Research Updates in Parkinson's Disease

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Motor Therapy Updates

- Levodopa and Other dopaminergic drugs
- Surgery
- Dyskinesia
- Gene therapies

Levodopa

- Since 1968, Levodopa is the most effective treatment for motor symptoms of slowness, stiffness and tremor
- Motor fluctuations and dyskinesia are long term problems associated with PD and use of dopamine drugs

Table 1 Medications currently in development for the treatment of Parkinson's disease

Drug	Classification	Mechanism	Clinical benefit
Melevodopa	Effervescent levodopa prodrug	Converted to dopamine	Improves motor symptoms
XP21279	Levodopa prodrug	Converted to dopamine	Improves motor symptoms
IPX066	Long-acting levodopa	Converted to dopamine	Improves motor symptoms
Istradefylline	Adenosine A2A antagonist	Reduces striatal-pallidal firing	Improves motor symptoms Potential for neuroprotection
Preladenant	Adenosine A2A antagonist	Reduces striatal-pallidal firing	Improves motor symptoms Potential for neuroprotection
ST-1535	Adenosine A2A antagonist	Reduces striatal-pallidal firing	Improves motor symptoms Potential for neuroprotection
SYN-115	Adenosine A2A antagonist	Reduces striatal-pallidal firing	Improves motor symptoms Potential for neuroprotection
Safinamide	MAO-b inhibitor Reduces reuptake of dopamine Inhibits glutamate release	Multiple	Improves motor symptoms Potential for neuroprotection

Abbreviation: MAO-b, monoamine oxidase type B.

From Hickey, Stacy Drug Design, Development and Theory 2011

DBS

- DBS involves high frequency stimulation of deep brain structures to improve motor symptoms and improve quality of life in well-selected patients
- With advancing PD, gait freezing and falls become more problematic, disabling for many. Medication and current DBS targets aren't very effective
- New targets may be better, but results have been mixed…

Is DBS "Neuroprotective"?

- Animal studies show evidence of protection of dopamine producing cells in experimental PD with DBS
- 2 studies in humans are evaluating the potential of early DBS

Levodopa induced Dyskinesia (LID)

- Common presentations of LID:
  - peak-dose (on) dyskinesia—most common
  - diphasic dyskinesia,
  - off-dystonia
- More likely to start on the side more severely affected
- Aggravated by dopaminergic medication, and usually improves as the treatment wears off.

- Movements are predominantly stereotypic or choreiform in nature
- Mild levodopa-induced chorea tends to be non-disabling, and is often first noticed by family members
- The mildest form is that of "action" chorea in which the involuntary movements, such as continuous head bobbing, occur only during active voluntary movements, such as talking or walking.

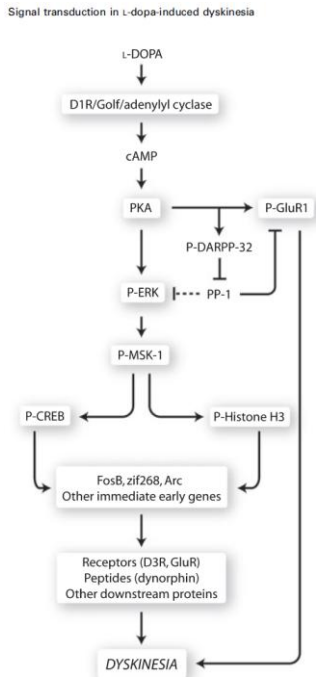
Table III

THERAPEUTIC ARRAY OF TREATMENTS FOR LEVODOPA INDUCED DYSKINESIA: CURRENT AND IN DEVELOPMENT.

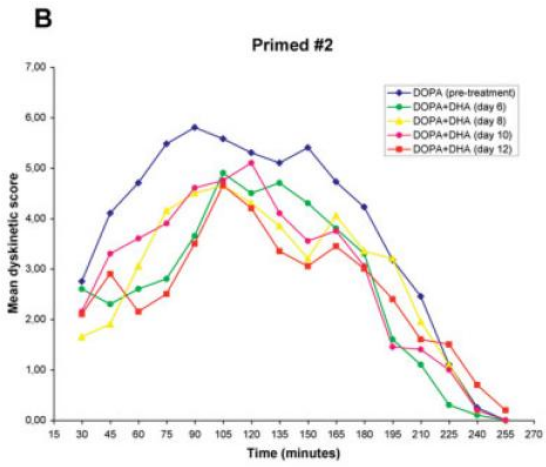
1. Amantadine
2. Deep brain stimulation
3. Continuous delivery of apomorphine
4. Continuous delivery of levodopa
5. Antiepileptics: Levetiracetam, Topiramate, Zonisamide
6. Atypical antipsychotics: Clozapine, Olanzapine, Quetiapine
7. 5 HT_{1A} agonist: Sarizotan
8. $mGlu_5$ receptor negative allosteric modulators: AFQ 056, ADX10059
9. NMDA receptor 2B antagonist: Taxoprodil
10. Selective AMPA receptor antagonist: Perampanel
11. Sodium channel inhibitor with MAO-B inhibitor: Safinamide
12. α-2-adrenergic antagonist: Fipamezole, Idazoxan

From Prashanth et al International Review of Neurobiology 2011

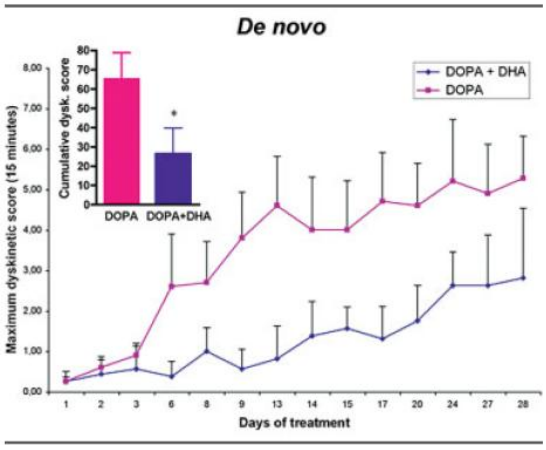
Biochemical Changes in the brain leading to dyskinesia.



Monkeys WITH dyskinesia given DHA

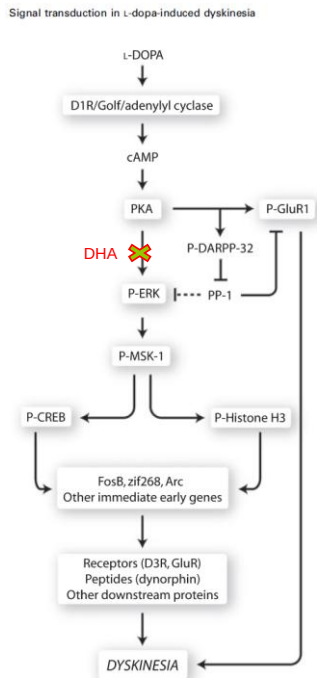


Monkeys taking DHA BEFORE ever taking levodopa



From Samadi et al Annals of Neurology 2006

How DHA may interfere with the development of dyskinesia.



VA Research Opportunity

- **Reducing Dyskinesia with Omega-3 Fatty Acids**
- First compound for testing to prevent or slow the development of dyskinesia
- Subjects: Patients who are ABOUT TO BEGIN levodopa…….NOT those who are already on levodopa.
- Compound being tested: Docosohexanoic acid (DHA) 2 g daily or placebo
- Duration of study : 2 years
- Visits: 5 inpatient (one overnight plus one day) visits over 2 years. One baseline screening visit.
- We carefully moniter for the beginnings of, and evolution of dyskinesia over 2 years.

Gene Therapy

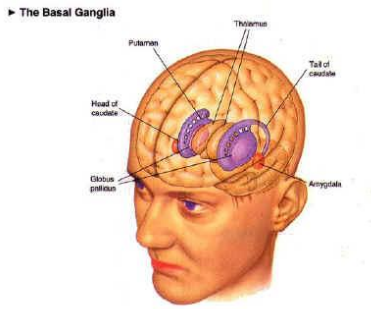
- Damaged/sickened cells are not producing needed enzymes and losing important connections
- Replacing these lost enzymes/functions is the idea behind gene therapy

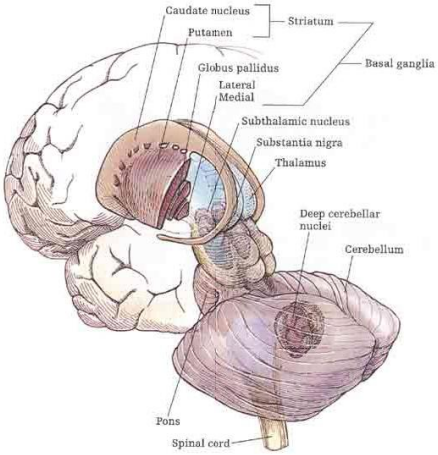
Table 2 Potential gene therapy targets for the treatment of Parkinson's disease

Genes	Target	Clinical benefit
TH, AADC, GCH (ProSavin)	Putamen	Improves motor symptoms
AADC	Striatum	Improves motor symptoms
GAD	STN	Improves motor symptoms
GDNF	Striatum	Improves motor symptoms Potential for neuroprotection
Neurturin	Putamen	Improves motor symptoms Potential for neuroprotection

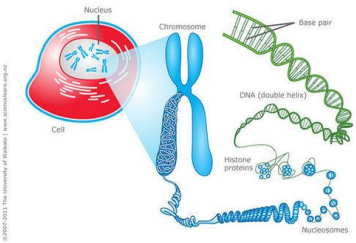
Abbreviations: TH, tyrosine hydroxylase; AADC, L-amino acid decarboxylase; GCH, GTP cyclohydrolase; GAD, glutamic acid decarboxylase; GDNF, glial-derived neurotrophic factor; STN, subthalamic nucleus.

From Hickey, Stacy Drug Design, Development and Theory 2011





Genetics Update



- In the last 25 years, a number of genes that cause PD have been found.
  - Some are "dominant" mutations, which carry 50/50 risk of passing to the next generation
  - Most are "recessive" mutations, which means a much lower chance of the next generation developing PD. (Table)

"Genetic" forms of Parkinson Disease

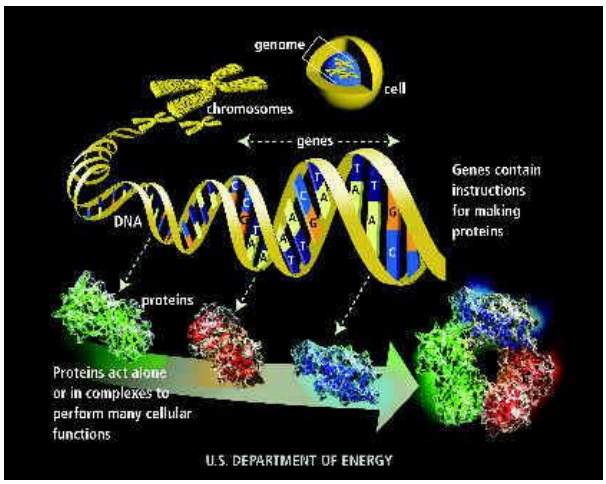
TABLE 1. Confirmed monogenic forms of PD

Locus	Inheritance	Gene	Mutations/comments	References
PARK1	AD	α-Synuclein	Rare, 3 mutations: A53T, A30P, E54K	Polymeropoulos et al, 1997[7]
PARK2	AR	*Parkin*	>100 mutations, point mutations, indels, and exon rearrangements	Kitada et al, 1998[42]
PARK4	AD	α-Synuclein	Duplications and triplications of the *SNCA* gene	Singleton et al, 2003[11]
PARK6	AR	*PINK1*	>20 mutations, point mutations, indels, and exon rearrangements	Valente et al, 2004[56]
PARK7	AR	*DJ-1*	Rare, 3-point mutations	Bonifati et al, 2003[58]
PARK8	AD	*LRRK2*	Six confirmed point mutations: R1441G, R1441C, N1437H, Y1699C, G2019S, I2020T,	Zimprich et al, 2004[21]; Paisan-Ruiz et al, 2004[22]
PARK9	AR	*ATP13A2*	Complex phenotype with parkinsonism, spasticity, and dementia	Ramirez et al, 2006[67]
PARK15	AR	*FBXO7*	Rare, complex phenotype	Di Fonzo et al, 2009[72]
		GBA	Multiple rare variants of intermediate-effect strength	Sidransky et al, 2009[77]

From Gasser et al Movement Disorders 2011

- Overall, these single gene mutations explain PD in a very small proportion of patients.
- In recent years, sophisticated genome-wide association (GWA) studies identified several novel low-risk susceptibility variants for Parkinson's disease
  - HLA-DRB5, BST1, ACMSD, STK39, MCCC1/LAMP3, SYT11, and CCDC62/HIP1R

- Rare gene variants with intermediate-effect strengths such as Gaucher's disease–associated glucocerebrosidase A have been discovered as important risk factors.
- "Next-generation" sequencing technologies may identify many more of these variants.
- These findings may provide the "genetic entry points" to identify molecular targets to help researchers understand the causes of PD and **disease-modifying treatments**.



- LRRK2 has been found to interact with the microRNAs processing protein "Argonaut", thereby affecting protein translation

VA Research Opportunity

- **"Multiplex Families" study**
- To identify more genes that may contribute to risk of developing PD
- Eligible: Families with 2 (or more) living members with PD.
  - Can be 2nd generation members ie cousins, aunt/uncle, grandparent
- 1 visit : history, neurologic examination, blood test for collecting DNA
- If the relative with PD lives far away, a kit will be sent to them to take to a local lab
- If the family is eligible, all members withOUT PD can offer a DNA sample.

Questions?