomes more permeable, allowing antigens to penetrate the cell and cause damage to intracellular mechanisms; second, as the RBC AA:EPA ratio rises, the propensity for inflammation increases. In addition, the decrease in DHA levels has a detrimental effect on neurodevelopment and mental health, as discussed next.

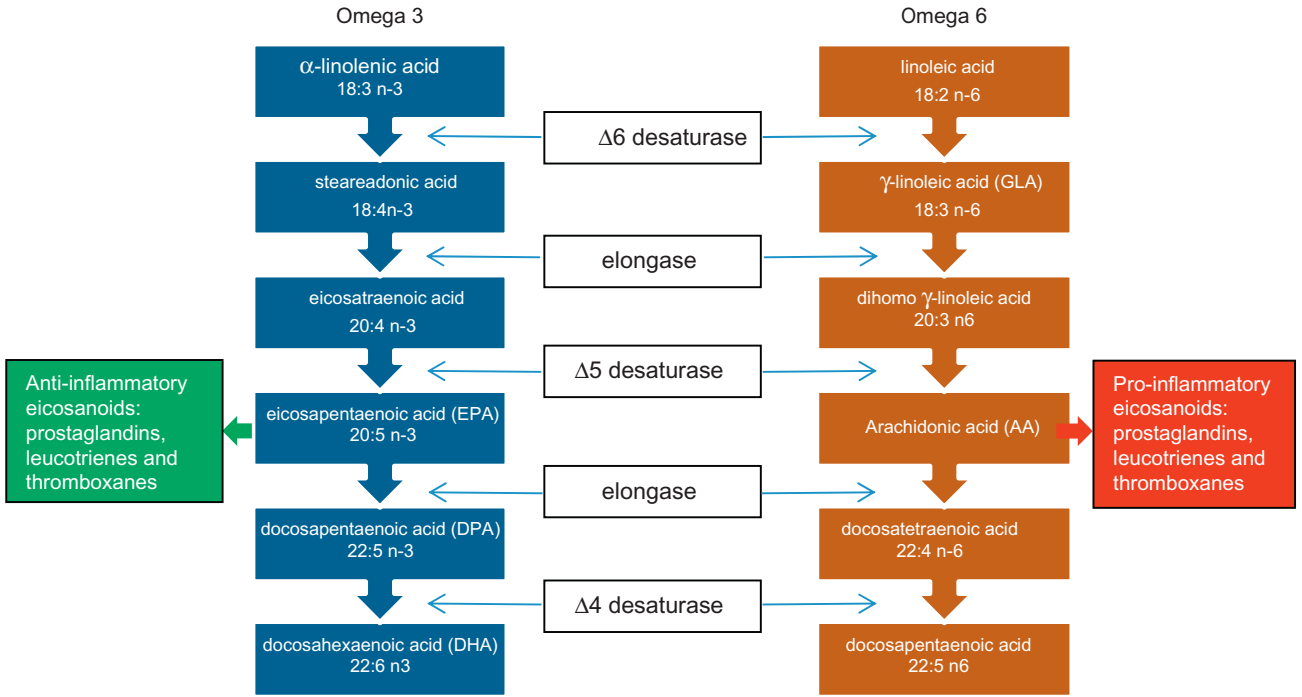

Figure 14.1 Conversion of dietary fatty acids to long-chain polyunsaturated fatty acids and eicosanoids.

The Role of DHA

DHA makes up around 25% of the dry volume of brain cells in all healthy mammals and concentrates in neuronal synapses,[11] where, in conjunction with proteins, it modulates the synthesis, transport and release of monoamine neurotransmitters.[12] The results of a retrospective study examining the RBC EFAs in ADHD, autism and typically developing children are shown in Tables 14.1 and 14.2.[13] The Australian Twin Behavioural Rating Scales (revised) is a DSM-IV behavioral screening questionnaire for ADHD, and the Test of Variables of Attention (TOVA) is a computer-administered continuous performance task.

Note the dramatically low percentage of RBC DHA in children with autism compared to those with ADHD and typically developing controls. The optimum RBC DHA level is >6%, and is achievable with a diet high in fatty cold-water fish or fish oil supplementation. In addition, children with autism spectrum disorder (ASD) had very low RBC AA, suggesting impaired cell membrane integrity, and therefore vulnerability to damage from toxins and antigens.[13]

These results indicate that children with ASD had by far the worst EFA profile, and those with ADHD were lagging behind their typically developing peers. Given that DHA modulates the synthesis, transport and release of neurotransmitters in synapses, this is not surprising. However, many of the children with autism and ADHD had RBC DHA as low as 0.1%, while others had ratios around 4.0%. These large fluctuations suggest that whereas DHA deficiency may constitute a major part of the etiology of neurodevelopmental disorders, other factors are also at play. During treatment, optimum levels (>6.0%) are achieved by aggressive supplementation with high-quality fish oil concentrate. Maintenance after 12 months can be achieved by consuming oily fish four or more times a week. However, our experience has shown that this is applicable only for some children. Others seem to need to take fish oil supplements and nutrient cofactors permanently. This is probably a result of the irreversible down-regulation of desaturase stages, as previously discussed.[9] A comprehensive review of all the nutrients and enzyme cofactors involved in brain function is beyond the scope of this chapter. Therefore, only an overview of those that have been shown to be involved in the attentional system and in mood regulation is provided next.

Table 14.1 Means and Standard Deviations of Age, TOVA, ATBRS, CARS, EPA, DHA and AA Between Typically Developing, ADHD and ASD Groups

	Age	TOVA	ATBRS	CARS	% EPA	% DHA	% AA
TD (n = 81)	8.31 (2.53)	3.88 (1.69)	14.14 (7.49) **		1.82 (0.96)	4.70 (1.02)	10.46 (2.08)
ADHD (n = 401)	9.10 (3.58)	−3.78 (3.28)	42.43 (14.43)		0.89 (0.56)	2.28 (0.89)	9.73 (2.71)
ASD (n = 85)	5.32 (2.12)			40.71 (8.04)	0.56 (0.52)	0.85 (1.02)	6.24 (3.28)

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; TD, typically developing; TOVA, Test of Variables of Attention; ATBRS, Australian Twin Behaviour Rating Scales; CARS, Childhood Autism Rating Scale.
**Parentheses denote SD.

Table 14.2 Independent Sample *t*-test Scores of EPA, DHA and AA in ADHD and ASD Groups Compared to a Typically Developing Sample

	EPA	DHA	AA
TD × ADHD	$t(480) = -11.91^{\star}$	$t(480) = -21.84^{\star}$	$t(480) = -2.30^{\star}$
TD × ASD	$t(164) = -10.64^{\star}$	$t(164) = -30.28^{\star}$	$t(164) = -30.28^{\star}$

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid.
$^{\star}p < 0.05$.

Monoamine Neurotransmission

There are five established biogenic amine neurotransmitters: the three catecholamines – dopamine, norepinephrine (noradrenaline) and epinephrine (adrenaline) – as well as serotonin and histamine. The main monoamine neurotransmitters, serotonin, dopamine and norepinephrine, are considered brainstem neuromodulators, because their neurons have cell bodies in the brain stem and have projections to the limbic system and to the neocortex. Neuromodulation refers to the process of dynamic modulation of neuronal activity, at rest and during information processing. It includes (a) the manufacture of the neurotransmitters in brain synaptic vesicles from dietary amino acid precursors; (b) their transport in vesicles through the synaptic cleft; (c) their release into the synaptic gap; (d) their migration to receptor sites on the receiving neurons; (e) their effect on the receiving neurons; and finally (f) the reuptake of any residual neurotransmitter back into the transmitting neurons for recycling (Figure 14.2).

When a neurotransmitter is released into the synapse, it migrates to receptors located on dendrites, cell bodies and presynaptic terminals of second (receiving) neurons. Almost all monoamine receptors are G protein-coupled receptors that activate intracellular second-messenger molecules, such as inositol triphosphate. These molecules relay signals from surface receptors to target molecules inside the cell, amplifying the strength of the signal, and have an effect on the postsynaptic membranes on the receiving neuron.

Embedded among the monoamine neurotransmitter receptors are also G protein-coupled receptors for trace amines.[14] These amines are usually formed by the breakdown of proteins in foods. Some of the most common are tyramine (from cheese), histamine (from wine) and phenylethylamine (found in chocolate). However, when the bowel environment has an acidic pH, some gut organisms, particularly lactic acid bacteria such as

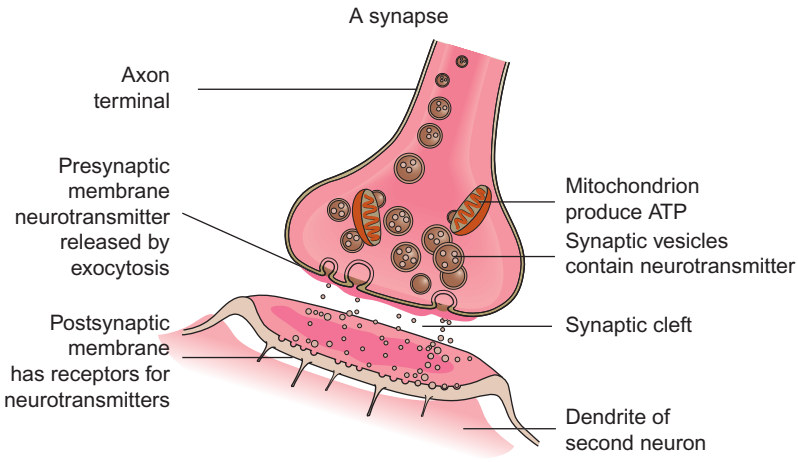

Figure 14.2 Synapse and neurotransmitters.

Bifidobacteria, overgrow and cleave proteins to produce large amount of amines, resulting in a much higher ratio of amines to amino acids than under neutral pH conditions.[15,16] In addition, the acidic gut conditions inhibit the growth of *Escherichia coli,* which is a major producer of the monoamine neurotransmitter precursors tryptophan, phenylalanine and tyrosine.[16] This reduces the amino acids available for neurotransmitter synthesis, whereas the amines key into amine receptors and scramble neurotransmission. Patients report a combination of symptoms, such as brain fog, poor concentration, muscle aches and pain, headaches, migraines and depression. It has been proposed that these biogenic amines may be involved in treatment-resistant depression.[17] In children the symptoms are feelings of unease, irritability, low frustration threshold, anger outbursts and poor concentration. Interestingly, a diet high in refined carbohydrates from cereal grains and dairy products is highly acid producing in the bowel and promotes the growth of lactic acid bacteria promoting amine production. These symptoms can easily be mistaken for those of ADHD. In our experience, symptoms improve or resolve with an alkaline-producing diet and nutrient supplementation.

Serotonin or 5-hydroxytryptamine (5HT)

Serotonin is both an excitatory and an inhibitory neurotransmitter. It is found in enteric neurons where it modulates peristalsis, and in the brain

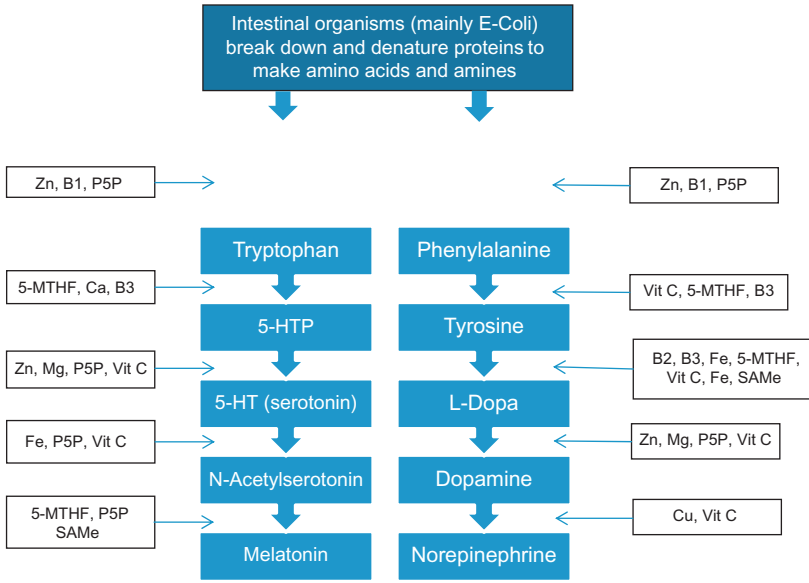

Figure 14.3 Neurotransmitter amino acid precursors and major nutrient enzyme cofactors.

where it modulates calmness and good feelings. Around 2% of the amino acid tryptophan in circulation is converted to 5-hydroxytryptophan (5HTP) by tryptophan hydroxylase, an enzyme that uses 5-MTHF (the active form of folate), iron, calcium and vitamin B3 as cofactors. 5-HTP is further converted to serotonin by the enzyme dopa decarboxylase, which uses magnesium, zinc, piridoxine-5-phosphate (P5P), the active form of vitamin B6 and vitamin C as cofactors. In the pineal gland and the retina, the enzyme *N*-acetyltransferase converts serotonin to *N*-acetyl serotonin, which in turn is converted to melatonin and released into the bloodstream and cerebrospinal fluid by the enzyme 5-hydroxyindole-*O*-transferase, a process requiring the active form of vitamin B6 (P5P) as cofactor. Melatonin promotes sleep, and its production is inhibited by daylight; even room lighting and television watching can inhibit melatonin production (Figure 14.3).

Suboptimal neuromodulation of brain serotonin has been linked to a variety of adverse behaviors and mental health issues, such as aggression, irritability, low frustration threshold, anger outbursts, depression, suicidality, obsessive–compulsive disorder, alcoholism, anxiety and affective disorders. Although these associations are known, the mechanism of action

responsible remains largely unknown. In brain synapses the principal source of release of serotonin is from serotonin neurons, which have cell bodies originating in the raphe nuclei, in the brain stem. Their axons form a neurotransmitter system that enervates almost every part of the central nervous system.

The serotonin transporter (SERT) protein transports residual serotonin back into the synapse for recycling and ends the action of serotonin. This protein is the target of many antidepressant medications, particularly selective serotonin reuptake inhibitors, which block the action of SERT. Polymorphisms in the promoter arm of the SERT gene can affect serotonin neurotransmission, causing irritability and aggressiveness as well as an increased susceptibility to depression.[18] Nutritionally, people with this mutation require more aggressive supplementation with 5HTP, vitamin B6 (P5P) and vitamin C.

Effect of Diet on Serotonin and Health Outcomes

The large neutral amino acids (LNAA) such as tyrosine, valine, isoleucine, leucine, phenylalanine and lysine compete with tryptophan for transport through the blood–brain barrier. Hence, foods with a high ratio of tryptophan to LNAA may improve 5HT production in the brain. Meals typical of those consumed in the United States and Australia have been shown to cause substantial variations in the plasma tryptophan:LNAA and tyrosine:LNAA ratios, depending on the ratio of protein to carbohydrates. The differences between the ratios generated by a high-carbohydrate low-protein and high-protein breakfast can be >50% for tryptophan:LNAA and 30% for tyrosine:LNAA.[19] Hence, a western diet high in refined carbohydrates, wheat and cereals, and low in proteins can cause a rise in tryptophan, thereby increasing serotonin. Concurrently, such a diet also causes a rise in insulin, which is required to control blood sugar levels.[20] However, these dietary increases in serotonin and insulin are not in keeping with the homeostasis that existed during our evolutionary history, when meat proteins, fish, nuts, fruit and vegetables were our primary source of food.[1,2]

Chronically elevated insulin levels can cause hypoglycemia, insulin resistance, metabolic syndrome, polycystic ovarian syndrome, obesity and type 2 diabetes. Over time, insulin resistance can cause serotonin levels to drop, thereby predisposing to depression.[21] Exercise is known to activate hundreds of genes and builds up muscles through a process that uses many amino acids, with the exception of tryptophan. Consequently,

people who exercise and build more muscle have more available tryptophan and higher serotonin levels, thereby downregulating depression.[22]

E. coli, which accounts for 80–90% of the aerobic bacteria in the healthy large bowel, produces chorismate, which is a precursor to folic acid, coenzyme Q10, tryptophan, phenylalanine and tyrosine. Low bowel *E. coli* can result in lower tryptophan levels, and therefore lower serotonin production. This is associated with slow bowel transit time, constipation, irritability and depressed mood. In the past 12 years we have assessed the extended fecal microbiology of over 300 children through Bioscreen Medical at Melbourne University and examined their bacteria distribution. Those children with low *E. coli* consistently display symptoms that include irritability, low frustration threshold, anger outbursts, poor sleep, moodiness and tantrums, and their Z-score quantitative electroencephalograph (qEEG) consistently shows low delta power. This is not surprising, because serotonin modulates delta frequencies. However, these children tick the boxes for ADHD and are often diagnosed as such, with a poor response to psychostimulants. Note that poor sleep quality is often caused by low serotonin, which is converted to melatonin to promote sleep.

Given that *E. coli* grows best in a neutral pH gut environment, it can be promoted with an alkalinizing diet, low in grains and dairy and rich in vegetables, legumes and pulses, and moderate meat intake. The diet should produce a first morning urine pH of 6.8–7.0. In addition, when delta power levels are low, 5HTP magnesium, zinc, vitamin B6 as P5P, and vitamin C can also be prescribed to promote serotonin and melatonin production.

The Role of Dopamine and Norepinephrine in the Attentional System

In order to understand ADHD and the effect of neurotherapy on the brain, an understanding of the attentional system is required. Tucker and Williamson reviewed the evidence for the underpinnings of the human attentional system, based on the biological mechanism of attention derived from animal dissections and studies carried out by Pribram and McGuinness.[23] They concluded that there was a self-regulating asymmetrical neural control network linking a frontal, primarily left, dopaminergic system to a posterior, primarily right, noradrenergic system. The two linked systems were described as a "frontal tonic activation system" and a "posterior phasic arousal system."[24]

The "tonic activation system," centering on the forebrain basal ganglia, was described as providing a state of tonic motor readiness for action.

This implied a state of alertness or vigilance, which Tucker and Williamson argued was mediated by two related dopaminergic systems: first, the primary nigrostriatal dopamine pathways, originating in the substantia nigra in the brain stem, enervating the caudate nucleus and putamen and handling sensorimotor integration. Increased dopamine modulation restricts the range of behaviors by increasing informational redundancy. In this context, redundancy refers to the processing of information of interest in related pathways, while simultaneously restricting the processing of other information. Thus increased redundancy not only increases reliability but also restricts alternative information from being processed. Second, a related dopamine pathway, the mesocortical or mesolimbic system, with cell bodies in the ventral tegmental bundle and connections to the nucleus accumbens, central amygdaloid nucleus and the lateral septal nuclei, supports controlled motivated interactions with the environment. They argued that this largely dopamine-mediated neural control system does not linearly increase activation but qualitatively facilitates vigilance, tight control of motor output and purposeful behaviors.

The "phasic arousal system" was described by Tucker and Williamson as a parietal noradrenergic system providing transient responses to changes in sensory information or novelty in sensory channels. They suggested that reiterative loops, which constantly compare new sensory channel patterns to previous ones, enable the detection of novelty. The primary noradrenergic pathway, from the dorsal tegmental bundle, originates in the pontine locus ceruleus and projects rostrally to the median forebrain bundle and the limbic system, including the amygdala, hippocampus, thalamus and neocortex. They proposed that norepinephrine does not linearly increase arousal, but "qualitatively" facilitates response to perceptual input from environmental novelty. Noradrenergic activity declines with repetitive input (habituation), inhibits neuronal discharge and reduces the spontaneous background activity of neurons. Thus norepinephrine may increase signal-to-noise ratio and augment the cell's evoked responses to stimuli, thereby increasing sensitivity to change.[24]

According to Tucker and Williamson,[24] the dopaminergic system appears to maintain the tonic level of neural activity by increasing the redundancy of the information (decreasing alternatives) in brain channels. This was demonstrated elegantly in the behavior of DAT-KO mice (mice with overstimulated dopamine pathways whose dopamine transporter was genetically knocked out).[25] In novel environments, the behaviors of DAT-KO mice became dominated by progressively fewer acts (repetitively exploring

the same arm of the maze) with increasing frequency. Hence, tonic activation produces a redundancy bias, which restricts change and tightly controls or restricts motor output or behaviors. The qualitative regulatory effect of activation is thus opposite to that of arousal, which reduces redundancy. Yet for motor functions a redundancy bias applies a negative control, not unlike the negative feedback on perceptual responsiveness provided by arousal. Behavioral output therefore requires constant change in motor channels.[24]

Duff[26] supported this proposed explanation of the attentional system by demonstrating its elements in a study that examined changes in the electrical activity of boys with ADHD following neurotherapy. The study used steady state visually evoked potential (SSVEP) probe topography before and after neurotherapy while the boys with ADHD performed the CPT-AX computer-administered task. The cognitive attention task requires subjects to press a response button on the appearance of the letter X, only if the previous letter was an A. Figure 14.4 illustrates the changes in activation, from pre- to postneurotherapy. A reduction in normalized amplitude can be interpreted as increased neuronal activation, while an increase in amplitude can be interpreted as a reduction in activation.

Note the dynamic changes in activation following neurotherapy. It has been suggested that children with ADHD may have difficulties allocating attentional resources[27] and may inefficiently tie up prefrontal circuitry, which is needed for behavior control, instead of using presupplementary motor areas.[28] This suggestion is supported by findings from a study of suppression of BOLD response in functional magnetic resonance imaging while performing a reaction-time task, which found that increased visual response time in children with ADHD was associated with an inability to deactivate the ventromedial prefrontal cortex under increased reaction-time task demands.[29] Increased visual response time in ADHD has also been interpreted as suggestive of reduced perceptual sensitivity and response consistency, and was related to most ADHD symptoms.[30] The suggestions of inefficient allocation of attentional resources in ADHD, tying up prefrontal circuits instead of using presupplementary motor areas, leading to reduced perceptual sensitivity and response consistency, are consistent with Silberstein's[31] suggestion that cognitive proficiency is associated with efficient functional connectivity, i.e., the rapid recruitment and release of coherence between relevant brain areas contingent with task demands.

Whereas neurotherapy appears to help redress the inefficient allocation of dopamine and norepinephrine resources in the brains of children with ADHD, the nutritional precursors needed to synthesize these

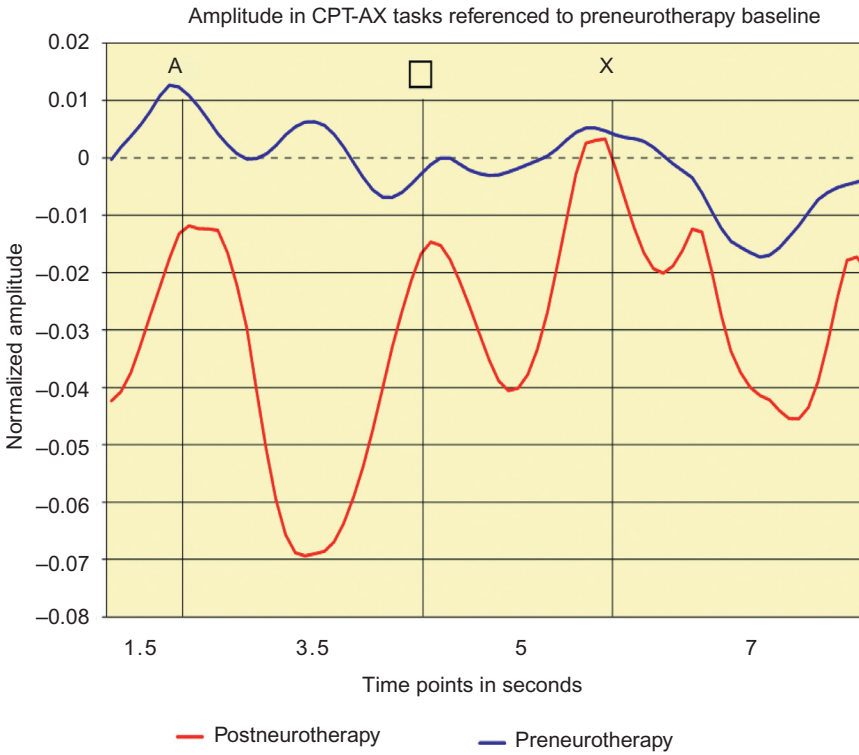

Figure 14.4 Steady-state visually evoked potential (SSVEP) amplitude during the target sequence in the CPT-AX task as a function of time in subjects with ADHD pre- and postneurotherapy. The dashed horizontal line represents the mean normalized amplitude for the baseline task, which was set to zero for both conditions. CPT-AX related amplitude changes are therefore expressed as differences from the baseline. The vertical lines represent the time points at which: the letter A is presented (A), the letter A disappears and the blanking interval commences (□) and the letter X appears (X).

neurotransmitters in synapses and to facilitate their transport and release in the brain need to be optimal to facilitate neuromodulation. The following sections explain the role of gene polymorphisms, enzymes, nutrient cofactors and amino acids in this process.

ZINC AS AN ESSENTIAL NUTRIENT FOR HEALTH

Zinc compounds are found in soil and water, and in many foods. However, the soil in many countries is generally much lower in zinc than in countries that have a soil rich in volcanic minerals – so much so that one-third of the world's population has an inadequate intake of dietary

zinc.[32] Zinc deficiency is one of the most prevalent nutritional deficiencies in the United States. Suboptimal zinc status has been noted in children of lower socioeconomic groups, low-birthweight infants, pregnant teenagers and some of the elderly.[33,34] In Australia, the Bureau of Statistics nutritional surveys have found that most of the population do not have the recommended daily intake of zinc. If too much zinc is consumed for the body's needs, less is absorbed and more is excreted in urine and feces; hence, zinc toxicity is rare. Individual requirements for dietary zinc are determined by the biological need to replace losses and maintain function, and the bioavailability of zinc from the foods consumed. The amount of dietary zinc required to replace tissue losses in individuals fully adapted to a diet low in zinc is considered the minimal zinc requirement and is often referred to as the recommended daily intake.[33,34] Blood serum zinc levels reflect recent dietary intake, are very variable and hence are poor indicators of tissue levels. RBC zinc is a better indicator of zinc status than serum zinc, because erythrocytes have a life of 3 months and RBC levels reflect the average level over that period. In one study, 31% of patients were found to have low RBC zinc levels, whereas only 10% had low plasma zinc.[35]

Zinc is an essential nutrient, involved in hundreds of biochemical pathways in the body, including many involved in neurotransmitter synthesis and synaptic function. Features of zinc deficiency are generally nonspecific, affecting the optimal function of a number of systems. In children deficiency may lead to poor appetite, a decreased sense of taste and smell, slow wound healing, skin lesions and decreased immune function. There is considerable evidence that maternal zinc deficiency has detrimental, possibly long-lasting, effects on fetal growth, neurodevelopment and immune system maturity. In the early 1970s a number of controlled studies of zinc supplementation in infants and toddlers in Colorado demonstrated the growth-limiting effect of zinc deficiency in otherwise healthy subjects. Zinc-supplemented children developed increased appetite and thrived compared to controls. These findings were replicated in studies from Ontario, and in school-aged children in Texas.[34]

Breast milk contains zinc citrate,[36] which animal studies have found to be twice as bioavailable as other forms, such as picolinate and sulfate.[37] Therefore, infants use the zinc in breast milk more efficiently than that in formula. During pregnancy, the fetus and other pregnancy tissue account for around 100 mg of zinc, which the expectant mother must provide,[4] and the additional zinc requirement occurs primarily in the last trimester, when fetal growth is most rapid.[34] This suggests that mothers should be

advised to optimize their intake with zinc citrate supplementation, at least throughout pregnancy and breastfeeding.

Zinc, Brain Function and ADHD

Approximately 15% of the zinc in the brain is found in synaptic vesicles, from which it is released to the extraneuronal space during synaptic transmission. In the surroundings of the synapse, zinc acts upon a variety of neuronal receptors and ionic channels, playing a modulatory role that is not yet fully understood.[38] Within the vesicles, zinc is a cofactor for the production of dopamine from L-dopa, serotonin from 5HTP, and melatonin from serotonin (Figure 14.3). Hence, zinc is likely to be an important modulator of synaptic transmission.[38] Research suggests that zinc may regulate *N*-methyl-D-aspartate receptors,[39] and animal studies have shown that zinc is an important regulator of gamma-aminobutyric acid receptors, affects the excitability of hippocampal glutamatergic neurons, and may play an important role in cerebellar function.[40] Indeed, recent studies have shown evidence for a significant reduction of the combined glutamate/glutamine to creatine ratio in the right anterior cingulate cortex in patients with ADHD,[41] and striatal glutamate, glutamate/glutamine and creatine concentrations were higher in ADHD subjects than in controls, providing evidence of a striatal creatine/glutamatergic dysregulation in ADHD.[42]

Several studies have associated low zinc status with symptoms of ADHD.[43–50] Children with the inattentive type of ADHD have been shown to have significantly lower levels of zinc and ferritin than controls, but not magnesium and copper. Children with the hyperactive type had significantly lower levels of zinc, ferritin and magnesium than controls, and no significant difference with regard to copper. Children with the combined type of ADHD had significantly lower levels of zinc and magnesium than controls, but not ferritin and copper levels.[44]

It has been observed in vitro that the dopamine transporter contains a high-affinity zinc-binding site on its extracellular face that modulates its function. Hence, it has been suggested that in ADHD patients with low zinc status, zinc supplementation may improve the binding status of insufficiently occupied zinc binding sites.[45] This is supported by a number of studies suggesting that response to stimulant medication is reduced in zinc-deficient ADHD patients and improved by zinc supplementation, resulting in lower medication dosages.[51–56] A double-blind placebo-controlled study of zinc supplementation in ADHD has found that zinc sulfate was statistically superior to placebo in reducing symptoms of

hyperactivity, impulsivity and impaired socialization, but not in reducing attention deficits. Zinc supplementation appears to be a useful adjunct in the treatment for some children with ADHD and low levels of zinc and fatty acids.[57]

Zinc and Thyroid Dysfunction

It has been suggested that children with ADHD and developmental learning disabilities should be checked for optimum thyroid function as a possible mediating factor for their difficulties.[58] Zinc in plasma and RBCs has been found to be lower in both hypothyroidism and hyperthyroidism. In one study, RBC zinc in hyperthyroidism was inversely related to plasma thyroxine concentration. The hyperthyroid group excreted significantly greater amounts of zinc than controls, indicating a catabolic process. This provides evidence for marked alterations in zinc homeostasis in persons with thyroid problems.[59] Thyroid problems have been found in some children with ADHD: one study found that thyroxine concentrations were associated with mood symptoms and unusual behaviors, but were less strongly related to attentional functioning and not related to hyperactivity.[60]

Zinc, Histidine and Histamine

The enzyme histidine decarboxylase produces histamine from the amino acid histidine. Histamine is best known for its release from mast cells as a response to allergic reactions or tissue damage. However, more importantly for the treatment of ADHD, histamine is found in high concentrations in neurons in the hypothalamus, from where it mediates arousal and attention. Pfeiffer and colleagues[61] found that approximately 50% of their outpatient schizophrenics were "histapenic" (low in blood histamine) and high in blood serum copper, and 20% were histadelic (high in blood histamine) and normal in serum copper. They also found that either group may be low in serum zinc and/or manganese. Zinc is needed by mast cell and hippocampus terminal vesicles to store histamine. Without adequate zinc, histaminergic neurotransmission may be impaired. These two suggested categories, histapenia and histadelia, accounted for around 70% of the schizophrenias in Pfeiffer's patients.[61]

Zinc, Vitamin B6 and Pyroluria

The remaining group of Pfeiffer's patients had normal blood histamine and serum copper levels. This group had excessive urine excretion

of "kryptopyrroles," also referred to as the "mauve factor." The pyrroles combine with pyridoxal (vitamin B6) and then complexes with zinc, producing symptoms of vitamin B6 and zinc deficiency. They found that these patients responded to large supplementary doses of vitamin B6, zinc and manganese.[61] Such individuals have very low RBC zinc and require heavy supplementation of zinc and vitamin B6. Pyrolurics can exhibit severe behavioral disorders, have a low frustration threshold and lose their temper easily. The disorder is familial and is responsible for the high incidence of behavioral disorders and schizophrenia in families, with an incidence of 30–40% in schizophrenics and only 5–10% in the normal population.[61] Kryptopyrroles increase in the blood during stress, and zinc and B6 rapidly become unavailable for neurotransmitter synthesis.

We have found that a number of children diagnosed with ADHD have very low RBC zinc, the levels of which are resistant to moderate supplementation. These children can be extremely unreasonable, have erratic moods, can easily lose control when stressed, and often have disruptive behavioral disorders. We typically test for RBC zinc and copper as well as serum histamine. In addition, we test for mauve factor in urine, which, when elevated, is indicative of pyroluria. When we aggressively add zinc citrate, vitamin B6 (P5P) and manganese to their supplementation regimen, their urinary kryptopyrrole excretion reduces significantly and in most cases behavioral symptoms improve significantly. However, symptoms return rapidly when supplementation is stopped.

MAGNESIUM

Magnesium is found in the soil and is present in vegetables. In the hunter–gatherer diet, magnesium-containing foods were common, but in the last 100 years or so industrialization of food sources, processing of cereal grains and changing diets have diminished dietary intakes of magnesium and other micronutrients.[2,62,63] The magnesium content of vegetables has declined by 25–80% compared to prior to 1950, and food refining processes remove most of the available magnesium from grains and cereals.[63] Consequently, the average American diet affords just over half of the conservative recommended daily allowance for magnesium.[64,65] National Health and Nutrition Examination Survey data show that a large percentage of North Americans fail to meet the recommendations for optimal calcium, magnesium and vitamin D intake.[66]

Intestinal interactions between vitamin D, magnesium and calcium have been demonstrated in both humans and animals.[67] The low levels of

vitamin D commonly seen in western society may be a cause for concern, given that animal studies have shown that severe vitamin D deficiency during lactation produces marked osteomalacia and secondary hyperparathyroidism in both mothers and their offspring. Vitamin D treatment during lactation reversed the mineral, hormonal and skeletal abnormalities in mothers, but not in offspring.[68] Although a substantial amount of magnesium absorption occurs independent of vitamin D status, there is evidence that pharmacological doses of vitamin D increase magnesium absorption in both vitamin D-deficient and vitamin D-replete animals.[67]

The diet of Palaeolithic hunter–gatherers and pre-agricultural societies contained more vegetables, fruit legumes and pulses than meats, and produced alkaline potential renal acid load values. In contrast, today's western diet contains high amounts of animal proteins, grains and dairy products and produces highly acidic potential renal acid load values.[69–72] Therefore, to buffer the acid and maintain normal blood pH, the blood's homeostatic system uses the base minerals such as magnesium, calcium, sodium and potassium. This leaching of these base minerals leads to a condition known as latent acidosis, associated with low availability of base minerals for biochemistry, including brain function.[71] Figure 14.3 illustrates the importance of magnesium and calcium as cofactors in neurotransmitter synthesis. Hence, deficiencies in base minerals are likely to have an impact on monoamine neurotransmitter synthesis and are expected to manifest as attention deficits and mood disorders.

Magnesium works synergistically with calcium to relax the nervous system, and symptoms of deficiency include irritability, restlessness, fidgetiness, muscle cramps and twitches. Kozielec and Starobrat-Hermelin[73] measured hair, plasma and RBC magnesium in 116 children (94 boys and 20 girls) aged 9–12 years with ADHD. Magnesium deficiency was found in 95% of the cohort, 77.6% in hair, 58.65% in RBC and 33.6% in serum. Further analysis indicated an inverse correlation between levels of magnesium and the Freedom from Distractibility Index. Several studies have identified magnesium deficiency in the RBCs of children with ADHD.[73–77]

Magnesium supplementation has been shown to reduce excitability and improve concentration in children with low serum and RBC magnesium levels.[74–76] Forty children with ADHD and 36 controls participated in a magnesium and vitamin B6 supplementation study. At baseline the children from the ADHD group showed significantly lower RBC magnesium values than controls. Magnesium and vitamin B6 were supplemented

for at least 8 weeks. Symptoms of ADHD, including hyperactivity, mood, aggressiveness and lack of attention at school, were scored from 0 to 4 at different times, and RBC magnesium and ionized calcium levels were monitored. The supplementation regimen significantly increased RBC magnesium values, and in almost all cases significantly reduced the clinical symptoms of ADHD. Hyperactivity, mood and aggressiveness were reduced, and attention at school improved. However, when the supplementation was stopped, clinical symptoms reappeared within a few weeks along with a decrease in RBC magnesium.[78,79] This study suggests that children with ADHD frequently have low magnesium levels, which is associated with their symptoms, and that supplementation improves those symptoms.

EVIDENCE-BASED PRESCRIBING OF NUTRIENTS

In order to maximize brain function, the nutrient cofactors necessary for neurotransmitter synthesis, including those of the enzymes involved in the conversion stages, must also be optimized. This is particularly important if the genes that encode these enzymes have polymorphisms that reduce their effectiveness, requiring more of the cofactors to upregulate the enzyme activity. Given what we know about how poor our western diet is at providing these nutrients, it makes sense for informed health practitioners to test these in blood and supplement deficiencies. The following is a list of biomedical tests frequently used at the Behavioural Neurotherapy Clinic for clients with ADHD: (a) RBC EFAs; (b) RBC zinc, copper, magnesium, manganese, selenium (in the United States these are available as a RBC minerals test); (c) serum: vitamin D3, homocysteine, iron studies; (d) extended fecal microbiology analysis from Bioscreen Medical; (e) SMART DNA genetic screen; and of course a TOVA and a qEEG analyzed through Neuroguide. Although useful, RBC magnesium is a poor indicator of tissue levels and needs. Each laboratory reference range for blood nutrients is determined from a statistical analysis of patients' blood test results in a population low in minerals and is therefore skewed toward abnormally low ranges. We generally supplement fish oils, magnesium, zinc, iron, selenium (as Brazil nuts) and vitamin B complex, and aim for RBC levels that are well into the highest quartile of the range. We use the SMART DNA test as an indicator of which genes are mutated and how aggressively we may need to supplement, and we use homocysteine levels as a rough guide for the need for methionine and *S*-adenosyl

methionine, P5P, methylcobalamine, folinic acid and tri-methyl glycine supplementation. The improvements observed in the TOVA, qEEG and behavioral measures are often outstanding.

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