So...for those of you who are not familiar with this program...what do we mean by excitotoxins...

Excitotoxins

- Glutamate, Glutamic Acid, Glutamine, MSG
- Aspartate, Aspartame, Aspartic Acid
- Nutra-sweet
- Cysteine (NOT N-acetyl-cysteine)
Glutamine can be converted to glutamate plus ammonia.
### Other “Names” For Excitotoxins

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Other Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>monosodium glutamate, nutrasweet / aspartame</td>
<td>malted barely flour</td>
</tr>
<tr>
<td>glutamate</td>
<td>hydrolyzed protein</td>
</tr>
<tr>
<td>natural flavor(s)</td>
<td>hydrolyzed vegetable protein (HVP)</td>
</tr>
<tr>
<td>natural flavoring(s)</td>
<td>hydrolyzed plant protein</td>
</tr>
<tr>
<td>maltodextrin</td>
<td>hydrolyzed oat flour</td>
</tr>
<tr>
<td>carrageenan</td>
<td>hydrolyze anything</td>
</tr>
<tr>
<td>gelatin</td>
<td>sodium caseinate</td>
</tr>
<tr>
<td>spice(s)</td>
<td>calcium caseinate</td>
</tr>
<tr>
<td>seasoning(s)</td>
<td>caseinate</td>
</tr>
<tr>
<td>seasoned salt</td>
<td>disodium guanylate</td>
</tr>
<tr>
<td>dough conditioner(s)</td>
<td>disodium inosinate</td>
</tr>
<tr>
<td>yeast extract</td>
<td>disodium caseinate</td>
</tr>
<tr>
<td>autolyzed yeast</td>
<td>chicken/pork/beef “flavoring”</td>
</tr>
<tr>
<td>autolyzed yeast extract</td>
<td>chicken/pork/beef “base”</td>
</tr>
<tr>
<td>autolyzed anything</td>
<td>bouillon</td>
</tr>
<tr>
<td>broth</td>
<td>vegetable gum</td>
</tr>
<tr>
<td>stock</td>
<td>plant protein extract</td>
</tr>
<tr>
<td>soup base</td>
<td>smoke flavoring(s)</td>
</tr>
<tr>
<td>stock</td>
<td>malt extract</td>
</tr>
<tr>
<td>stock</td>
<td>malt flavoring(s)</td>
</tr>
<tr>
<td>stock</td>
<td>malted barley / barley malt</td>
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<tr>
<td>stock</td>
<td>malted anything</td>
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<tr>
<td>stock</td>
<td>textured protein</td>
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<tr>
<td>stock</td>
<td>guar gum</td>
</tr>
<tr>
<td>stock</td>
<td>soy extract</td>
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<tr>
<td>stock</td>
<td>soy protein</td>
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<tr>
<td>stock</td>
<td>soy protein concentrate</td>
</tr>
<tr>
<td>stock</td>
<td>soy protein isolate</td>
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<tr>
<td>stock</td>
<td>soy sauce</td>
</tr>
<tr>
<td>stock</td>
<td>whey protein</td>
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<tr>
<td>stock</td>
<td>whey protein isolate</td>
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<td>stock</td>
<td>kombu extract</td>
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<tr>
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<td>l-cysteine</td>
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</tbody>
</table>
Protein Breakdown

Proteins breakdown

Amino Acids

Glutamate
Aspartate
Cysteine
Proteins breakdown

Amino Acids

Glutamate
Aspartate
Cysteine
Glutamate is an excitatory neurotransmitter.

Natural Foods
High in Glutamate

- Peas
- Tomatoes
- Mushrooms
- Parmesan Cheese

Glutamate Receptors

Glutamate is an excitatory neurotransmitter.
Glutamate is an excitatory neurotransmitter.

Natural Foods High in Glutamate

• Peas
• Tomatoes
• Mushrooms
• Parmesan Cheese
• **Sulfur** containing amino acids lead to increased norepinephrine release.

• This effect appears to be mediated via stimulation of glutamate receptors implying an excitotoxin mechanism.

Note: relationship between excess sulfur via CBS upregulations and glutamate
The issue is both the amount of glutamate as well as the number of glutamate receptors.
Glutamate Receptors

Increased Number of Glutamate Receptors

In conjunction with...

Excessive Glutamate

Neurological inflammation
Receptor recycling may give inaccurate measurements of the number of glutamate receptors on autistic brain cells.
Postmortem brain abnormalities of the glutamate neurotransmitter system in autism

A.E. Purcell, BA; O.H. Jeon, PhD; A.W. Zimmerman, MD; M.E. Blue, PhD; and J. Pevsner, PhD

Article abstract—Background: Studies examining the brains of individuals with autism have identified anatomic and pathologic changes in regions such as the cerebellum and hippocampus. Little, if anything, is known, however, about the molecules that are involved in the pathogenesis of this disorder. Objective: To identify genes with abnormal expression levels in the cerebella of subjects with autism. Methods: Brain samples from a total of 10 individuals with autism and 23 matched controls were collected, mainly from the cerebellum. Two cDNA microarray technologies were used to identify genes that were significantly up- or downregulated in autism. The abnormal mRNA or protein levels of several genes identified by microarray analysis were investigated using PCR with reverse transcription and Western blotting. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)- and NMDA-type glutamate receptor densities were examined with receptor autoradiography in the cerebellum, caudate-putamen, and prefrontal cortex. Results: The mRNA levels of several genes were significantly increased in autism, including excitatory amino acid transporter 1 and glutamate receptor AMPA 1, two members of the glutamate system. Abnormalities in the protein or mRNA levels of several additional molecules in the glutamate system were identified on further analysis, including glutamate receptor binding proteins. AMPA-type glutamate receptor density was decreased in the cerebellum of individuals with autism (p < 0.05). Conclusions: Subjects with autism may have specific abnormalities in the AMPA-type glutamate receptors and glutamate transporters in the cerebellum. These abnormalities may be directly involved in the pathogenesis of the disorder.

NEUROLOGY 2001;57:1618–1628
Glutamate Receptors

Actual amount of mRNA for glutamate receptors is higher in autistic children.

Levels of mRNA in 10 autism (A = autism) and 10 control (C = control) postmortem cerebellum samples were compared using reverse transcriptase PCR (RT-PCR). The mean autism versus mean control band intensity (± SEM) is summarized to the right of each RT-PCR. The Y axis of each graph represents average normalized intensity of cDNA product signals. (A) RT-PCR confirmation of altered mRNA levels in autism. All gene transcripts are increased in autism postmortem cerebellum (*p < 0.05). (B) Investigation of mRNA levels of additional glutamate-related genes. Excitatory amino acid transporter 2 (EAAT 2) and the AMPA-type glutamate receptors 2 and 3 have increased mRNA levels in autism (*p < 0.05). Glyceraldehyde-3-phosphate dehydrogenase band intensity (right, lower panel) was used for normalization of cDNA product in each sample.

Reference: Purcell, Neurology 2001; 57:1618-1628
mRNA levels of additional glutamate-related genes. Excitatory amino acid transporter 2 (EAAT 2) and the AMPA-type glutamate receptors 2 and 3 have increased mRNA levels in autism (*p < 0.05). Glyceraldehyde-3-phosphate dehydrogenase band intensity (right, lower panel) was used for normalization of cDNA product in each sample.
Figure 4. Glutamate receptor autoradiography. (A) Density of AMPA- and NMDA-type glutamate receptors (± SEM) in the cerebellum (granule and molecular cell layers), prefrontal cortex, and caudate-putamen of subjects with autism (filled bar) and control subjects (open bar). There is a decrease in the density of AMPA receptors in the granule cell layer (*p < 0.05) and the molecular cell layer (**p < 0.01) of patients with autism compared with matched controls. (B
Developmental Depression of Glutamate Neurotransmission by Chronic Low-Level Activation of NMDA Receptors

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Chronic stimulation of NMDA leads to depression of AMPA
Similar to studies examining other forms of learning and memory (De Leonibus et al. 2003; Stefani et al. 2003; Harris et al. 2004), we report that the AMPA/KA receptor antagonist LY293558 administered pre-trial within the NAc core dose-dependently impaired the acquisition of an instrumental lever-pressing task.

An analysis of the microstructure of behavior revealed that rats pretreated with the high-dose of LY293558 failed to inhibit their tendency to make consecutive nose pokes into the food magazine or increase their tendency to lever-press after nose-poking as is normally observed in rats learning the response. These results suggest that the rats tended to nose-poke perseveratively, unable to inhibit that behavior or redirect their attention to other stimuli in their environment (e.g., the newly introduced lever). Thus, glutamate acting on AMPA/KA receptors within the NAc may contribute to proper behavioral set switching, which is critical for the expression of exploratory behaviors needed to first learn the lever-pressing task.
nist, however, that impaired performance after the task had been well-learned, indicating at least a dual role for dopamine in the striatum for both associative and motor functions. Indeed, there is much evidence implicating striatal dopamine in both cellular plasticity (Konradi et al. 1993; Cepeda and Levine 1998; Floresco et al. 2001; Thomas and Malenka 2003) and behavioral activation (Fibiger et al. 1976; Salamone 1987; Floresco et al. 1996). Thus, it is possible that under these circumstances both D1 and AMPA/KA receptors could be used to guide proper behavioral set switching early in learning (Koob et al. 1978; Gelissen and Cools 1988; Bakshi and Kelley 1991; van den Bos et al. 1991; Baldo et al.

positive outcome. In addition to encoding information, glutamate and dopamine D1 receptors within the NAc may also be required for the animal to act on important environmental stimuli and monitor the results of their own actions—a mechanism critical for behavioral flexibility of the kind needed to deal with ongoing environmental changes.
Consequences of Elevated Glutamate

- Glutamate → excitotoxin damage → opioids
- Glutamate → glutathione → TNF alpha → leaky gut
- Glutamate → sleep
- Glutamate → eye contact
- Glutamate → acetylcholine → bladder contraction, strabismus
- Glutamate → stims
Glutamate in relation to GABA levels
Gaba and Speech

- Gaba is necessary for speech.
- Gaba creates the “gap” between words

\[ \text{GABA} \]

word GAP word GAP word GAP word
Gaba and Speech

- Gaba is necessary for speech.
- Gaba creates the "gap" between words.
Consequences of Decreased Gaba

- Language/speech
- Anxiety
- Aggressive behavior
- Social behavior
- Eye contact
- Bowel function
Pancreas

Glutamate  Gaba

×  Autoantibodies to GAD/rubella

Pancreas
Glutamate is the gun.
Calcium is the bullet.
Glutamate and Calcium

Glutamate  calcium flow into neurons

Calcium flow  nerve damage

Nerve damage  inflammation
Glutamate and Calcium

↑ Glutamate → calcium flow into neurons

↑ calcium flow → nerve damage

nerve damage → inflammation
Interaction between glutamate and glycine.

Glutamate, a simple amino acid, is an essential currency of the human nervous system and is transmitted from one neuron to another at specialized junctions called synapses. The tightly regulated release of glutamate from one neuron, coupled with its detection by glutamate receptors on the adjacent neuron, forms the basis of synaptic transmission at many of the \( \sim 10^{14} \) synapses in the human brain. Specificity of synaptic signalling by glutamate in space and time is conferred by the precise positioning of synapses and by the neuron-specific expression of a subset of genes encoding glutamate receptors. Pharmacological studies provided initial clues to the diversity of glutamate receptor proteins, and early studies partitioned them into two classes depending on their response to the synthetic agonist NMDA. Subsequent cloning of glutamate receptor genes and analysis of their predicted protein sequences facilitated the clustering of NMDA and non-NMDA receptors into distinct protein families.

NMDA receptors are unusual ligand-gated ion channels because activation not only requires the binding of two agonists, glycine and glutamate, but also demands the relief of \( \text{Mg}^{2+} \) block by membrane depolarization. The opening of NMDA receptors leads to an influx of cations including \( \text{Ca}^{2+} \), and the permeation of \( \text{Ca}^{2+} \) through NMDA receptor ion channels initiates signal transduction cascades that in turn modulate synaptic strength. The rates at which the responses of NMDA receptors rise (activate) and decline (deactivate) upon application and removal of agonists, respectively, are markedly slower than those of non-NMDA receptors and it is the slow deactivation rate of NMDA receptors that governs the duration of the excitatory postsynaptic potential, a measure of the ‘strength’ of synaptic signalling. The integration of chemical and electrical stimuli by NMDA receptors into a \( \text{Ca}^{2+} \) signal is crucial for activity-dependent synaptic plasticity, which in turn underpins many higher functions including learning and memory. By contrast, dysfunction of NMDA receptors has been implicated in many diseases and injuries including stroke, Parkinson’s disease, Huntington’s disease and schizophrenia.
polyamines
Calcium Transport

• Calcium requires vitamin D and vitamin K for transport

• Vitamin D and vitamin K are fat soluble vitamins

• Lower vitamin D and lower vitamin K associated with gut absorption issues

Remember vitamin K is made in the gut by bacteria and requires SAMe
Inflammation and Calcium

- Limiting calcium will help limit inflammation
  - **Magnesium** blocks the door for calcium reversibly
  - **Zinc** blocks the door permanently! Too much zinc will stimulate glutamate at non NMDA glutamate receptors.
Why simply balancing glutamate and gaba along with other step 1 support is enough to trigger metal excretion in some cases
“In the absence of glutamate, neurons are unaffected by acute exposure to mercury, suggesting that neuronal dysfunction is secondary to disturbances in astrocytes.”

“Coapplication of nontoxic concentrations of MeHG and glutamate leads to the typical appearance of neuronal lesions associated with excitotxin stimulation”

Brookes, 1992/Matyja and Albrecht, 1993
Aluminum interferes with glutamate dehydrogenase

Mercury inhibits glutamine synthase