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The Biochemistry of Attentional/Behavioral Problems

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Nutrients are compounds that we ingest that work within our bodies to keep our biochemical systems functioning normally. Toxins, on the other hand, are compounds which can be natural or synthetic in origin, that interfere with the normal biochemical work of the body. The normal metabolic pathways include the chemical conversion of toxins into harmless substances, in a process called detoxification. Because of its enormous biochemical complexity, the brain is often the first organ to show signs of toxicity, when the load of harmful chemicals taken into the body exceeds the capacity of our detoxification pathways to remove them. These toxic effects may be subtle, such as an attention problem, or severe, as in autistic-like behavior.

Research has shown abnormal quantities of certain substances in the urine of children with autism. Similar, though generally milder, abnormalities are being discovered in the urine of children with attention and behavior problems. It is sensible, therefore, to study the biochemical abnormalities that accompany these disorders. With this approach, we can reasonably hope to devise treatments that take sharp aim at the basic mechanisms of these conditions, instead of merely addressing their symptoms.

The abnormalities found in the urine of these children include fragments of incompletely digested proteins from milk and wheat, organic acids produced by microbes within the intestine, and abnormal amounts of certain chemicals produced by the body itself. This paper concerns substances in this last category, MHPG, MHPG Sulfate, and MHPG Glucuronide, natural products of the body's own metabolism, found in abnormal amounts in the urine of children with a wide spectrum of attentional and behavioral disorders.

The Feingold Program, a diet free of certain natural and synthetic compounds, was developed by the late Ben F. Feingold, MD, a pediatrician and allergist. Without knowing the biochemical mechanism at work, many parents have found this treatment effective.

Instead of, or in addition to, this elimination diet, physician-ordered treatment with antifungal medicines has also been helpful in treating certain children with attention and behavior problems. Until recently, there has not been any research addressing a way to predict if these treatments will work in certain individuals. The MHPG test on children and adults with behavior and attention problems is a promising area of research.

Phenolic Compounds

A group of natural and synthetic compounds that are ingested or produced to varying degrees by the body or by microbes in the intestine contain a benzene ring with one or more hydroxyl (OH) groups attached to it. When this attachment occurs, they become phenolic compounds. These compounds possess unique chemical properties. They are very soluble both in organic solvents (like alcohol, ether, and the fatty components of the body) and in water (aqueous solution), where they are strongly acidic. They exert toxic effects in the brain, where normally certain enzymes prevent their accumulation.

The Feingold Program is a diet regimen which eliminates many dietary sources of phenolic compounds. Similarly, antifungal medications eliminate microbes (yeasts and other fungi) in the intestine which produce a wide variety of phenolic compounds.

Phenol Sulfotransferase (PST)

The chemical substances that make up our bodies are always changing—being broken down or combining with one another. In this way, we get rid of unwanted chemicals in the body, including the brain, and build the complex molecules needed for health, including optimum brain function. An enzyme is a biological catalyst, a protein

which when linked to appropriate cofactors (vitamins, minerals), increases the speed of a chemical conversion in the body. Enzymes are found in every organ and tissue of the body. The enzyme (actually a group of enzymes) which, in a process called sulfoconjugation, attaches sulfate to phenolic compounds, allowing the body to rid itself of these potentially harmful chemicals, is called phenol sulfotransferase (PST). PST is deficient in over half of the autistic children tested by Dr. Rosemary Waring in Birmingham, England. In the absence of adequate PST activity, the body accumulates abnormal amounts of phenolic compounds, such as those in the diet and those produced by microbes in the intestine.

What Is MHPG and Why Do We Measure It?

MHPG (3 methoxy-4-hydroxy-phenylglycol) is a natural breakdown product of a certain class of neurotransmitters (chemical messengers which pass across the narrow space, or synapse, between nerve cells) called catecholamines. One of the catecholamine neurotransmitters which is broken down to MHPG is norepinephrine (NE). Since the 1970's, the urine of autistic children has been known to contain abnormally low amounts of MHPG (Young, J.G. et al, Decreased 24-Hour Urinary MHPG in Childhood Autism. Am J.Psychiatry 136, August 1979, pp. 1055-7).

In order for the body to get rid of MHPG, it has to convert it, in a process called "conjugation," either to MHPG sulfate or MHPG glucuronide.

By measuring the amount of MHPG sulfate, MHPG glucuronide, and total MHPG (the sum of the sulfate and the glucuronide) excreted in the urine in 24 hours, we can find out two things:

1. The turnover rate of the catecholamine neurotransmitters, especially NE, in the body. It is the use (i.e., the release) of NE that leads to the breakdown of NE to MHPG. Low total urinary excretion of MHPG suggests that smaller than normal amounts of NE are being released into the synapses of the brain. (Young, J.G., et al. Cerebrospinal Fluid, Plasma, and Urinary MHPG in Children, Life Sciences, Vol. 28, 1981, pp. 2837-45) and Peyrin, L, Urinary MHPG Sulfate as a Marker of Central Norepinephrine Metabolism: A Commentary, J. Neural Trans [Gen.Sect], Vol. 80, 2990, pp.51-65) 2. The relative efficiency of the two main conjugation pathways for MHPG (and by extension, for other phenolic compounds, such as salicylates and artificial food colors): sulfoconjugation and glucuronidation.

Some Interesting Facts About Norepinephrine (NE)

NE is an important neurotransmitter in the brain, and it also has a role in immune regulation:

1. NE is the neurotransmitter whose effect in the brain is augmented by stimulant drugs such as amphetamine and methylphenidate (Ritalin). In 1980, a placebo-controlled study was published (Swanson, J.M. and Kinsbourne, M., Food Dyes Impair Performance of Hyperactive Children on a Laboratory Learning Test. Science 207, March 1980, pp. 1485-7) demonstrating that a mixture of artificial colors could interfere with learning in children with ADD. Children whose learning was affected by the challenge dose of artificial color mixture proved to be those who had an earlier "positive" effect with this type of stimulant medication. In other words, children who respond to the Feingold Diet, which eliminates all artificial colors and certain other compounds, are the same children who may lack sufficient NE effect in their brains. 2. Normally, NE's role in the regulation of immunity is one of "fine tuning" and adjusting the timing of the various phases in the immune response. Some evidence suggests that the brain's supply of NE may become depleted if the immune system is constantly stimulated by infection or allergy.

Sulfation Ratio as a Measure of PST Activity

Conjugation means the joining of two dissimilar molecules. In the body, MHPG can be conjugated (joined) to sulfate (sulfoconjugation) or to glucuronide (glucuronidation). In either case, the conjugation of MHPG facilitates the removal of MHPG from the brain and its excretion by the kidneys. The ratio of the amount of MHPG conjugated to sulfate to the amount conjugated to glucuronide is the "sulfation ratio" of MHPG. The sulfation ratio of MHPG is a measure of the efficiency with which the enzyme PST is functioning in the body. Certain areas of the brain appear to lack

the glucuronidation pathway, and in those areas deficient PST activity might allow the accumulation of toxic phenolic compounds.

We know that when the body is faced only with a small load of phenolic compounds (such as those avoided on the Feingold diet or those produced by yeasts and fungi in the intestine), even a rather PST-deficient individual will sulfoconjugate a normal proportion of these phenolic substances. in this case, the term used for the behavior of PST is "first order kinetics." With first order kinetics, the greater the need for an enzyme, the faster it works.

At first, as we increase the phenolic load through this "first order segment" of the sulfoconjugation curve, sulfoconjugation keeps pace with the increasing need. But as larger amounts of phenolic compounds are introduced into the body, the enzyme PST can become saturated, so that a higher proportion of the phenolic load is conjugated to glucuronide instead of sulfate. By this process, as illustrated in the above figure, the sulfoconjugation curve transitions from its first order segment into its saturation segment, where the sulfoconjugation rate can no longer increase as a function of need. With additional phenolic loading (see diagram below), the glucuronidation pathway is utilized relatively more heavily, and the sulfation ratio falls.

There are two techniques that are used to measure PST activity in the body:

1. The Tylenol Test

Developed by Rosemary Waring, this pioneering test measures the "sulfation ratio" (SR) of acetaminophen sulfate to acetaminophen glucuronide in the urine after an oral test dose of acetaminophen (Tylenol), which serves as a phenolic chemical "probe." It requires an accurate dose of Tylenol (not always easy), and a timed urine collection.

2. The 24-hour Urinary MHPG Test

The other technique is the 24 hour urinary MHPG test. This gives a value called the Sulfation Ratio MHPG (SR MHPG). For this test, it is not necessary to introduce any foreign substance into the body. It gives the total MHPG, and the amounts of MHPG sulfate and HPG glucuronide, in a 24 hour urine collection, so that the SR MHPG can be easily calculated. It is useful whether or not a person is already maintaining a diet eliminating problem foods and chemicals. A disadvantage of the MHPG test is that it requires an accurate 24 hour urine collection. The test is available from SmithKline Beecham Clinical Laboratories, at a cost (March 1996) of $144.00.

In general, and based on a small patient sample, the results with the two tests have been comparable. But there is a theoretical source of inaccuracy in the Tylenol test: the acetaminophen test dose artificially increases the overall phenolic load on the body, so it might, under some circumstances, push a patient from the first order segment, through the transitional segment, and into the PST saturation segment of the sulfoconjugation curve. When the enzyme PST is artificially saturated, the effective sulfation ratio will be lower than in the natural state. Once into the saturation segment, as more Tylenol is given, the measured sulfation ratio falls even more. This possible reduction of the sulfation ratio by the probe drug might lead the Tylenol test to underestimate PST activity under some circumstances.

In addition to its ability to measure the sulfation ratio without altering it, the MHPG test has perhaps yet another advantage: because it measures the total 24 hour urinary MHPG, it provides a quantitative estimate of norepinephrine turnover, reflecting directly the rate at which NE is being used, and indirectly, the strength of noradrenergic neurotransmission.

Stimulant Drugs, Elimination Diets & Brain Function

At this point, it is important to understand the key concept of "signal to noise ratio." If you are listening to music on a radio station located in a particular city while driving your car away from that city, the music (radio signal) gets weaker. You might try turning up the volume, but that doesn't really help, because you are also turning up the volume of the static (background noise). Nearer the transmitter, the signal to noise ratio is high, so the music is clear. Driving farther away, the signal to noise ratio becomes lower, and any extraneous source of static (such as an electrical storm or overhead power lines) may drown out the music altogether. Communication theorists call this lamentable state a "low signal to noise

ratio." Neurotransmission is generally like radio transmission, working most efficiently with a strong signal and little noise, and less efficiently if the noise level rises too high relative to signal strength.

Theoretically, the brains of children who have abnormally low NE turnover suffer from abnormally weak noradrenergic (i.e., transmitted via norepinephrine) signal. Chemical "noise" may be introduced by foreign phenolic compounds. When these "false neurotransmitters" pass into the synapses of the brain, they engage the specialized detector-proteins called receptors, drowning out the true signal. If NE is in short supply in the synapses of the brain, false neurotransmission will be more likely to intensify disturbances of noradrenergic brain functions, such as attention and arousal.

The beneficial effects of stimulant medications most likely result from their known strengthening of noradrenergic signals in the brain. Building from the other side of the critically important "signal to noise ratio," the Feingold Program, with its avoidance of foreign phenolic chemicals, works by reducing the "noise."

Interpreting the 24-hour MHPG Test

The children upon whom I have obtained the 24 hour urine MHPG test have thus far sorted themselves into four groups:

1. Normal SRMHPG (>1) and normal total 24-hour urinary MHPG:

In my experience, these children do not respond dramatically to the Feingold Program. They may improve with antifungal medication, especially if they are allergic to molds and fungi and have heavy chronic fungal or yeast overgrowth of the bowel, due to frequent or prolonged courses of broad spectrum antibiotics. Those patients with normal SRMHPG and normal total MHPG who respond well to antifungal medication usually have high levels of circulating antibodies to a variety of fungi, evident from such tests as the IgG food and mold MAST.

2. Low SRMHPG (<1) and normal total 24-hour urinary MHPG:

Children who have a low SRMHPG do well on the Feingold Program and, especially if they have been on multiple courses of broad-spectrum antibiotics, on antifungal medication as well. Since, in these children, excretion of phenolic compounds is inefficient, phenolic toxins accumulate in the synapses, where they produce neurotransmissional noise, drowning out signal and degrading signal to noise ratio.

3. Normal SRMHPG (>1) and subnormal 24-hour urinary MHPG:

These children also do well with the Feingold Program and on antifungal medication. They can excrete phenolic compounds efficiently, but because their noradrenergic signal amplitude is low, even a small amount of phenolic "noise" in the form of residual phenolic food additives or phenolic fungal products from the intestine, will degrade the signal to noise ratio in the noradrenergic synapses of the brain.

4. Subnormal SRMHPG (<1) with subnormal total 24-hour urinary MHPG:

In my experience, it is these children who respond most dramatically to the Feingold Program and to antifungal medications as well. Since their noradrenergic pathways suffer both from "low signal" and "high noise," these children do best if the chemical noise level in the noradrenergic synapses can be reduced to an extremely low level. This is more difficult to accomplish while ingesting food chemicals which increase neural excitation or absorbing potentially neurotoxic microbial products."

Conclusion:

The MHPG test appears helpful in predicting response of children with disorders on the ADD-autism spectrum to diet and antifungal medications. This summary represents the results of preliminary and uncontrolled clinical observations, and while I feel that these clues are now starting to form a cohesive picture that warrants sharing with interested parties, I must emphasize my belief that the exploration of the Attentional Behavioral Continuum will always remain a journey into the unknown, where cherished assumptions are refuted daily. By pressing forward on many fronts, we insure that all children will some day succeed to their fullest potential.