New Biotic INC.
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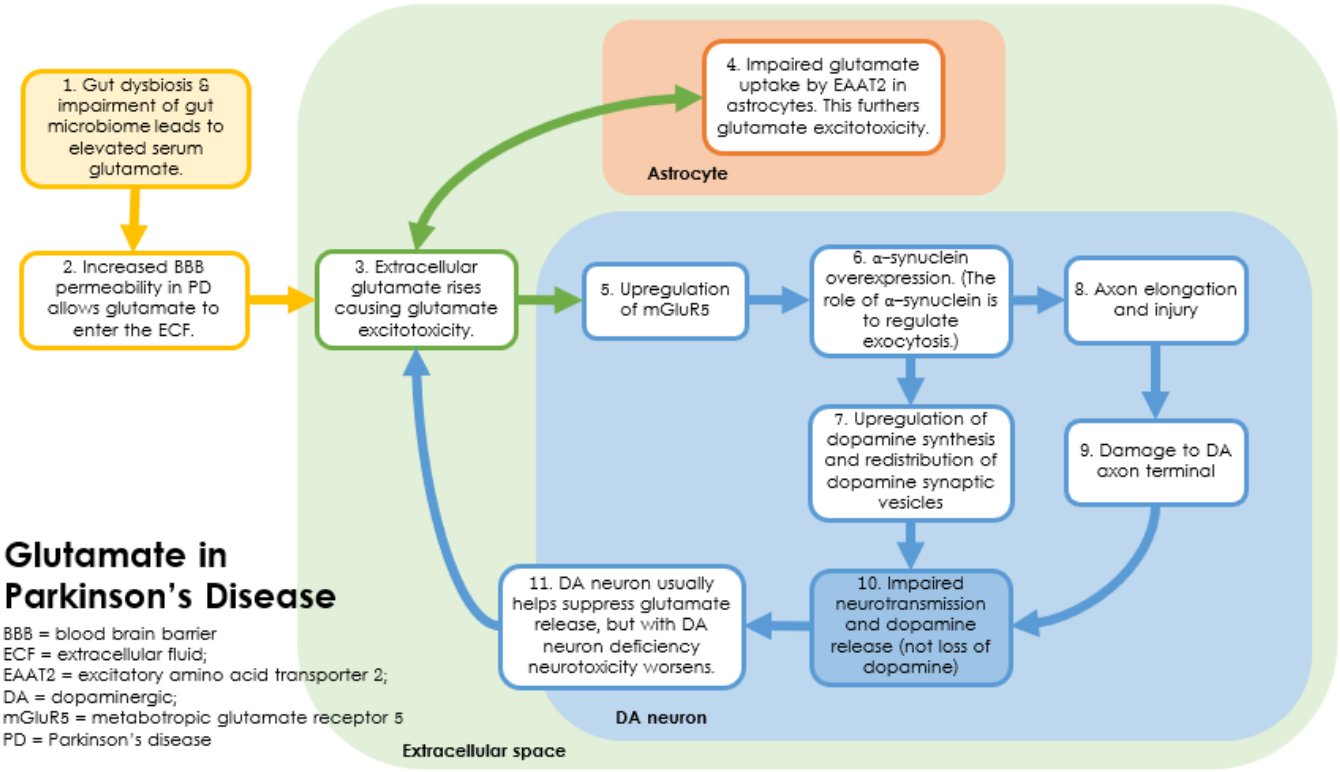
NBI's Synopsis of Parkinson's Disease



1. **Elevated serum glutamate** due to:
    a. **Loss of glutamate metabolize bacteria**
        - **Chronic intake of alkaline water** - which changes the pH of the small intestine from acidic levels at 6.0 to alkaline levels as high as 8.4, which are too alkaline for glutamate metabolizing bacteria to survive.
        - **Chronic intake of antacid medication** – which shifts intestinal pH from 6.0 towards 8.4, causing the glutamate metabolizing bacteria to leave the digestive system.
        - **Frequent intake of broad-spectrum antibiotics** – which contributes to the loss of glutamate metabolizing bacteria.
    b. **Excessive consumption of dietary protein** (Meldrum B. , 1993) - Normal fasting serum glutamate should be between 5 to 30 µmol/L but NBI has seen fasting serum glutamate as high as 215.6 µmol/L after 12 hours of fasting. Serum glutamate levels should be always less than 30 µmol/L (4.4 ppm) (Stegink, 1979).

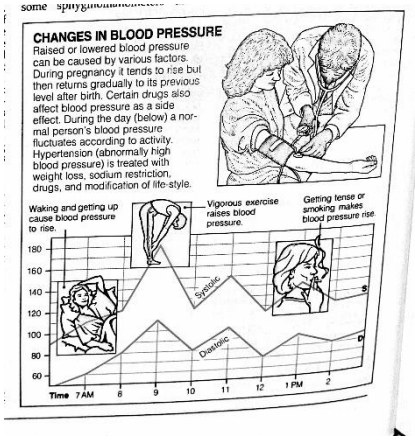
	Fasting Serum Glutamate (FSG)	Postprandial Serum Glutamate (PSG)	PSG - FSG
Nomral Level (µMol/L)	< 30	< 60	< 30
Minimun level (µMol/L)	11	22.7	0.9
Maxiumun level (µMol/L)	215.6	340.4	285

FSG higher than 60 µmol/L indicate diet related glutamate toxicity from consuming too much protein

PSG - FSG higher than 60 µmol/L indicate glutamate toxicity from lost of glutamate metabolize bacteria

PSG by itself has no clinical meaning

2. **Increased permeability of BBB** (blood brain barrier) due to:
    a. **High protein diet** - (Meldrum B. , 1993) led to elevated serum glutamate that disrupts BBB function.
    b. **High serum glutamate** due to loss of glutamate metabolizing bacteria.
    c. **Hypertension** - Studies by the Tang team in 1993 (Jian-ping Tang, 1993) indicate chronic hypertension increases brain levels of glutamate by 600 to 1,200%.
    d. **Diabetes** - Increased blood–brain barrier permeability in type II diabetes is demonstrated by gadolinium magnetic resonance imaging (J M Starr, 2003).
    e. **Vigorous exercise** can easily increase systolic pressure to 180 mmHg.



3. **Over-excited NMDARs** of astrocytes led to glutamate excitotoxicity (Jolanta elks, 1994) (Silburt, 2016).

Glutamate: concentrations and affinities[1]

Approximate concentration in	
CSF	<1 μmol/L
Brain ECF	0.5–2 μmol/L
Plasma	30–100 μmol/L
Synaptic cleft	2–1,000 μmol/L
Brain (homogenate)	10 mmol/L
Synaptic vesicle	100 mmol/L
"Affinity" (ED_{50})	
GLT-1	1–20 μmol/L
NMDAR	2.5–3 μmol/L
mGluR2,3,4,8	5 μmol/L
mGluR1,5	10 μmol/L
AMPAR	200–500 μmol/L
mGluR7	1,000 μmol/L

[1] CSF, cerebrospinal fluid; ECF, extracellular fluid; ED_{50}, 50% effective dose; GLT, rat glial glutamate transporter; NMDAR, *N*-methy-D-aspartate receptor; mGluR, metabotropic glutamate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptor.

(Meldrum B. S., 2000)

4. **Glutamate-induced excitotoxicity** - A lack of enzymatic decomposition of extracellular glutamate results in glutamate accumulating at synapses, which is mainly absorbed by excitatory amino acid transporters (EAATs). Glutamate exerts its physiological effects by binding to and activating ligand-gated ion channels [ionotropic glutamate receptors (iGluRs)] and a class of G-protein-coupled receptors [metabotropic glutamate receptors (mGluRs)]. Timely clearance of glutamate from the synaptic cleft is necessary because high levels of extracellular glutamate overactivate glutamate receptors, resulting in excitotoxic effects in the central nervous system (Ji Wang, 2020).

   Glutamate induced excitotoxicity is mainly linked to an impaired ability of glial cells to reuptake and respond to glutamate. This is considered a common hallmark in many neurodegenerative diseases, including Parkinson's disease (L. Iovino, 2020).

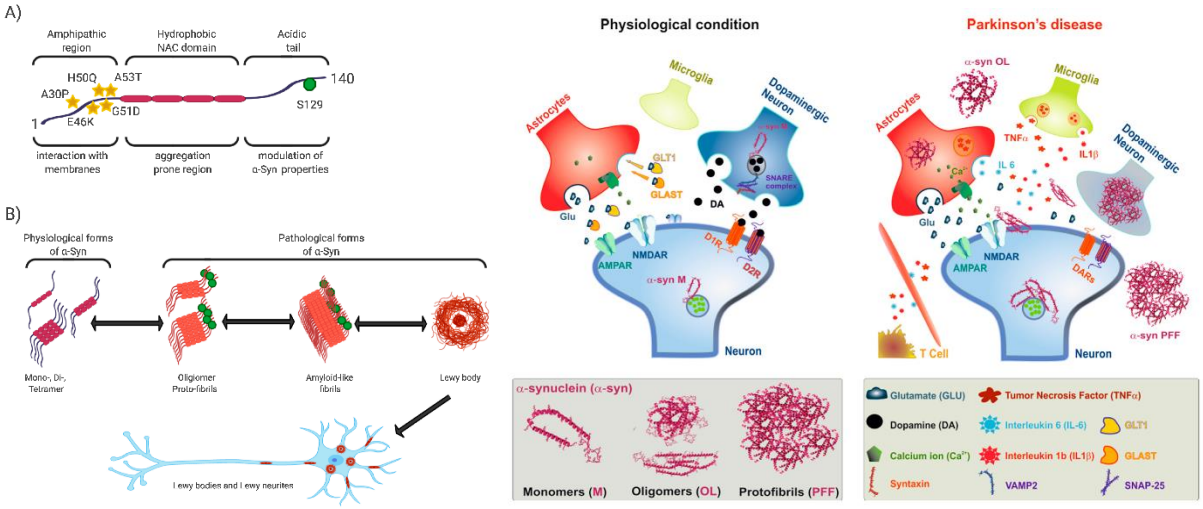
5. **Upregulated mGluR5** - Glutamate exposure upregulates the expression of mGluR5 in hippocampal HT-22 cells and mGluR1 in cortical primary cultures (Schubert, 1998).

6. **α-Synuclein overexpression** - Over the last two decades, many experimental and clinical studies have provided solid evidence that α-Synuclein (α-Syn), a small, natively unfolded protein, is closely related to Parkinson's disease pathology. α-Syn is mainly expressed in presynaptic sites at several neurotransmitter systems in the central nervous system (CNS). The first function described for α-Syn was its chaperone function and in particular its ability in controlling exocytosis through management of synaptic vesicle pool and trafficking (Veronica Ghiglieri, 2018). Parkinson's disease is a neurodegenerative disorder of the aging population characterized by the abnormal accumulation of α-synuclein (α-Syn); many studies have suggested that glutamate excitotoxicity contributes to neurodegeneration in these disorders. Studies suggest that mGluR5 may directly interact with α-Syn resulting in its overactivation and that this overactivation may contribute to excitotoxic cell death in select neuronal regions (Diana L. Price, 2010).

7. **Disruption of dopamine homeostasis** - α-Synuclein overexpression results in upregulation of dopamine synthesis and content, and redistribution of dopaminergic synaptic vesicles, which significantly contribute to dopaminergic neuron degeneration (Pengxiu Cao1., 2010).

8. **Axon elongation & injury** - α-Syn enhanced axonal growth with evidence for axonal injury. In relevance to disease mechanisms, we detect in human brains evidence for a higher degree of corticostriatal glutamatergic plasticity within WMTs at early stages of PD (Meir Schechter1, 2020).

9. **α-Synuclein aggregates led to damage to the dopaminergic neuron axonal terminals which impaired neurotransmission** - *In Parkinson's disease, damage to axons and axonal terminals precedes any overt dopaminergic neuron cell death*, suggesting that the disease process may start at the axon terminal level and progress retroactively to affect the cell bodies. Support of this idea comes from autopsy studies of brains from PD patients, which suggest that the extent of damage to the dopaminergic neuron axonal terminals in caudate nucleus and putamen at the time of disease onset is more extensive than the loss of dopaminergic neurons in the substantia nigra.
10. **Actual pathology of Parkinson's disease** - *Impairment in dopamine release (**not loss of dopamine**)* evolved in parallel with the development of degenerative changes in the nigrostriatal axons and terminals. Striatal innervation density was reduced by 60–80% and accompanied by abundant signs of axonal damage in the form of α-synuclein aggregates, axonal swellings, and dystrophic axonal profiles (Martin Lundblad1, 2012).



Comments:

Since Parkinson's disease is not about the loss of dopamine, but the impairment of dopamine release, this explains why synthetic dopamine provides the benefit of mobility but fails to stop or reverse the progression of Parkinson's disease.

Treatment strategy should be focused on:

1. Limiting dietary protein to 5 grams per meal.
2. Restoring glutamate metabolizing bacteria if GluTox™ biomarker indicates the need to do so.
3. Restoring EAATs, NMDARs, and mGluR5 functions.
4. Dissolving the α-Synuclein plagues in the brain.
5. Reconnecting and regrowing axon terminals.
6. Repairing brain damage through neurogenesis.

This is a tall order for any single ingredient drug to perform so many different tasks. The hope lies in a nutraceutical grade medicinal supplement such as RaphaN+ that contains multiple ingredients to perform these tasks, hence allowing the substantia nigra and its dopamine delivery pathway to function normally.

RaphaN+ does not replace synthetic dopamine, rather RaphaN+ works synergically with synthetic dopamine. RaphaN+ treats the cause of Parkinson's Disease and repairs all the downstream damages in the brain due to the loss of glutamate-metabolizing bacteria, while synthetic dopamine provides instant mobility.

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