Glutamate: How to monitor and mediate its effects in Down Syndrome

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Objectives

- Glutamate physiology
- Glutamate activity in DS
- Symptoms of excess glutamate
- Measuring glutamate
- Agents that modulate glutamate

The Glutamate System

- Glutamate is the major excitatory neurotransmitter in the central nervous system.
- Nearly 50% of the neurons in the brain are believed to use glutamate as their neurotransmitter.
- Glutamate is balanced with GABA (main inhibitory chemical transmitter)
- Both neurotransmitters influence almost every other chemical transmitter in the brain.

The Glutamate System

- Glutamate acts via two classes of receptors which are found on both neuron and glial cells:
  - Ligand gated ion channels (I
tonotropic receptors):
  - G-protein coupled (Metabotropic receptors).

Glutamate Receptors

Ionotropic
(I) Ligand-gated ion channels
- NMDA
- AMPA
- Kainate

Metabotropic
(G) G-protein coupled receptors
- mGluR1
- mGluR2
- mGluR3
- mGluR4
- mGluR5
- mGluR6
- mGluR8
**Glutamate Physiology**

- Glutamate binds with glutamate receptors on postsynaptic neurons and open allowing Na⁺ and Ca²⁺ to flow into the neuron.
- Glutamate must be removed quickly from synaptic cleft or these channels will be left open.
- Astrocytes, a type of glial cell, take up glutamate via EAAT channels.
- Once inside the astrocyte glutamate is converted to glutamine which is transferred back to the presynaptic neuron to be made into more glutamate.

**Glutamate as Excitotoxin**

- Overstimulation of glutamate receptors causes neurodegeneration and neuronal damage through a process called excitotoxicity.
- Excessive glutamate, or excitotoxins acting on the same glutamate receptors, overactivate glutamate receptors (specifically NMDARs), causing high levels of calcium ions (Ca²⁺) to influx into the postsynaptic cell.
- High Ca²⁺ concentrations activate a cascade of cell degradation processes involving proteases, lipases, nitric oxide synthase, and a number of enzymes that damage cell structures often to the point of cell death.
Glutamate as Excitotoxin

• Excess glutamate implicated in other neurodegenerative diseases
  – Huntington’s
  – ALS
  – MS
  – AD
  – Parkinson’s
  – Epilepsy

Stuart A. Lipton. Failures and Successes of NMDA Receptor Antagonists: Molecular Basis for the Use of Open-Channel Blockers like Memantine in the Treatment of Acute and Chronic Neurologic Insults. NeuroRx. 2004

Glutamate as Excitotoxin

• Excess calcium in cytoplasm of cell is taken up by mitochondria which inhibits production of ATP (energy).

Excess glutamate produces a vicious cycle involving glutamate excitotoxicity, oxidative stress, and mitochondrial dynamics.
Glutamate Homeostasis

- Elevated GABA levels in the presence of elevated glutamate levels is a normal compensatory mechanism of the body.
- Focusing on blocking GABA does not address the true underlying problem.

Glutamate in DS

“The up-regulation of mGluR5 was observed in DS.”

...the human GLUR5 gene, which is located on human chromosome 21q22.1...
Glutamate in DS

...these results show that NMDA-induced calcium rise is altered in TgDyrk1A cerebellar neurons and indicate that calcium signaling is dysregulated in TgDyrk1A mice cerebella.

Symptoms of excess glutamate

- Aggression
- Hyperactivity
- Irritability
- Headaches/Migraines
- Anxiety
- concentration/focus
- Poor
- Nocturnal bed wetting
- Insomnia
- Areas of heightened intelligence
- Seizures
- Eosinophilia?

Measuring Glutamate

- Testing glutamate is done non-invasively with a urine test
- Test results are used as a guide for treatment, not diagnosis
- Assuming neurotransmitter levels and guessing appropriate intervention is not helpful.
- All children with DS do not have the same biochemistry.
- Test, don’t guess

Measuring Glutamate

Novel ELISAs for Screening of the Biogenic Amines… can result in relevant information on neurological processes, or pharmacological response to therapeutic intervention…

Measuring Glutamate

- Urinary neurotransmitter testing objectively establishes the need for intervention
- Guides therapeutic decisions
- Qualitatively assesses intervention effectiveness
Measuring Glutamate

Peer-review article provides comprehensive overview of validity & clinical applicability of urinary neurotransmitter testing.

Mitochondria Support

“During synaptic activity, the clearance of neuronally released glutamate leads to an intracellular sodium concentration increase in astrocytes that is associated with significant metabolic cost.”

Singh P, Mann KA, Maneghi HK, Kaur G. Prolonged glutamate excitotoxicity: effects on mitochondrial antioxidants and antioxidant enzymes. Med Cell Biochem. 2003

Mitochondria Support

- Acety-l-carnitine
- Ubiquinol (CoQ10)
- Liposomal glutathione
- Antioxidants
- D-Ribose

ATP consists of three phosphate groups, ribose, and adenosine.

Glutamate Antagonists

- Bacopa monnieri
- Gotu kola
- Ginkgo biloba
- St. John’s Wort
- Zinc
- Taurine

Bacopa monnieri

- Neuroprotective
- Anti-inflammatory
- Nootropic

Antioxidant
- Reduces SOD
- Glutamate antagonist

Gotu kola

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Antioxidant
- Raises glutathione levels

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**Ginkgo biloba**

- Neuroprotective
- Anti-inflammatory
- Nootropic
- Antioxidant
- Glutamate antagonist
- GABA antagonist

"We conclude that, while antagonism of GABA(A) receptors may contribute to bilobalide’s neuroprotective effects, additional mechanisms must be postulated to fully explain bilobalide’s actions."

**Magnesium**

- Neuroprotective
- Nootropic
- Glutamate antagonist

**B6**

- Neuroprotective
- Anti-inflammatory
- Nootropic
- Glutamate antagonist

"In a double-blind study, 89 children with Down’s syndrome were given 5-hydroxytryptophan and pyridoxine hydrochloride in the first three years of life…these children showed consistently higher levels of accomplishment."

**EGCG**

- Blocks activation of microglial cells
- Neuroprotective
- Antioxidant
- Supports mitochondria

"EGCG strongly promoted mitochondrial biogenesis in DS cells."

**Zinc**

- Neuroprotective
- Nootropic
- Glutamate antagonist

**L-theanine**

- Neuroprotective
- Nootropic
- Glutamate antagonist

*Also involved in activating microglia*
Curcumin

- Blocks microglial activation
- Glutamate antagonist
- Reduces neuroinflammation
- Blocks amyloid β protein
- Antioxidant


Lee HS, et al. Neuroprotective effects of curcumin is mainly mediated by blockade of microglial cell activation. Pharmazie. 2007

5. K. Kulkarni, A. Sh. An Overview of Curcumin in Neurological Disorders. Indian J Pharm Sci. 2010

Populations in India, who eat a diet high in turmeric, experienced a 4.4-fold lower incidence of AD and dramatically lower rates of colon cancer than those eating a typical Western diet.

Taurine

- Avoid all hidden forms of MSG
  - Hydrolyzed vegetable protein
  - Yeast Extract
  - Calcium caseinate
  - et al
- Avoid all food and drink with aspartame

Dr. Russell Blaylock

MSG