Updates from Movement Disorders Congress 2019

Melita Petrossian, MD
Medical Director, Pacific Movement Disorders Center
Pacific Neuroscience Institute
Providence Saint John’s Health Center
Providence Little Company of Mary Medical Center, Torrance
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Outline

• Highlights in basic research 2018-2019
• Highlights in clinical research 2018-2019
• Role of insulin resistance/diabetes
Gut bacteria inhibits levodopa action

Side effects: nausea, lightheadedness

Positive effects: reduced tremor, bradykinesia, rigidity
Gut bacteria inhibits levodopa action

Levodopa (L-dopa) → Dopamine

PLP-dependent decarboxylase (TyrDC) → Enterococcus faecalis

Carbidopa (FDA-approved drug) → L-dopa metabolizing human gut microbiota

L-DOPA → DOPA decarboxylase → Dopamine

Gut → Brain

- Maini Rekdal et al., Science 2019
Gut bacteria inhibits levodopa action

What affects levodopa metabolism?

• Levels of specific bacteria:
  – *Enterococcus faecalis* and *Eggerthella lenta*

• Levels of specific enzymes:
  – tyrosine decarboxylase from *E. faecalis*

• Specific SNPs (gene variant) from *E. lenta* gene that codes for a specific enzyme (dopamine decarboxylase, *dadh*)

• Maini Rekdal et al., Science 2019
Prolonged use of levodopa and disease duration are associated with increased $tdc$ gene-carrying bacteria

- Altered levels of gut dopamine ➔ Impaired GI motility ➔ SIBO ➔ worsening of motor fluctuations ➔ higher doses ➔ vicious cycle
- In small intestinal bacterial overgrowth (SIBO) associated with PPI use, *Enterococcus* tends to dominate
- Prolonged use of levodopa appears to favor growth of $tdc$ bacteria, further lowering efficacy of levodopa
- May identify biomarker for proper levodopa dose
- Some Probiotics contain $tdc$ gene-carrying *Enterococcus*
- Van Kessel et al., Nature Communications 2019
Carbidopa does not block bacterial metabolism

- Carbidopa blocks human peripheral decarboxylase enzyme
  - Making levodopa more present in serum and thus brain
  - BUT NOT BACTERIAL decarboxylase!

- Alpha-fluoromethyl-tyrosine (AFMT), an amino acid, can block bacterial tyrosine decarboxylase
  - Making levodopa more avail in mice serum
  - potential rx for managing motor fluctuations

- Maini Rekdal et al., Science 2019
Highlights in Clinical Research 2018-2019
Is levodopa disease-modifying (neuroprotective)?

• No.
• Does earlier start of levodopa induce dyskinesias earlier?
  – No*
• Double blind (DB), PCT (Placebo-controlled trial): carbidopa/levodopa x 80 weeks (early-start group) vs placebo x 40 weeks then carbidopa/levodopa x 40 weeks (delayed-start group)
• No difference between early vs late in motor scores (UPDRS) or quality of life (PDQ39) or in dyskinesias / motor fluctuations
• 40% of patients in the delayed-start group switched to active treatment, vs 11% in the early-start group. However, per-protocol vs intention-to-treat analysis was similar.
• Verschuur et al., NEJM 2019
Verschuur et al., NEJM 2019

Seifert et al., PLoS ONE 2015
Focused ultrasound applications in PD

• Recently FDA approved (2018) for tremor-predominant PD
• Incisionless brain surgery
• Targets thalamus only on one side
• ~60% tremor reduction
• Alternative to DBS
• Side effects include dizziness, imbalance, speech disturbance, tingling, usually temporary

Courtesy of Insightec
Focused ultrasound applications in PD

- Lower frequency focused ultrasound can open the blood brain barrier (bbb)
- Allowing therapies too large to naturally cross the bbb to enter the brain
  - Gene therapy
  - Immunotherapy
  - GDNF

Lin et al., Sunnybrook Research Institute
Ongoing and recent research using FUS in PD

• Dyskinesias and motor fluctuations (pallidotomy)
  – Stanford (Vyvian Ngo, 650-498-0817; vyviann@stanford.edu)
  – Sham-controlled, crossover design

• Safety and feasibility of BBB opening in PD
  – Madrid

• Motor symptoms in asymmetric PD (subthalamotomy): Pilot study
  – Improvement of ~50% both “on” and “off” meds in the treated side
  – Side effects of gait ataxia, facial droop, speech issues, dyskinesias were seen
  – Martinez-Fernandez et al., Neurology 2018
Ongoing research in clearing Alpha-synuclein
Ongoing Research in Alpha-synuclein antibodies

Movement Disorders, 2018
Ongoing Research in Alpha-synuclein antibodies

• PASADENA
  – First results expected Spring 2020
  – Hoffman LaRoche
  – Prasinezumab
  – Early stages of PD (no use of levodopa)
  – DB, PCT, high vs low dose vs placebo x 1 yr, then high vs low dose for the 2nd year
  – No longer enrolling
  – High preference for abnormal form of a-syn, sparing normal a-syn

• SPARK
  – First results expected August 2020
  – Biogen
  – BIIB054
  – Early stages of PD (no use of levodopa)
  – DB, PCT, high vs medium vs low dose vs placebo x 1 yr, then high vs medium vs low dose for the 2nd year
  – No longer enrolling
Ongoing Research in Alpha-synuclein management

• **MEDI1341**
  – MedImmune / Astra Zeneca

• **Active vaccination**
  – AFFITOPe PD03a
  – Affiris
  – Safe and tolerable in phase 1 trial
  – Immune reaction (antibody formation) was successful
  – Phase 2 trial pending

• **NPT200-11/UCB0599**
  – Alpha-synuclein stabilizer (reduces clumping)
  – Neuropore / UCB
  – phase 1b enrolling in Long Beach
  – Ellie Oxnevad
    [EllieOxnevad@cntrial.com](mailto:EllieOxnevad@cntrial.com)
    562-304-1742
Ongoing research in alpha-synuclein management

- **Nilo-PD (phase 2a): tyrosine kinase inhibitor**
  - Results expected November 2019
  - Nilotinib low vs high dose vs placebo
  - DB, PCT, closed for enrollment
  - Novartis
- **LRRK2 inhibitor in pts w/LRRK2 mutation**
  - DNL201, DNL151
  - Denali
  - Phase 1 study enrolling in Long Beach
  - DB, PCT, high vs low dose vs placebo
  - 562-304-1759
  - EdwinGhil@cntrials.com

GCase activation in patients with GBA mutation

- **MOVES-PD**
  - Sanofi/Genzyme
- **AIM-PD**
  - Ambroxol
  - Chaperone protein
  - Phase 2 trial active, no longer enrolling

- **Gene therapy**
  - PR001 vs placebo
  - Medpace/Prevail
  - AAV9 vector carrying normal GBA gene into brain
  - Enrolling in Chicago & NY
Relation of diabetes and PD

• Impaired glucose metabolism...
  – Diabetes (A1c >6.5)
  – Prediabetes (A1c 5.8-6.4)
  – Insulin resistance
  – Metabolic syndrome
    • Central obesity
    • Hypertension
    • insulin resistance
    • hyperlipidemia

• ... associated with worse symptoms and outcomes in PD
  – Tremor / motor symptoms
  – Cognitive functioning
  – Rate of progression
  – DaTscan findings
Relation of diabetes and PD

- Insulin and IGF1 signaling affect many functions
  - Energy balance
  - Glucose levels
  - Maintenance of neurons and supporting brain cells
  - Regulation of cell death vs survival
  - Maintenance of synapses

- GLP1 agonists act like glucagon, regulating blood sugar
  - Blocks inflammatory effect
  - Reduces alpha-synuclein toxic formation
  - Preserves neurons (in mice)
  - Injectable meds

- Exenatide (GLP1 agonist) once a week
  - Less progression compared to placebo after one year
  - Athauda et al., Lancet 2017

- Liraglutide once daily
  - DB, PCT
  - Enrolling at Cedars
  - 424-315-2870 tina.wux@cshs.org

- Lixisenatide once daily
  - DB, PCT
  - Enrolling in France

- Semaglutide once weekly
  - DB, PCT
  - Not yet enrolling in Oslo

Kim et al., Cell Transplantation 2017
Mediterranean-DASH Intervention for Neurodegeneration Delay (MIND diet)

- 10 “healthy” foods
  - Green leafy vegetables
  - Vegetables
  - Nuts
  - Berries
  - Whole grains
  - Fish
  - Poultry
  - Wine (no more than 1 glass per day)
  - Olive oil
  - Beans

- 5 “unhealthy” foods
  - Red meat
  - Cheese
  - Butter/margarine
  - Fried foods
  - sweets

- Associated with reduced risk of PD (HR 0.89)
- Associated with delayed progression of PD
- Agarwal et al., J Nutrition Health Aging 2019