

# NBI's Synopsis of Parkinson's disease:

Loss of glutamate metabolizing bacteria or excessive consumption of dietary protein → Chronic elevated serum glutamate → Increases permeability of BBB → Over-excited NMDARs → Glutamate-induced excitotoxicity → Upregulated mGluR5 →  $\alpha$ -Synuclein overexpression → Axon elongation & injury → Disruption of dopamine homeostasis →  $\alpha$ -Synuclein aggregates → Damage to the dopaminergic neuron axonal terminals → Impaired neurotransmission → Actual pathology 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  $\mu\text{mol/L}$  but NBI has seen fasting serum glutamate as high as 215.6  $\mu\text{mol/L}$  after 12 hours of fasting. Serum glutamate levels should be always less than 30  $\mu\text{mol/L}$  (4.4 ppm) (Stegink, 1979).

	Fasting Serum Glutamate (FSG)	Postprandial Serum Glutamate (PSG)	PSG - FSG
Normal Level ( $\mu\text{mol/L}$ )	< 30	< 60	< 30
Minimum level ( $\mu\text{mol/L}$ )	11	22.7	0.9
Maximum level ( $\mu\text{mol/L}$ )	215.6	340.4	285

FSG higher than 60  $\mu\text{mol/L}$  indicate diet related glutamate toxicity from consuming too much protein

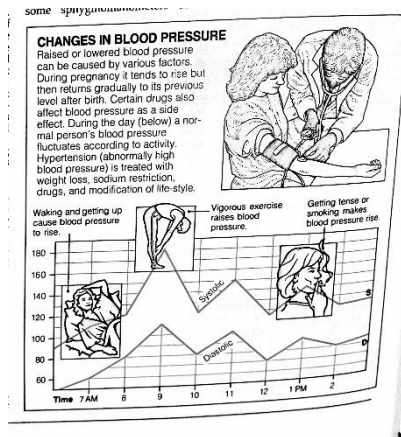
PSG - FSG higher than 60  $\mu\text{mol/L}$  indicate glutamate toxicity from loss of glutamate metabolize bacteria

PSG by itself has no clinical meaning

## 2. Increased permeability of BBB (blood brain barrier) due to:

- High protein diet** - (Meldrum B. , 1993) led to elevated serum glutamate that disrupts BBB function.
- High serum glutamate** due to loss of glutamate metabolizing bacteria.
- 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%.
- 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<sup>1</sup>*

Approximate concentration in	
CSF	<1 $\mu\text{mol/L}$
Brain ECF	0.5–2 $\mu\text{mol/L}$
Plasma	30–100 $\mu\text{mol/L}$
Synaptic cleft	2–1,000 $\mu\text{mol/L}$
Brain (homogenate)	10 mmol/L
Synaptic vesicle	100 mmol/L
"Affinity" (ED <sub>50</sub> )	
GLT-1	1–20 $\mu\text{mol/L}$
NMDAR	2.5–3 $\mu\text{mol/L}$
mGluR2,3,4,8	5 $\mu\text{mol/L}$
mGluR1,5	10 $\mu\text{mol/L}$
AMPA	200–500 $\mu\text{mol/L}$
mGluR7	1,000 $\mu\text{mol/L}$

<sup>1</sup> CSF, cerebrospinal fluid; ECF, extracellular fluid; ED<sub>50</sub>, 50% effective dose; GLT, rat glial glutamate transporter; NMDAR, N-methyl-D-aspartate receptor; mGluR, metabotropic glutamate receptor; AMPAR,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

(Meldrum B. S., 2000)

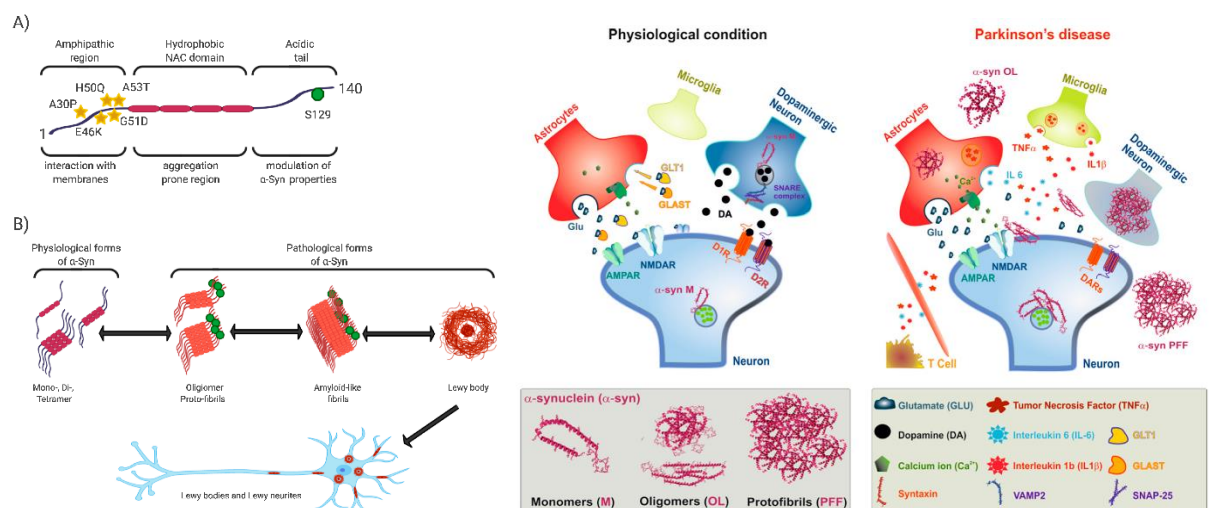
4. **Glutamate-induced excitotoxicity** - A lack of enzymatic decomposition of extracellular glutamate results in glutamate accumulating at synapses, which is mainly absorbed by excitatory amino acid transporters (EAATs). Glutamate exerts its physiological effects by binding to and activating ligand-gated 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.  **$\alpha$ -Synuclein overexpression** - Over the last two decades, many experimental and clinical studies have provided solid evidence that  $\alpha$ -Synuclein ( $\alpha$ -Syn), a small, natively unfolded protein, is closely related to Parkinson's disease pathology.  $\alpha$ -Syn is mainly expressed in presynaptic sites at several neurotransmitter systems in the central nervous system (CNS). The first function described

for  $\alpha$ -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  $\alpha$ -synuclein ( $\alpha$ -Syn); many studies have suggested that glutamate excitotoxicity contributes to neurodegeneration in these disorders. Studies suggest that mGluR5 may directly interact with  $\alpha$ -Syn resulting in its overactivation and that this overactivation may contribute to excitotoxic cell death in select neuronal regions (Diana L. Price, 2010).

7. **Axon elongation & injury** -  $\alpha$ -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 White Matters Tracts at early stages of PD (Meir Schechter1, 2020).
8. **Disruption of dopamine homeostasis** -  $\alpha$ -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).
9.  **$\alpha$ -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  $\alpha$ -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 (Glutamate Toxicity) level indicates the need to do so.
3. Restoring EAATs, NMDARs, and mGluR5 functions.
4. Dissolving the  $\alpha$ -Synuclein plaques in the brain.
5. Reconnecting and regrowing axon terminals.
6. Repairing brain damage through neurogenesis.

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