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SUPPORT GUIDE

Urinary Polypeptides

Urinary polypeptides have been measured and correlated with medical problems for the past 50 years, including a clinical relationship with behavioral problems such as autism, ADD/ADHD, schizophrenia, and depression. Total urinary peptides are globally associated with an increase in neurologic and psychiatric imbalance. There are four basic types of urinary polypeptides noted:

Indolyl-acryloylglycine (IAG) – metabolic by-product of tryptophan; often the result of abnormal bacterial colonization of the large intestine

Serotonin uptake stimulators – peptides that stimulate the serotonin transporter, thus decreasing serotoninergic activity

Hyperkinese Peptides – recently discovered urinary peptides associated with ADHD

Exogenous morphine-like compounds (exorphins) – opioid peptides derived from food. These include:

- Gluten (wheat) derivatives
  - Gluten-derived peptides
  - Glutemorphins
- Gliadin derivatives
  - Gliadinomorphins
- Casein (milk) derivatives
  - Bovine casomorphins
  - Human casomorphins

Polypeptides circulating in the bloodstream are found in the urine of children (and adults) with neuro-psychiatric problems. This can be a consequence of incompletely digested protein within the gastrointestinal tract (from a variety of different sources) that then migrates through the gastrointestinal mucosal lining. This is due to increased intestinal permeability,[1] also known as leaky gut.[2,3] We all have levels of peptide and protein uptake from the gut. However, too great an uptake is a problem which can be related to a lack of peptidases in the gut wall.[4,5]

Increased intestinal permeability increases passage of peptides due to infection, dysbiosis, parasites, yeast, and food allergies. Nutritional deficiencies causing damage to the intestinal lining may also be involved. The process by which intact peptides can pass from the intestines to the brain and affect development and activity may be complex, but the notion is comparatively simple.

Many parents have observed that certain foods exacerbate the symptoms of autism. As a result, they have eliminated those foods from the diets of their children. The two foods most consistently reported were wheat and dairy. Parents have found that these dietary changes improved their children's symptoms. It has been determined that these symptoms arise from proteins, including gluten (from wheat and other cereals) and casein (derived from milk). Some of the peptides obtained from gluten and casein are very similar to endorphins found in the brain. These polypeptides are known as casomorphins and glutemorphins, and their structures are now well established.

Exorphins (or exomorphins) are opioid peptides made from food proteins. Peptides and exorphins have been observed in the urine and serum. These opioid peptides and exorphins are noted to be increased in autism, schizophrenia and some forms of depression, as demonstrated by mass spectrometry,[6,7] and by HPLC of first morning urines.[8,9] Exorphins have been demonstrated to have behavioral effects, which may explain many of the neuro-psychiatric symptoms noted.[10,11,12] Since we find peptides that have a dietary origin, it is reasonable to reduce the input of precursors to these peptides with dietary interventions.[13,14]

Recently it has been shown that gluten, gliadin and casein can mobilize inflammatory interleukins in the gut mucosa of patients with autism.[15,16,17,18] This provides the therapeutic basis for recommendations of restrictive dietary changes (gluten-free/ casein-free) in autism.

These opioid peptides act as neuro-regulators or modulators. They can affect the function of all the main types of neurons in the brain and cut down (or enhance) transmission

in all of the systems. The consequences will include perceptual and cognitive problems, changes in behavior, mood and emotional response. Opioid peptides are also implicated in the functioning of the immune system, and, at certain times, in brain development and maturation.

It was hypothesized that these peptides are absorbed from the intestines into the blood- stream. The brain is protected from such compounds circulating in the blood by a "blood-brain-barrier" (BBB). However, this barrier is not totally impervious and a proportion of these peptides will cross into the brain. Once there they may either have a direct opioid effect, or form a substrate for the enzymes which would, under normal circumstances, break down the endorphins once they had done their job. Either way, the effect would be the same; there would be increased opioid activity.

These peptides have now been isolated from the urine and identified precisely. Bovine casomorphins and glutemorphins have been shown to be present using a number of techniques. These are not human products, and, given the quantities involved, can only have been derived from ingested food. One compound, Indolyl Acryloyl Glycine (IAG), is present in all urine specimens. It has been demonstrated that people with autism excrete considerably higher levels of IAG.

IAG is an abnormal metabolite of the amino-acid tryptophan. The limited amount of available evidence suggests that IAG itself is comparatively innocuous, but as tryptophan is converted into IAG, it is then converted into Indole Acrylic Acid (IAcrA). It is the IAcrA which may have the more serious consequences. It has been postulated that this compound leads to greatly increased permeability of the intestinal wall and of the blood brain barrier. In the presence of IAcrA, the passage of peptides from the intestines to the brain would be greatly facilitated.

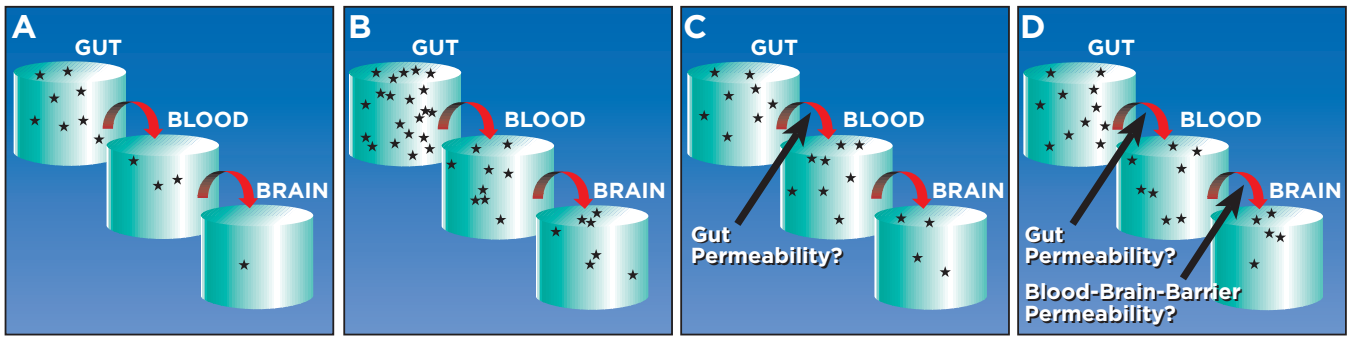
Inside the intestines themselves, we should look for deficiencies in the process by which proteins are broken down into amino-acids. We must seek reasons for the process becoming arrested at the peptide stage. These may include:

- The presence of levels of gluten and casein which are beyond the capabilities of the digestive process in the individual (remove from diet)
- A shortage of the natural peptidase enzymes (supplement directly with pancreatic enzymes or encourage the pancreas to produce appropriate levels with secretin)
- Insufficient acid in the stomach (betaine hydrochloride supplementation)
- Insufficient co-factors (supplement vitamins and minerals)
- Presence of intestinal parasites such as yeasts, Giardia or worms (eradicate)

In addition, there are factors that may increase the permeability of the intestinal wall and thereby lead us to a number of interventions used to ameliorate this problem:

- Incomplete sulphation (sulphate, in the form of Epsom Salts (Magnesium Sulphate) in bathwater or patches; MSM) (removal of phenolic or salicylate containing foods)
- Inappropriate acids in the membrane lipids (evening primrose oil followed by other oils such as fish and flax oils)
- Insufficient nutrients for the intestinal wall (L-glutamine)

Recognizing the presence of urinary polypeptides and IAG determines the therapeutic recommendations for healing the gastrointestinal tract. Any use of these dietary and gastrointestinal interventions must be seen as a part of an overall treatment plan. There is absolutely no point in taking the brakes off the car (removing the peptides) unless there is fuel in the tank (intensive education and therapy). The best results are seen in those children whose therapy combines these two elements.



Graphic concept courtesy of Dr. Paul Shattock, University of Sunderland, UK.

In the figure above, the stars represent peptides. **A** represents the normal situation. We all produce low levels of peptides when we digest proteins. Small quantities will pass from the intestines into the bloodstream and thence on to the Central Nervous System (CNS). **B** represents excessive levels of peptides in the urine. This result will be the passage of elevated levels of peptides to the CNS. There may be, (as in **C**) increased permeability of the intestines. In **D**, there is also excessive permeability of the Blood Brain Barrier. This could result from physical injury or infectious or other diseases.

Indolyl-3-Acryloylglycine (IAG)

Low molecular weight gut uptake, reliable marker to autistic syndrome when high. May also indicate leaky gut. Indolyl-Acryloylglycine (IAG) is a metabolic byproduct of tryptophan metabolism by intestinal bacteria. IAG is a membrane disrupter and high levels are found with intestinal hyperpermeability or "Leaky Gut" and may increase permeability of the blood-brain barrier. Increased levels are found in some cases of autism and other behavioral disorders. Anecdotal reports (based on very small patient cohorts or individuals submitting samples prior to definitive diagnosis) says that urinary IAG is elevated in ADHD and dyslexia.

Serotonin Uptake Stimulators (PyroGlu-trp-gly-NH2)

Tripeptide from reelin. Stimulates serotonin transporter with decreasing serotoninergic activity: more frequent in depression, causing excessive sensory inputs, lack of habituation, sleep problems and impulse behaviour. Low levels of serotonin may be associated with several disorders, namely increase in aggressive and angry behaviors, clinical depression, obsessive-compulsive disorder (OCD), migraine, irritable bowel syndrome, tinnitus, fibromyalgia, bipolar disorder, anxiety disorders.

Hyperkinese Peptide (HK 1, HK 2)

- Hyperkinese 1 (HK 1) reflects caseinopioid sensitivity and is related to hyperactivity and attention.
- Hyperkinese 2 (HK 2) reflects glutenopioid sensitivity and is related to hyperactivity and attention.

Gluten Derivated Peptides (I, II & III)

Increased levels of these gluten peptide derivates may indicate gluten intolerance. These gluten-derived peptides are increased in Celiac disease in some cases.

Gluten Morphins

In general these opioide peptides may be increased in patients with autism, ADHD/ADD, schizophrenia, depression and other related diseases/conditions. Opioids from gluten affect the CNS and opioid peptides inhibit CNS maturation. Gluten morphin A5 reflects glutenopioid sensitivity and is related to hyperactivity and attention.

Gliaidinomorphins

Opioid peptides from gliadin. Increased levels of Gliadomorphin are found in intestinal hyperpermeability and wheat intolerance. Gliadomorphins have been shown to affect behavior in children and adults. Removal of wheat from the diet results in decreased levels. Gliadorphin (also known as gluteomorphin) is an opioid peptide which is formed during digestion of the gliadin component of the gluten protein. It is usually broken down into amino acids by digestion enzymes. It has been hypothesized that children with autism have abnormal leakage from the gut of this compound, which then passes into the brain and disrupts brain function. This is a basis for the gluten-free, casein-free diet.

Casomorphins

In general, these opioid peptides increase in patients with autism, ADHD/ADD, schizophrenia, depression and other related diseases/conditions. Research shows increased fatigue after ingestion, increased aggression after ingestion, may increase dopamine activity in the synaptic cleft. Opioids from casein affect the CNS and opioid peptides inhibit CNS maturation.

- Unpublished data indicates that β-casomorphin 1-4, amide is of special importance to epilepsy in autism. This peptide is fat-soluble and may easy penetrate the cell membrane making it potentially more toxic.
- Increased levels of β-Casomorphin (1-7) and Casomorphin (1-8) are found in intestinal hyperpermeability (Leaky Gut) and dairy intolerance. Casomorphins have been shown to affect behavior in children and adults.
- β-Casomorphin (1-7) in particular has been implicated in a number of medical conditions including diabetes, heart disease, and the symptoms of autism and schizophrenia. However, it appears that only some individuals are susceptible.
- β-Casomorphin 1-7 was found to cause histamine release from peripheral leukocytes of healthy adult volunteers. These findings suggest that β-casomorphin-7 can be regarded as a non-cytotoxic, direct histamine releasing agent in humans. Removal of dairy from the diet results in decreased levels.
- Increased levels of Casomorphin (1-8) is often seen in schizophrenia. Removal of dairy from the diet results in decreased levels.
- Human Casomorphin (1-4,1-7) may be increased in Postpartum Depression

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