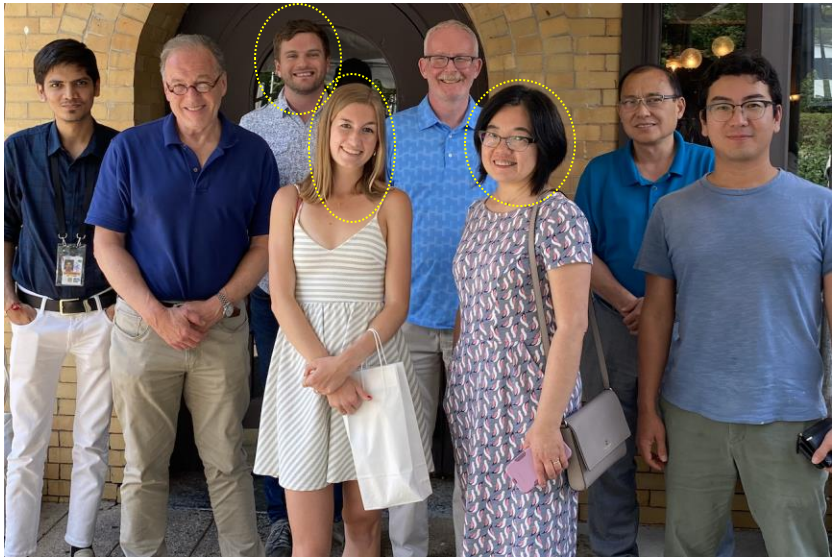
Preclinical evidence of GLP-1 receptor activity in neurodegenerative disorders

Drug Design & Development Section, Translational Gerontology Branch, NIA, NIH, Baltimore, MD



Left to right: Pathik Parekh, Nigel Greig, Elliot Glotfelty, David Tweedie, Katie Kopp Yazhou Li, Weiming Luo, Buka Batsaikhan

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MUSC, USA
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Conflict of interest statement

The National Institutes of Health (NIH), USA, has patent rights on the use of GLP-1 agonists for the treatment of neurodegenerative disorders (inventors: Nigel Greig and colleagues).

All rights have been assigned in entirety by Nigel Greig to NIH.

Hence, Nigel Greig has **no** financial or other conflicts of interest to report.

There are commonalities between type 2 diabetes mellitus (T2DM) and neurodegenerative disorders – especially related to cell death mechanisms.

Hence, a drug efficacious in T2DM may be effective in neurodegenerative disorders for which useful drugs are unavailable.

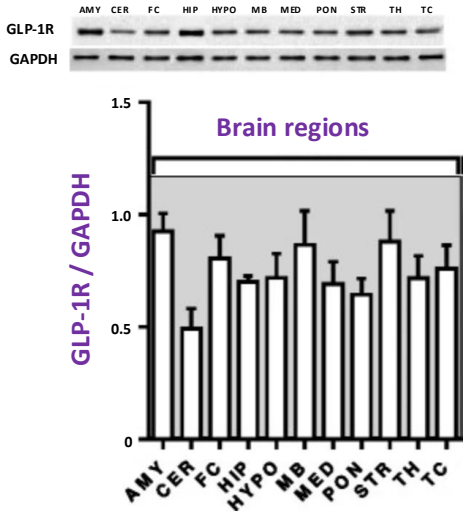
Individuals with T2DM prescribed GLP-1R agonists (incretin mimetics) and gliptins (DPP-4 inhibitors) are 36-60% less likely to develop PD (Brauer et al., *Brain.* 143:3067-76, 2020)

Outline

- GLP-1R brain expression
- GLP-1R agonists in neurodegeneration - brief history
- GLP-1R target across age/disease
- GLP-1R agonists in Parkinson's disease preclinical models – two examples
- Potential directions ahead

GLP-1R Expression in Brain

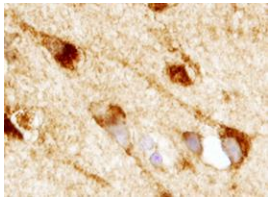
A Present across brain areas



GLP-1R distribution male ferrets (n=3, SEM)
Lu et al., *J Transl Med*. 12: 327, 2014.

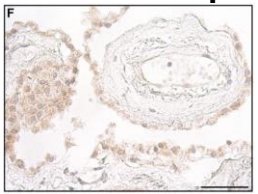
B Present on neurons

Human hippocampus



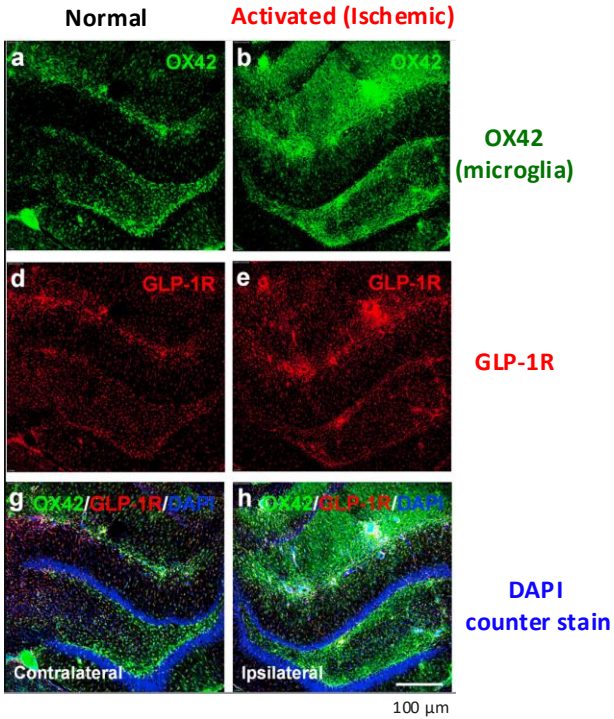
Biotechne MAB28141

C Present on epithelial cells of the choroid plexus



MAB3F52
Botfield et al., *Sci Transl Med.* 9:eaan0972, 2017.

D Present on microglia (and astrocytes)



GLP-1R distribution rat hippocampus 48 hr after ischemia, Jia et al., *Pharmacol Res.* 102: 276–285, 2015.

GIPR expression: neurons, microglia, astrocytes, oligodendrocytes
GcgR expression: neurons, microglia.

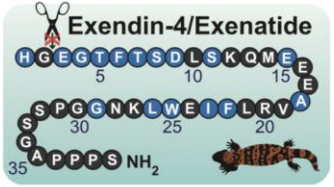
Incretin mimetic studies in neurodegeneration

GLP-1R agonists to mitigate neurodegenerative disorders: 2002 onwards
(Perry et al., *J Pharmacol Exp Ther*. 300: 958-66, 2002
Perry et al., *J Pharmacol Exp Ther.* 302: 881-8, 2002).

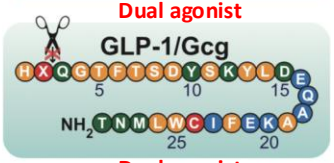
Perry & Greig 2002
(NIA/NIH)

Current monomeric GLP-1 based receptor agonists

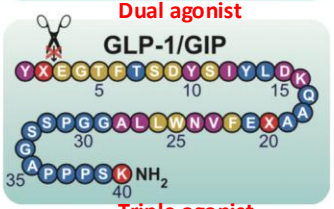
Single agonist



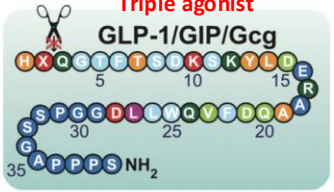
Dual agonist



Dual agonist

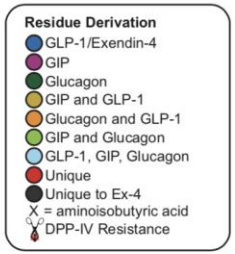


Triple agonist



Neurotrophic/protective/anti-inflammatory actions and mitigating brain insulin resistance in cellular and/or animal models:

Parkinson's disease, Alzheimer's disease, Traumatic brain injury, Multiple system atrophy, ALS, Huntington's disease, peripheral neuropathy, ischemic stroke, idiopathic intracranial hypertension and others……..



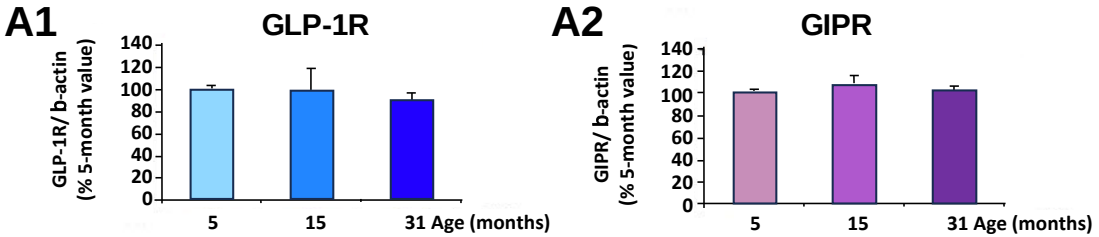
…… but do these actions translate to human disease?
…… which agonists should best be evaluated?
…… when in the disease process?

To gain a quick overview of the field:
Short perspective: Kopp KO et al., *Ageing Res Rev*. 98:102343, 2024
(5 to 10 min read)

Katie Kopp
(NIA/NIH)

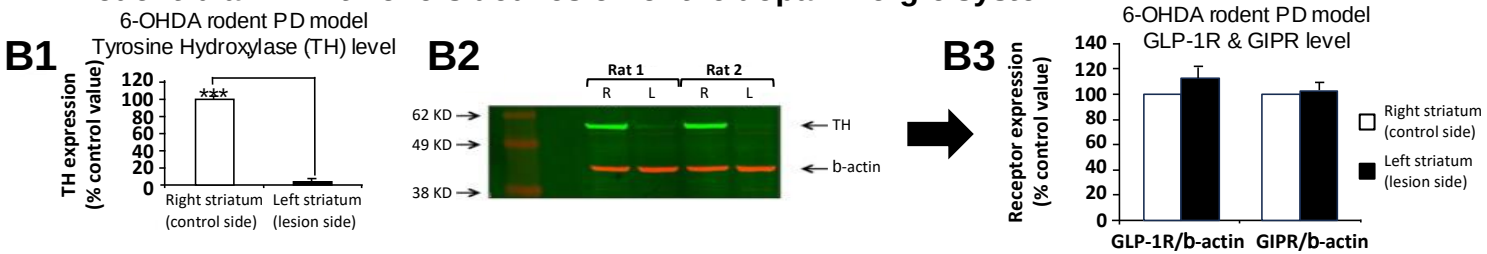
Drug target availability across age and disease:

Rodent brain



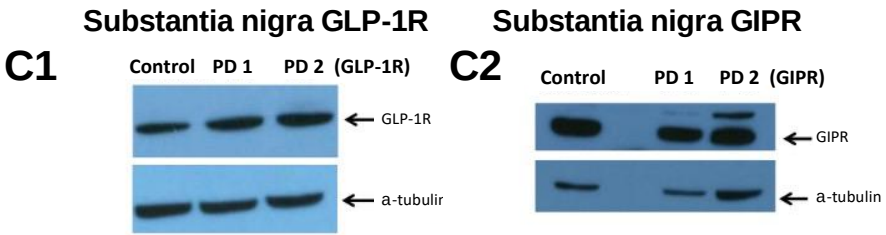
GLP-1R/GIPR expressed across age in brain

Rodent brain – with one-sided lesion of the dopaminergic system



GLP1R/GIPR expressed in the disease state in PD rodent model

Human brain: control vs. Parkinson's disease



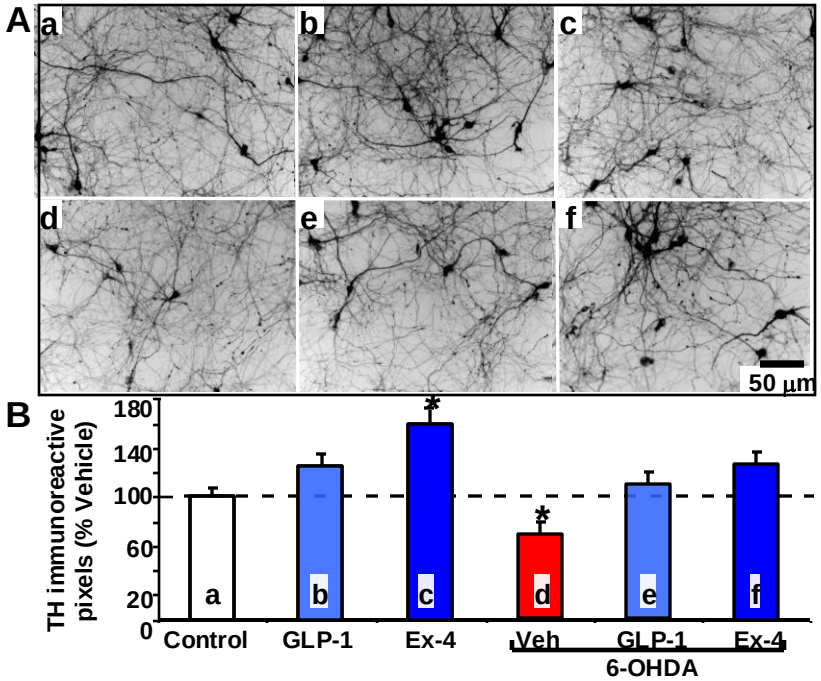
GLP-1R/GIPR expressed in human PD brain

Seong-Jin Yu
(NHRI Taiwan)

Yazhou Li
(NIA/NIH)

Yu SJ et al. *Geroscience*. 46: 4349-71, 2024

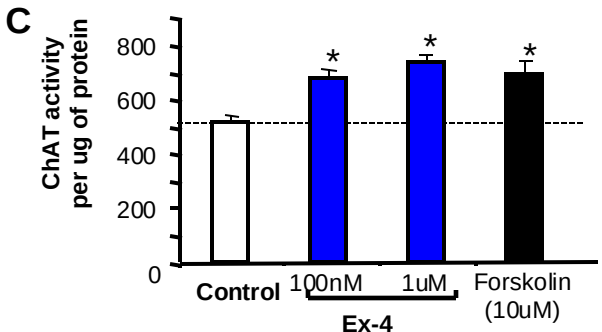
Consequences of GLP-1R activation: neurotrophic/protective actions - stronger phenotype



Tyrosine hydroxylase activity:
Ventral mesencephalic (VM) (dopaminergic) primary neurons challenged with GLP-1 or Exenatide (Ex-4) (100 nM)
+/- 6-OHDA (dopaminergic poison)

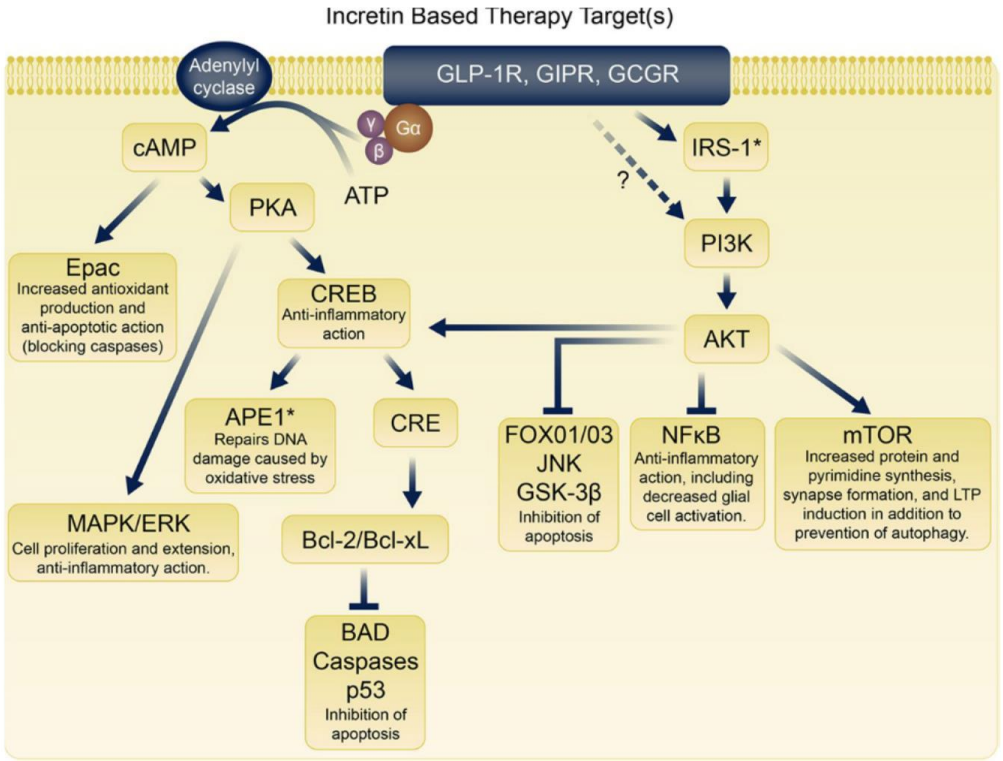
Significantly different from control ($p<0.05$)
Li Y, *PNAS* 106: 285-90

Map pathways: +/- pathway inhibitors



Choline *acetyltransferase activity:*
Motor neurons
Li Y, *PLoS One* 7(2):e32008

Key signaling pathways in neurons activated by incretins – particularly by GLP-1R activation – can be determined in cell culture

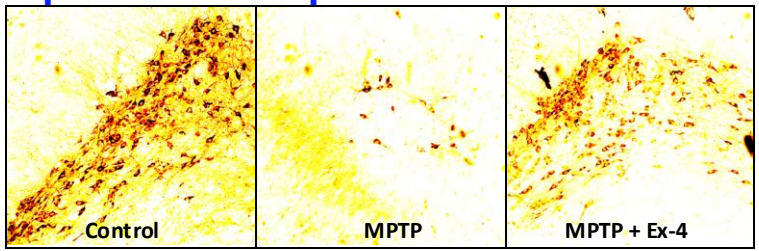


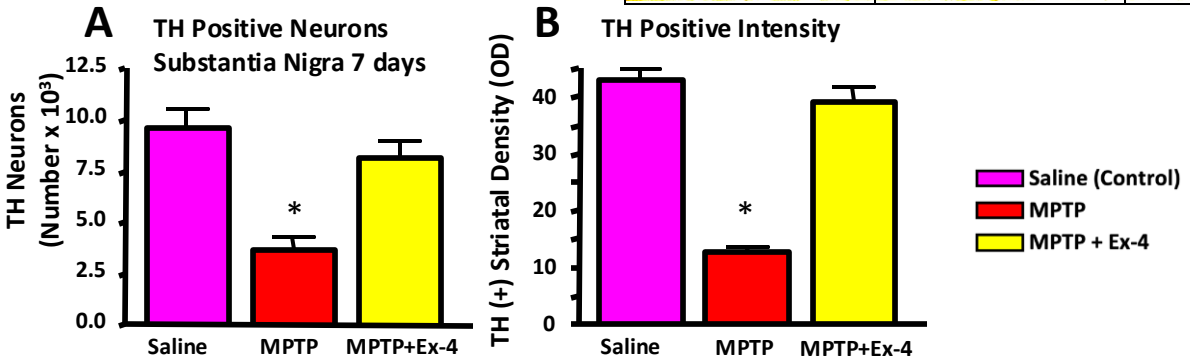
Markers of these pathways can be used in human studies as biomarkers of target engagement by assaying brain derived exosomes from plasma

Athauda et al., *JAMA Neurol.* 76:420-9, 2019.

Athauda & Foltynie, *Neuropharmacology*. 136(Pt B): 260-70, 2018
Glotfelty et al., *ACS Pharmacol. Transl. Sci.*, 2: 66-91, 2019
Kopp et al., *Pharmacol Res.* 186: 106550, 2022.

GLP-1R stimulation protects tyrosine hydroxylase (TH) positive neurons from MPTP toxicity and preserves dopamine and metabolite levels in





MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (dopamine cell poison)

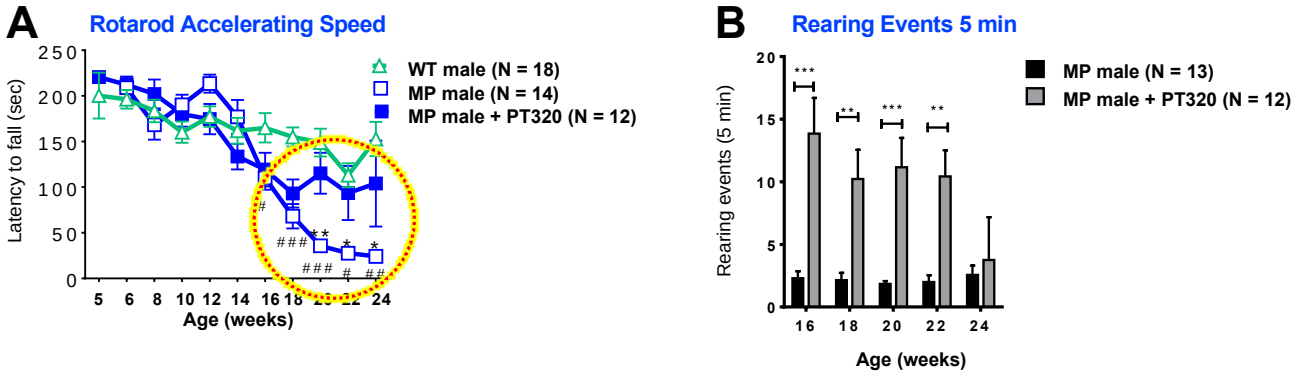
TH-immunoreactive neurons were quantified in the substantia nigra @ 7 days

Dopamine (DA), dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were quantified by HPLC

*Significant difference between MPTP vs. controls and MPTP + Exendin-4 ($p<0.05$, Bonferroni t test). No difference between control & MPTP + Exendin-4

Yazhou Li et al, *PNAS* 106:1285-90, 2009

MitoPark mouse, a progressive PD model involving deleted mitochondrial transcription factor TFAM (respiratory chain function) in midbrain DA neurons: PT320 (Exenatide) delays disease progression across multiple parameters



Yuan-Hao (Howard) Chen
National Defense Medical Center, Taiwan

Wang et al., *ACS Pharmacol Transl Sci* 4: 858-69, 2021

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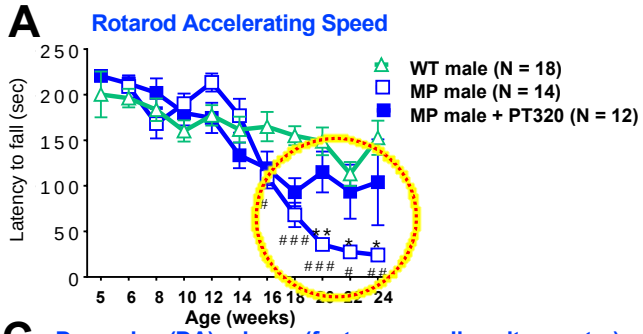

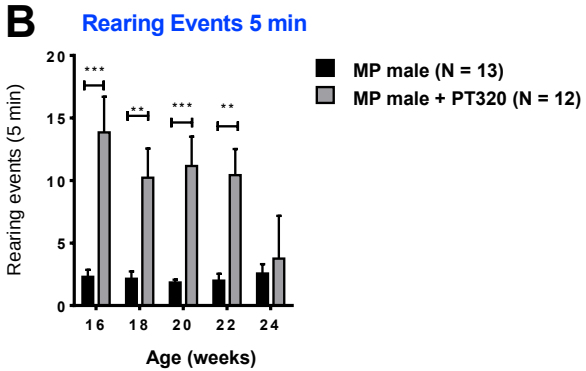

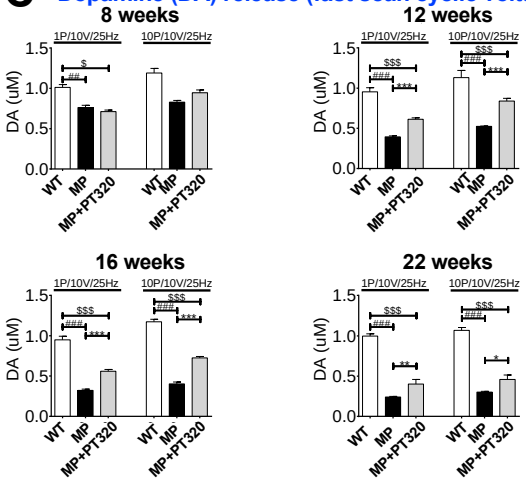

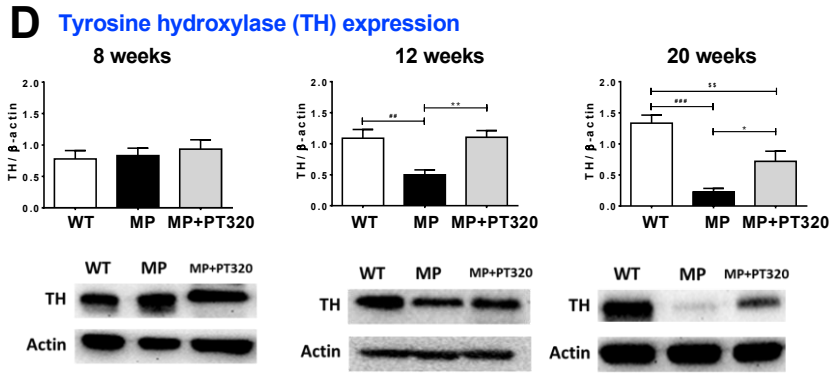

Yuan-Hao (Howard) Chen
National Defense Medical Center, Taiwan

Wang et al., *ACS Pharmacol Transl Sci* 4: 858-69, 2021

Replicated MitoPark mouse PD Exenatide study and attenuated mitochondrial dysfunction (Wang et al., *J Biomed Sci.* 31: 38, 2024)

Summary

- GLP-1-based receptor agonists (RAs) have been evaluated across multiple preclinical neurodegenerative and neuropsychiatric disorders models since 2002 – and, largely, have been found highly promising.

- Dual/Triple RAs are generally more potent than single GLP-1RAs (but brain uptake is important)

- Multiple actions underpin efficacy in preclinical models (neurotrophic, neuroprotective/antiapoptotic, anti-inflammatory, insulin resensitization, neurogenesis, mitochondrial, autophagy, ….. others)
…… do any of these translate into human studies and how can they be measured? (Biomarkers)

- Single GLP-1RA human clinical trials in Parkinson's disease are demonstrating promise… and Alzheimer's disease clinical trials are ongoing

- Other neurological disorder clinical trials should be considered (…….. TBI, ischemic stroke, peripheral neuropathy…….. ?)

Future

- Dual/Triple RAs, ….. DPP-4 inhibitors and combination chemotherapy ?

Concerns

- Selecting the best agent(s) / when to initiate treatment in the disease process