Neuroprotective effects of HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist in the neurodegenerative disease models

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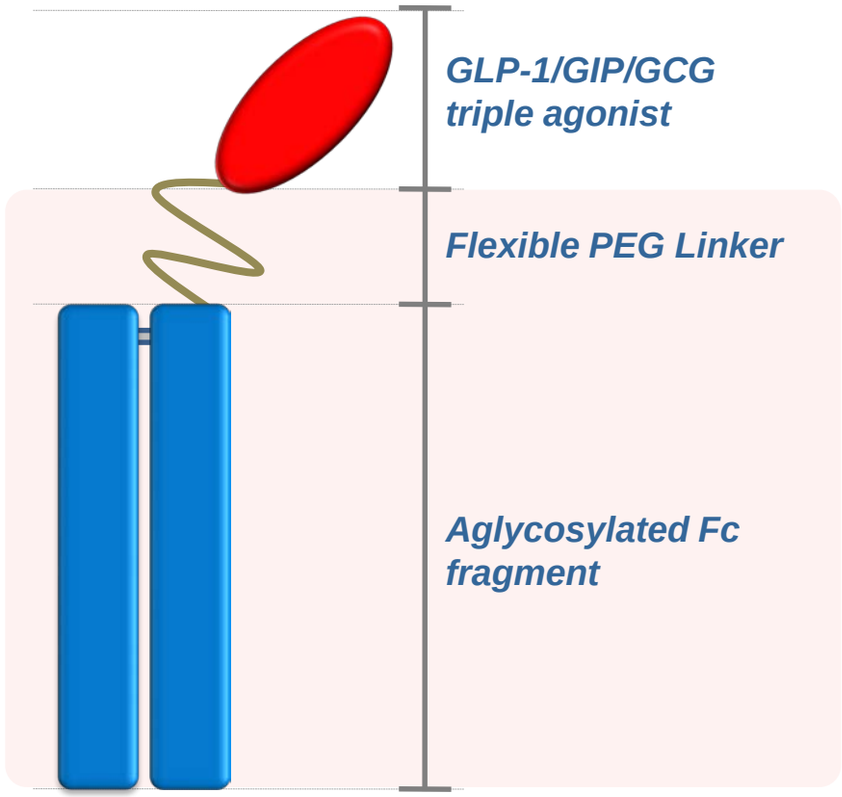
Presenter Disclosure

Employee of Hanmi Pharm. Co., Ltd.

HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist



Hanmi's GLP-1/GIP/GCG triple agonist is conjugated with a human IgG Fc fragment *via* flexible linker

[General profile]

- Extended half-life ($t_{1/2}$ = 42.7 ~ 55 hrs in mice; 82.8 ~ 85.7 hrs in rats)
- High glucagon (GCG) activity suitable for obesity treatment
- Balanced GLP-1 and GIP to neutralize hyperglycemic risk of high GCG
- Anti-inflammatory effect by GIP activity
- Recently completed for FIH clinical study in healthy obese subjects

LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

Incretin hormones in central nervous system

- **Obesity is one of the risk factors for neurological disorders**

Parkinson's disease

- Insulin resistance, T2DM ↑ PD
- ↑ Insulin levels ↑ α-synuclein aggregation
- Leptin ↑ survival of DA cells

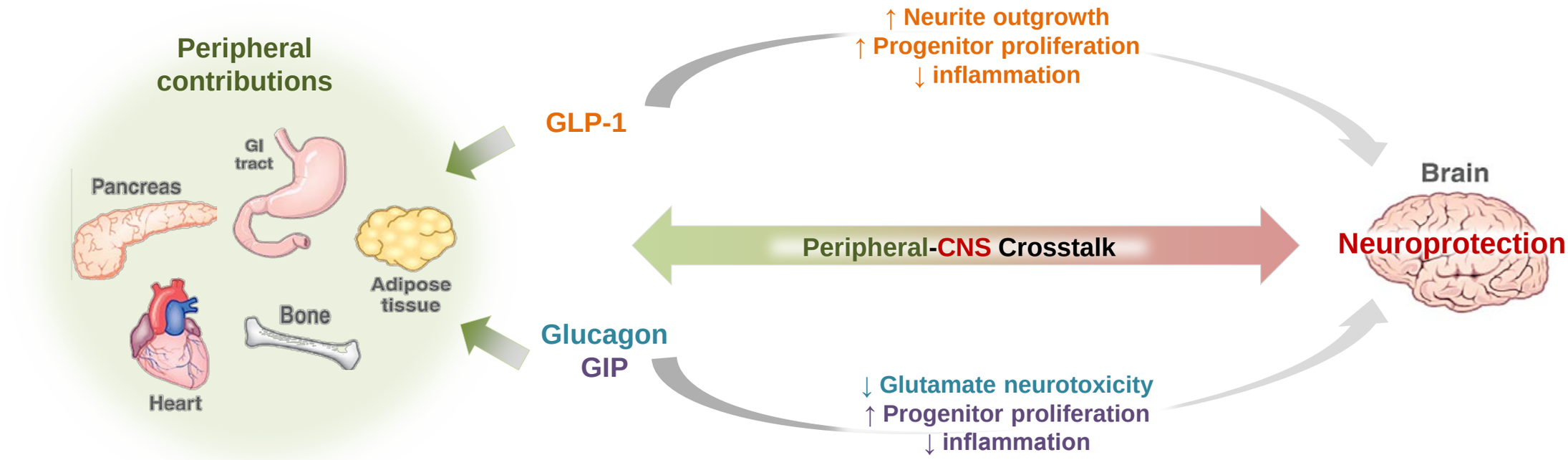
Alzheimer's disease

- ↑ BMI, T2DM ↑ AD risk
- Leptin/insulin resistance ↑ AD
- Leptin ↓ Aβ, p-tau

Multiple sclerosis

- Obesity ↑ MS risk
- Caloric restriction ↑ EAE lifespan
- ↓ insulin sensitivity in MS

- **Neuroprotective effects of GLP-1, glucagon and GIP**



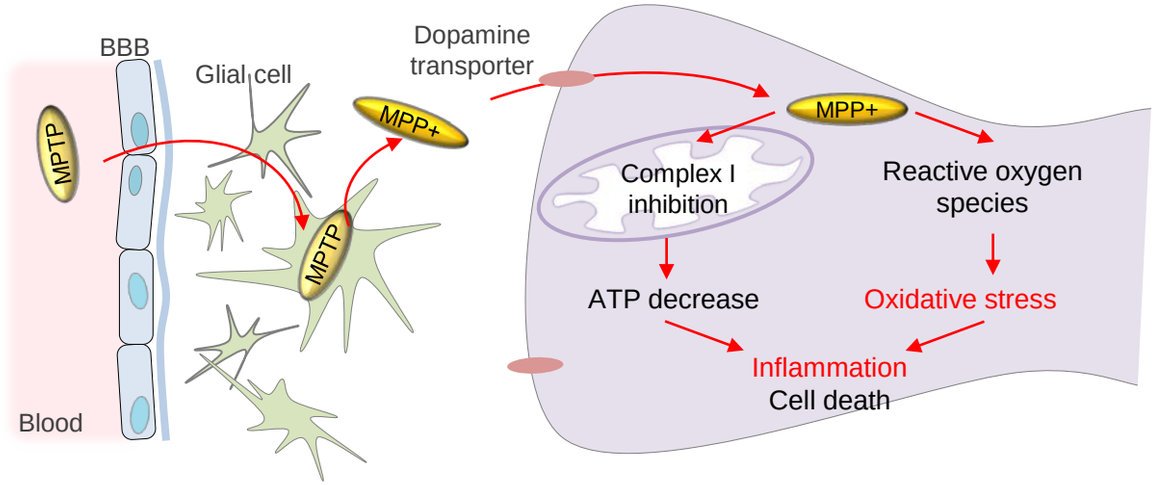
Evaluation of neuroprotective potential of HM15211…

- **To assess the efficacy and related mode of actions**
  a. in Parkinson's disease mice model
  b. of Alzheimer's disease in diabetic mice model

Efficacy and related MoAs in Parkinson’s disease mice model

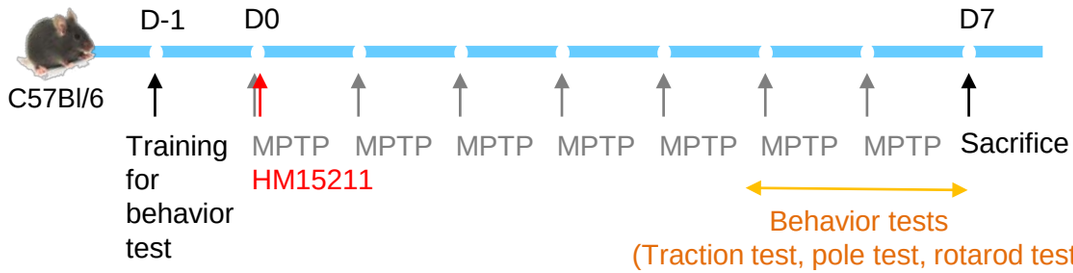
Parkinson's disease mouse model

- **MPTP is a specific neurotoxin affecting the nigrostriatal system.**

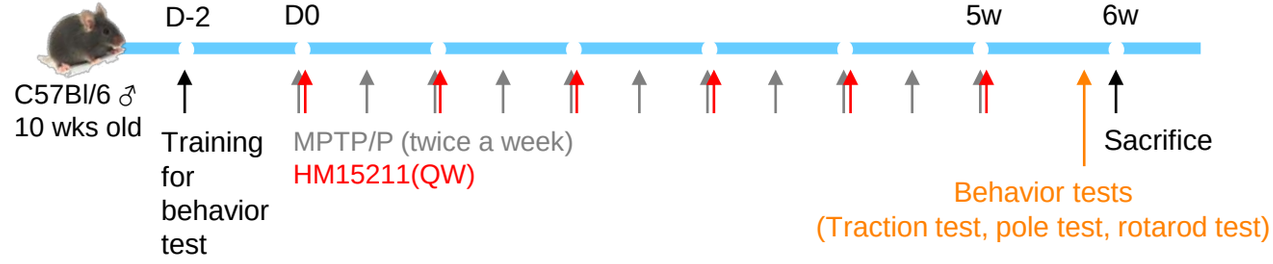


- **Experimental scheme**

Subchronic PD model

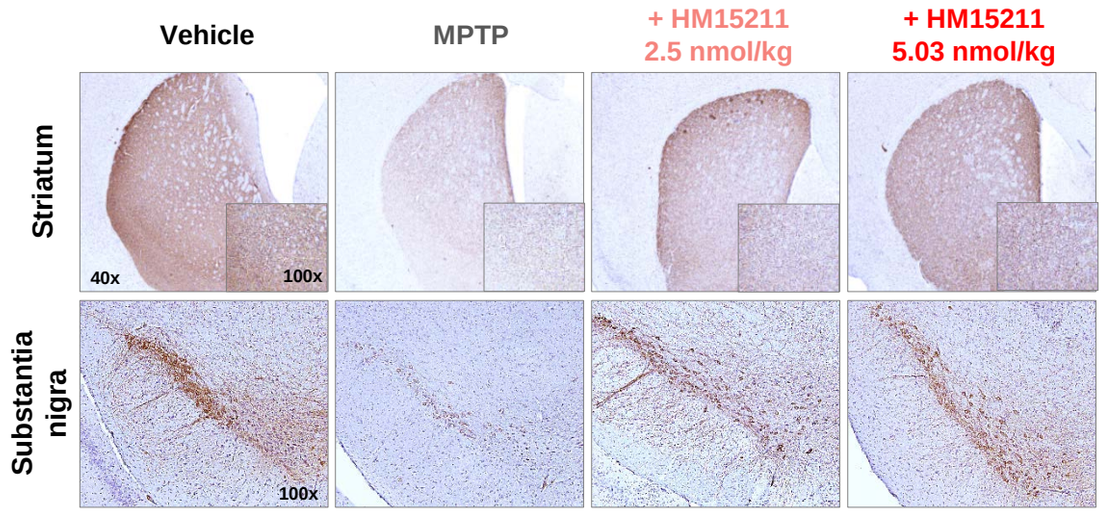


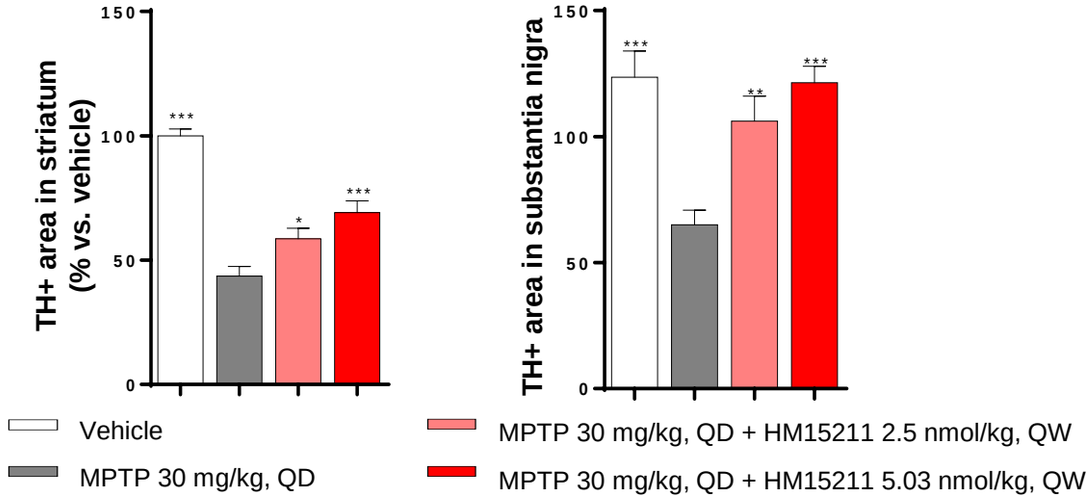
Chronic PD model



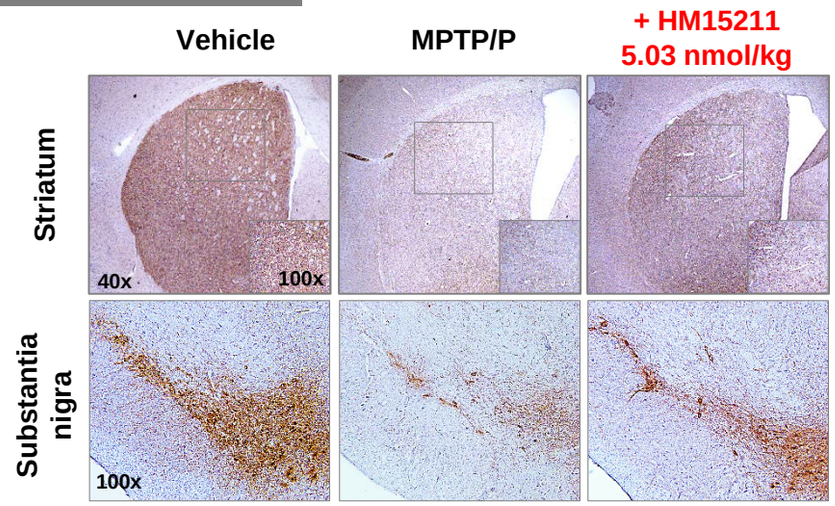
Dopaminergic neuroprotection by HM15211

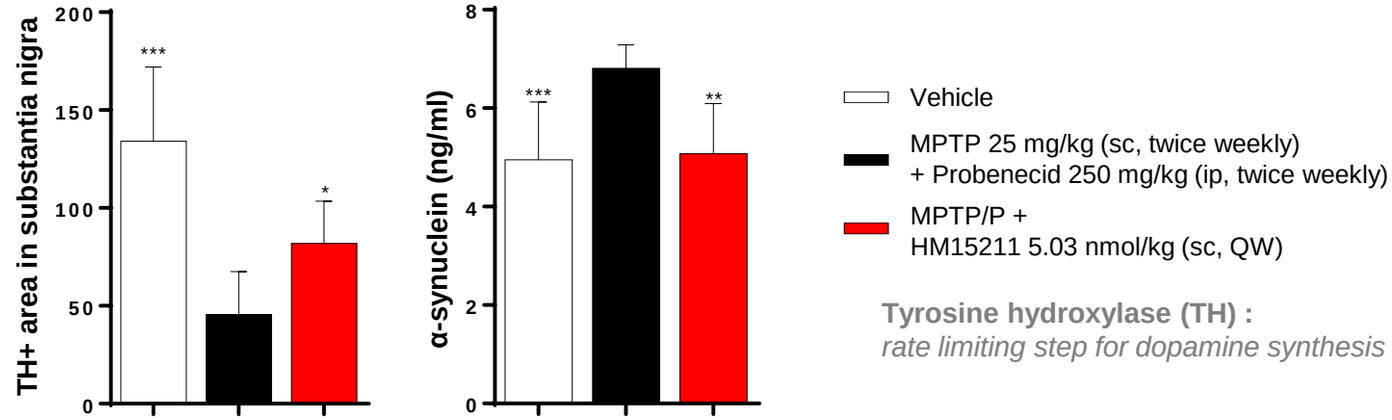
Subchronic PD model





Chronic PD model



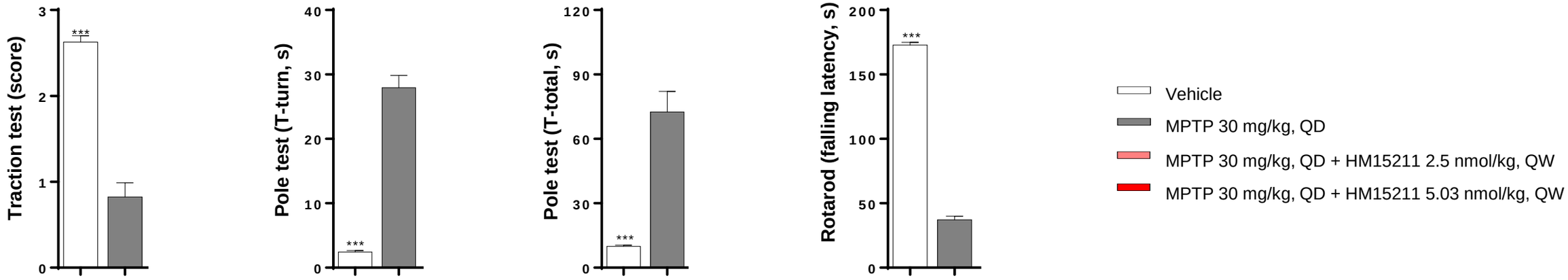


Tyrosine hydroxylase (TH) :
rate limiting step for dopamine synthesis

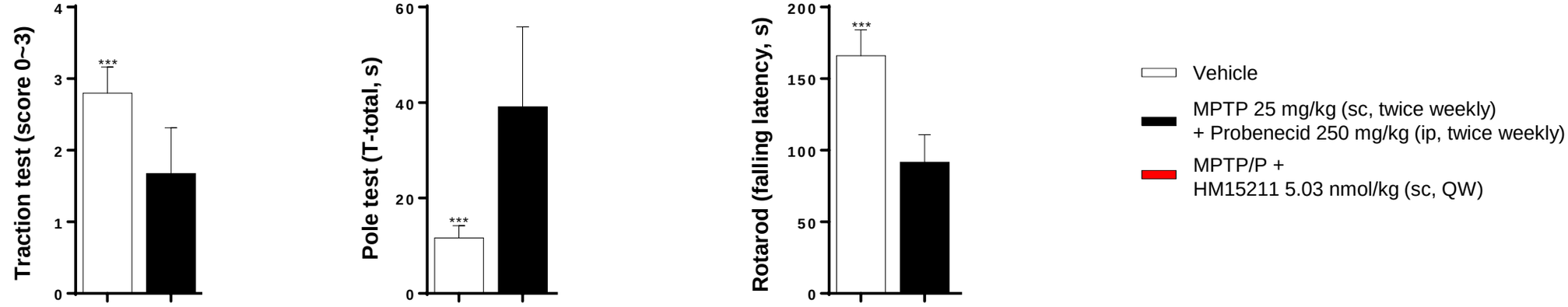
*~***p*<0.05~0.001 *vs.* MPTP or MPTP/P by One-way ANOVA

Motor function restoring by HM15211

Subchronic PD model



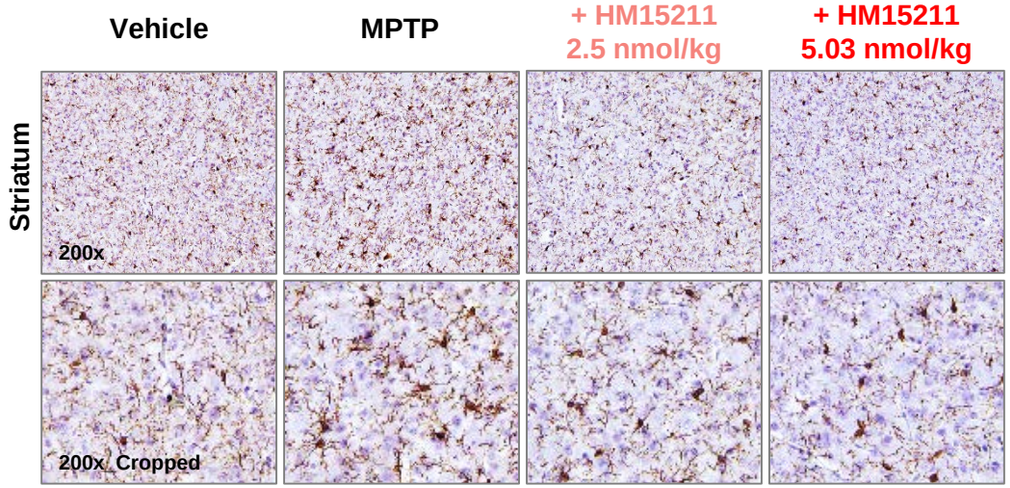
Chronic PD model

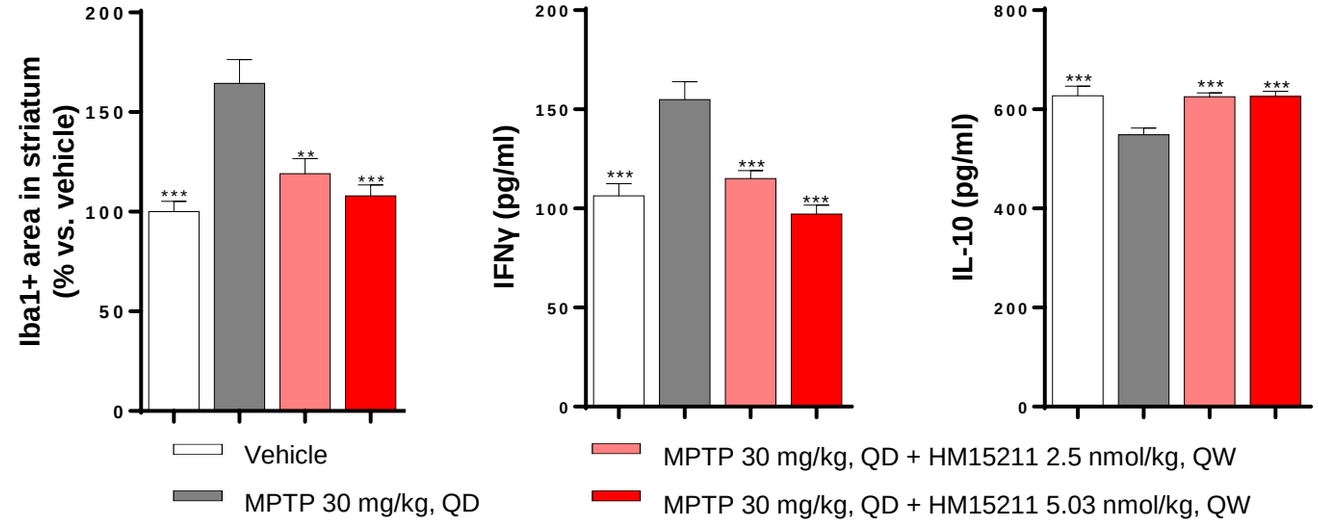


*~***p<0.05~0.001 *vs.* MPTP or MPTP/P by One-way ANOVA

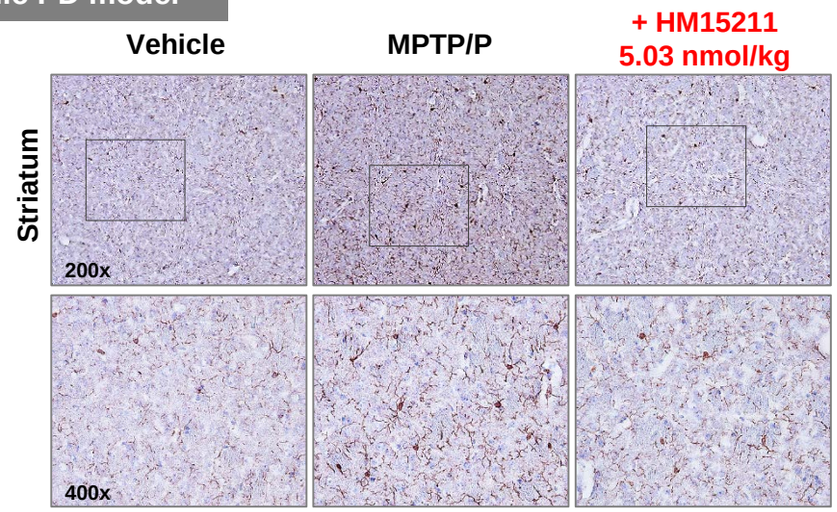
Anti-inflammatory effect of HM15211

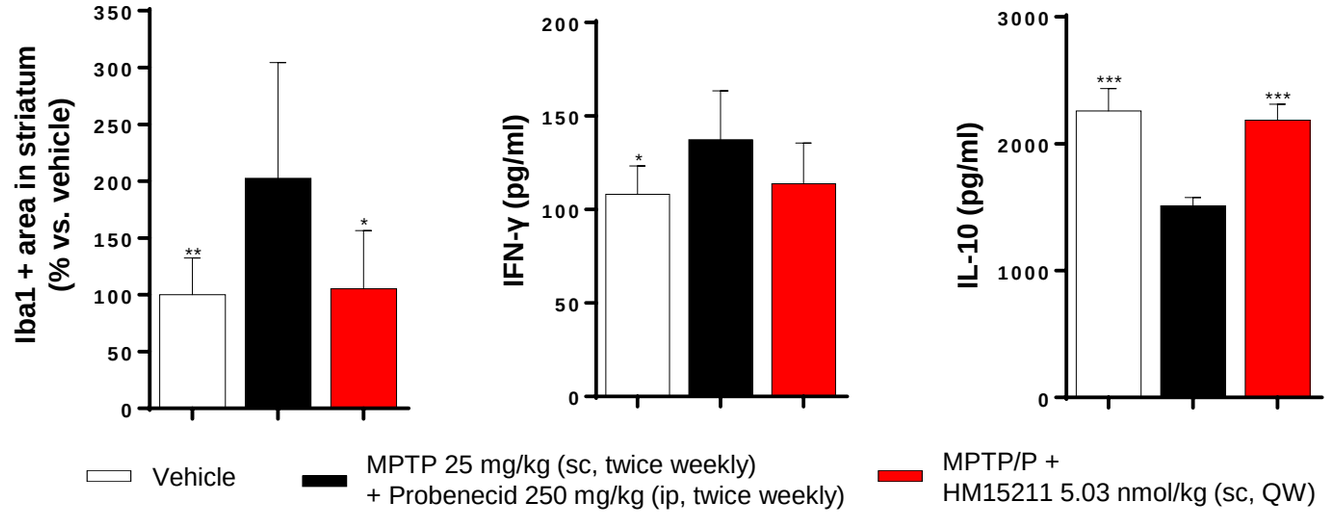
Subchronic PD model





Chronic PD model





*~***p<0.05~0.001 *vs.* MPTP or MPTP/P by One-way ANOVA

Efficacy and related MoAs of Alzheimer’s disease in diabetic mice model

Alzheimer' disease in diabetic mouse model

Diabetes / Obesity

Increased insulin resistance
Accumulation of AGE : Vasculature

AGE : Advanced Glycated Endproduct

Impaired glucose metabolism (Peripheral & brain)
Hyperactivation of RAGE

RAGE : Receptor for AGE

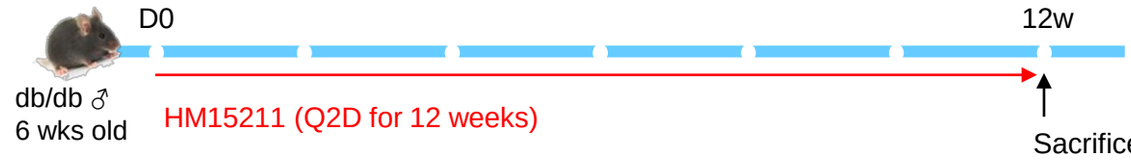
Release of proinflammatory factors

Reactive oxygen species
Cytokines

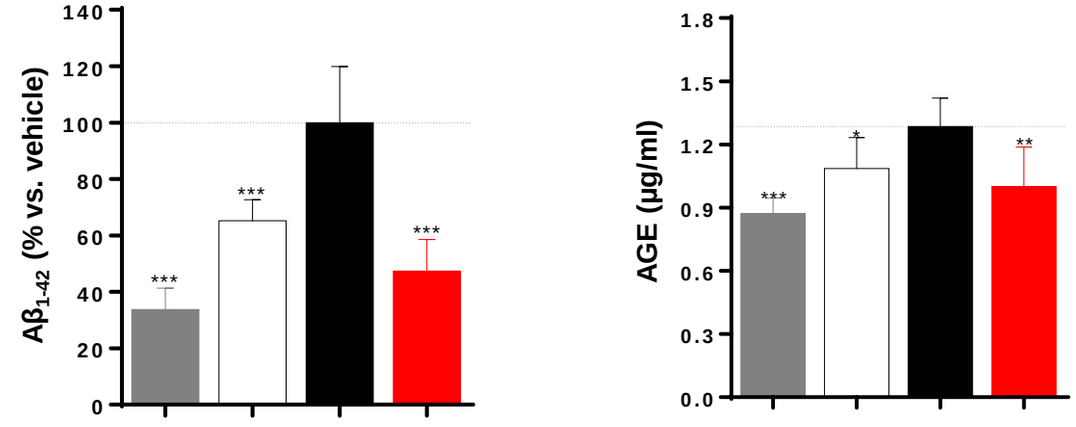
Worsening of diabetes
Increased risk of Alzheimer's disease

Accumulation of Aβ, AGE : Brain

- **Experimental scheme**

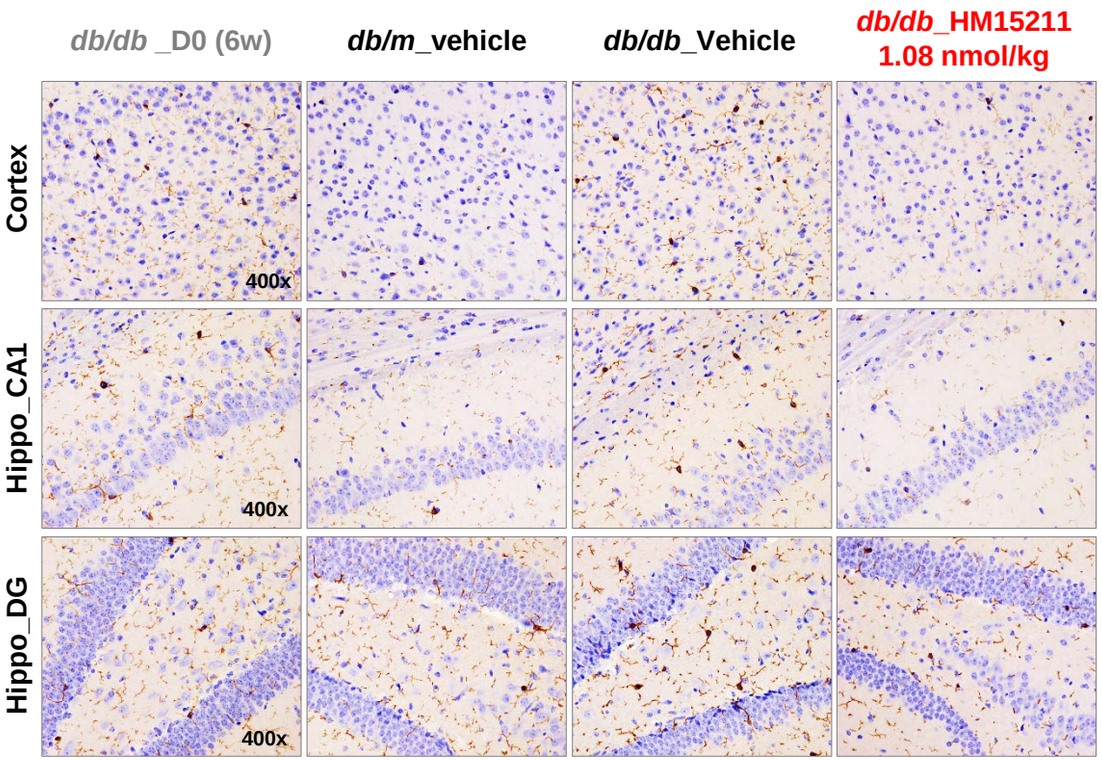


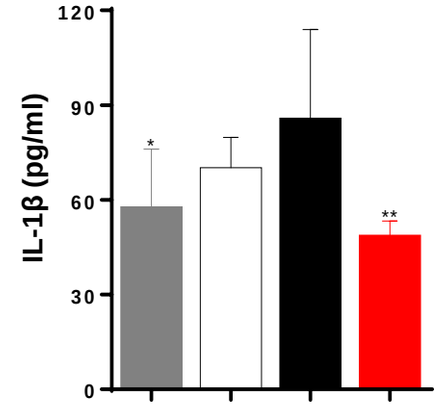
- **Inhibition of Aβ1-42 and AGE accumulation by HM15211**

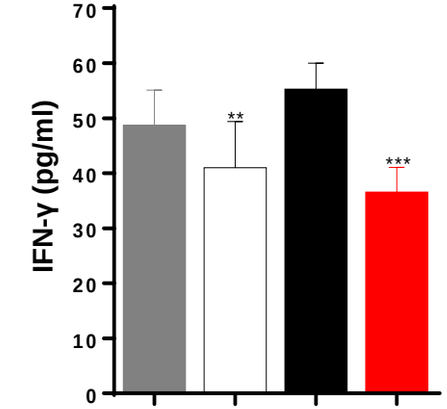


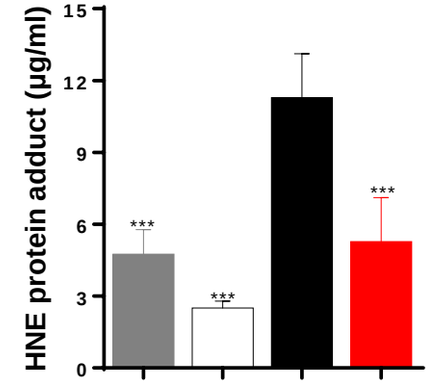
*~***p<0.05~0.001 *vs. db/db* (18w) vehicle by One-way ANOVA

Reduction of inflammation and oxidative stress by HM15211









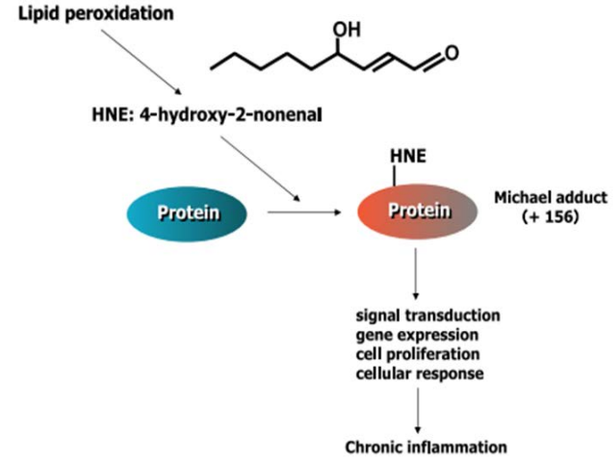


Fig. 2. 4-Hydroxyl-2-nonenal (HNE) protein adducts as a second messenger

J Clin Biochem Nutr. 2007 Jul;41(1):18-26

db/db D0 (6w)

db/m (18w) vehicle

db/db (18w) vehicle

db/db (18w) HM15211 1.08 nmol/kg, Q2D

*~***p<0.05~0.001 *vs.* MPTP or MPTP/P by One-way ANOVA

Summary & Conclusion

- **In MPTP/Probenecid induced chronic Parkinson's disease model, HM15211 inhibited the increase of alpha synuclein, which is the most prominent pathological biomarker of Parkinson's disease.**
- **In aged db/db mice, pathological characters of Alzheimer's disease such as Aβ1-42 and AGE accumulations were shown. These were reversed by HM15211 treatment.**
- **These neuroprotective effects of HM15211 are derived from anti inflammatory effect through the altered cytokine expression and reduced lipid peroxidation.**

Based on these results, the novel long-acting GLP-1 / GIP / Glucagon tri-agonist, HM15211 might have therapeutic potential for neurodegenerative diseases

Please note presentations reporting more information about HM15211:

119-OR : Therapeutic effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in NASH and fibrosis animal models
500-P: Bone protective effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in the obese-osteoporosis rodent model
719-P: A novel combination of a long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) and once weekly basal insulin offers improved glucose lowering and weight loss in a diabetic animal model