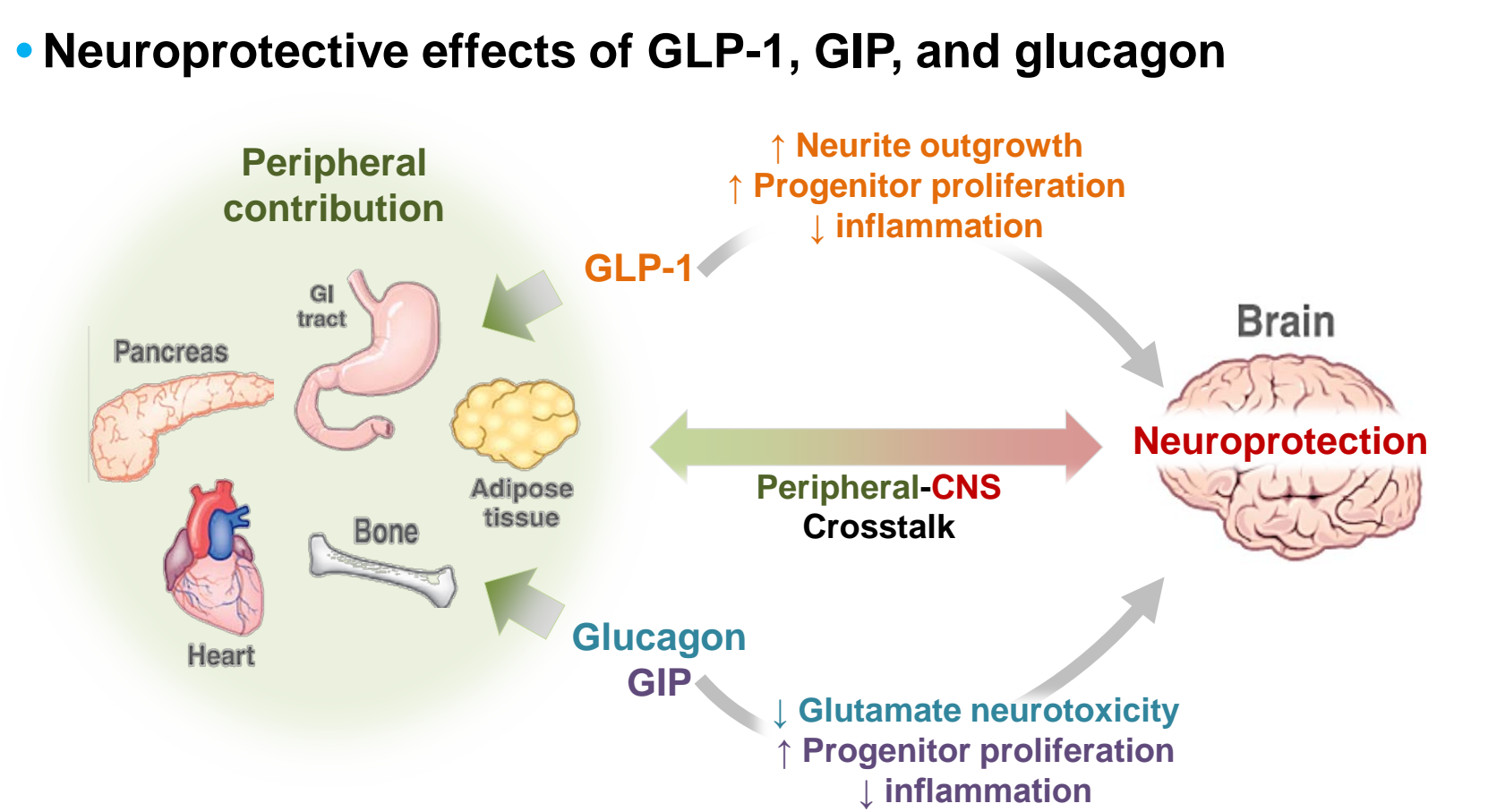


Neuroprotective effects of HM15211, a novel long-acting GLP-1/GIP/Glucagon tri-agonist in the MPTP Parkinson's disease mouse model

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BACKGROUND

- Obesity is one of the risk factors of neurological disorder¹**
 - Alzheimer's disease**
 ↑ BMI, T2DM ↑ AD risk
 Leptin/insulin resistance ↑ AD
 Leptin ↓ Aβ, p-tau
 - Parkinson's disease**
 Insulin resistance, T2DM ↑ PD
 ↑ Insulin levels ↑ α-synuclein aggregation
 Leptin ↑ survival of DA cells
 - Multiple sclerosis**
 Obesity ↑ MS risk
 Caloric restriction ↑ EAE lifespan
 ↓ insulin sensitivity in MS
 - Huntington's disease**
 Obesity, leptin/insulin resistance ↑ HD onset
 Abnormal fat cells function in HD

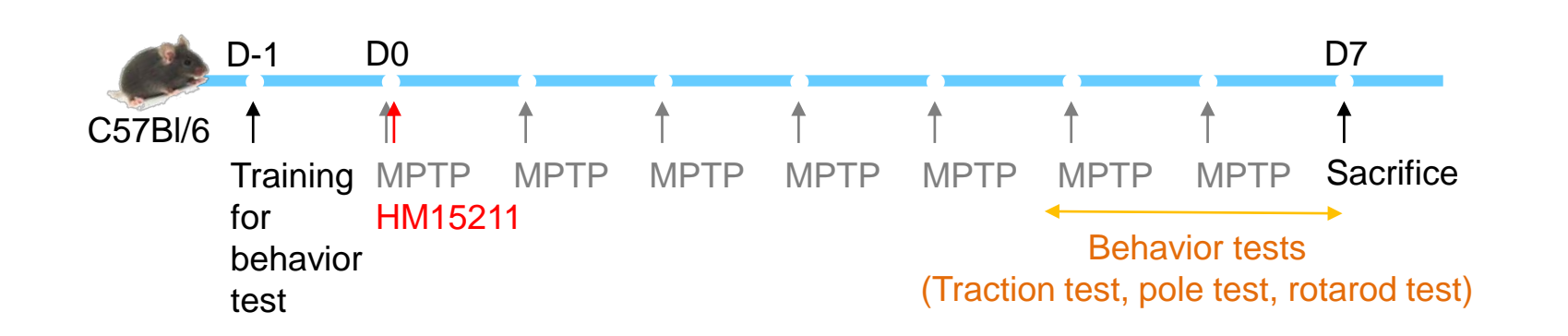


AIMS

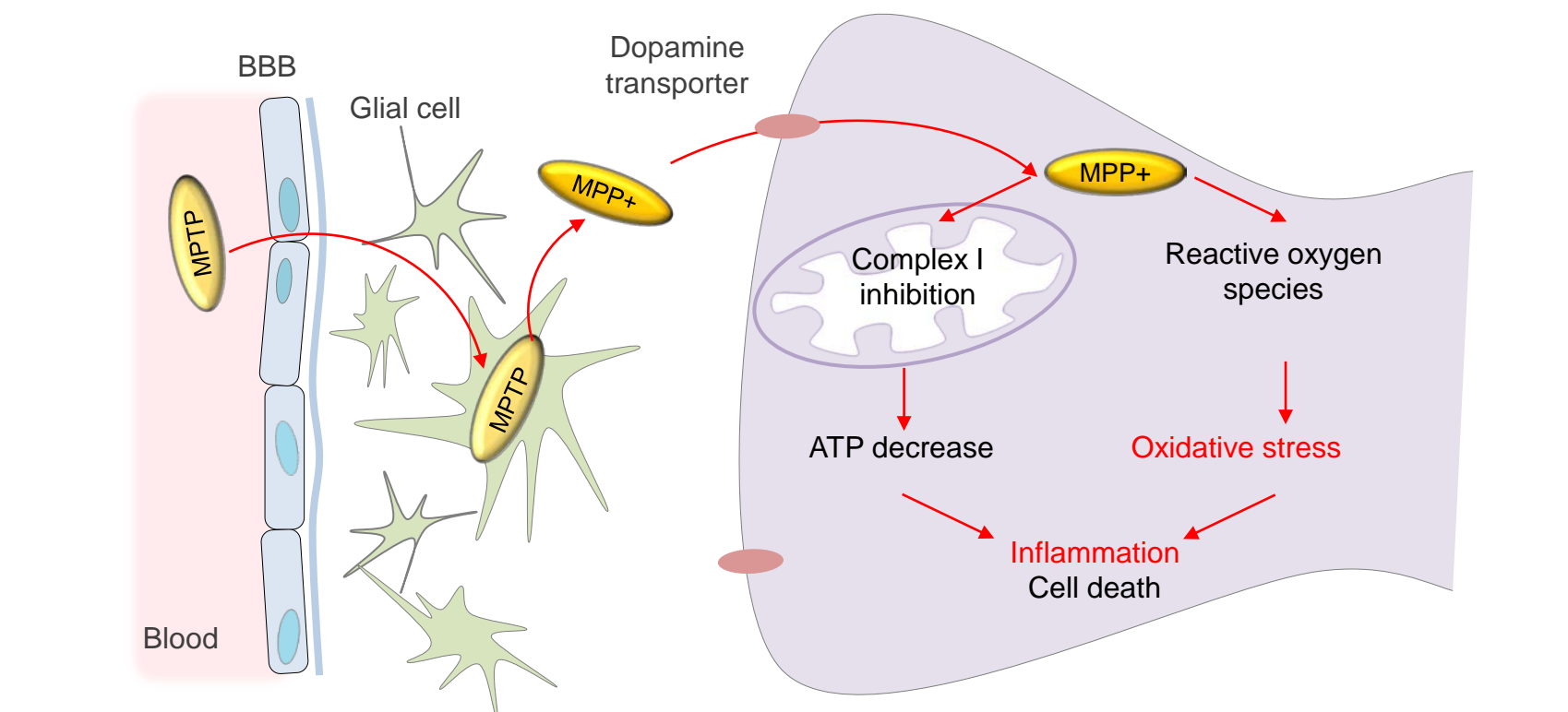
This study investigated the therapeutic potential of HM15211 in MPTP induced Parkinson's disease mouse model in behavior, pathologic and molecular aspects.

METHODS

- MPTP 30 mg/kg was intraperitoneally injected once-daily for 7 days into 9 weeks old C57Bl/6 male mice. HM15211 (2.5 and 5.03 nmol/kg) was subcutaneously administered once at the first day, 30 min after the 1st MPTP administration.
- For motor function evaluation, behavior tests (traction test, pole test and rotarod test) were conducted before sacrifice. (n=19-20)
- To assess histological changes, hemisphere of all mice brain were sectioned using cryotome and stained. (n=7-10)
- The striatum were dissected from the other half of the brain and lysed with RIPA buffer to detect molecular changes using ELISA (n=7-10)
- Statistical analysis was performed using GraphPad Prism by one-way ANOVA, followed by Dunnett post-hoc analysis. A value of $p < 0.05$ was considered as statistically significant.



MPTP is a specific neurotoxin affecting the nigrostriatal system.



RESULTS

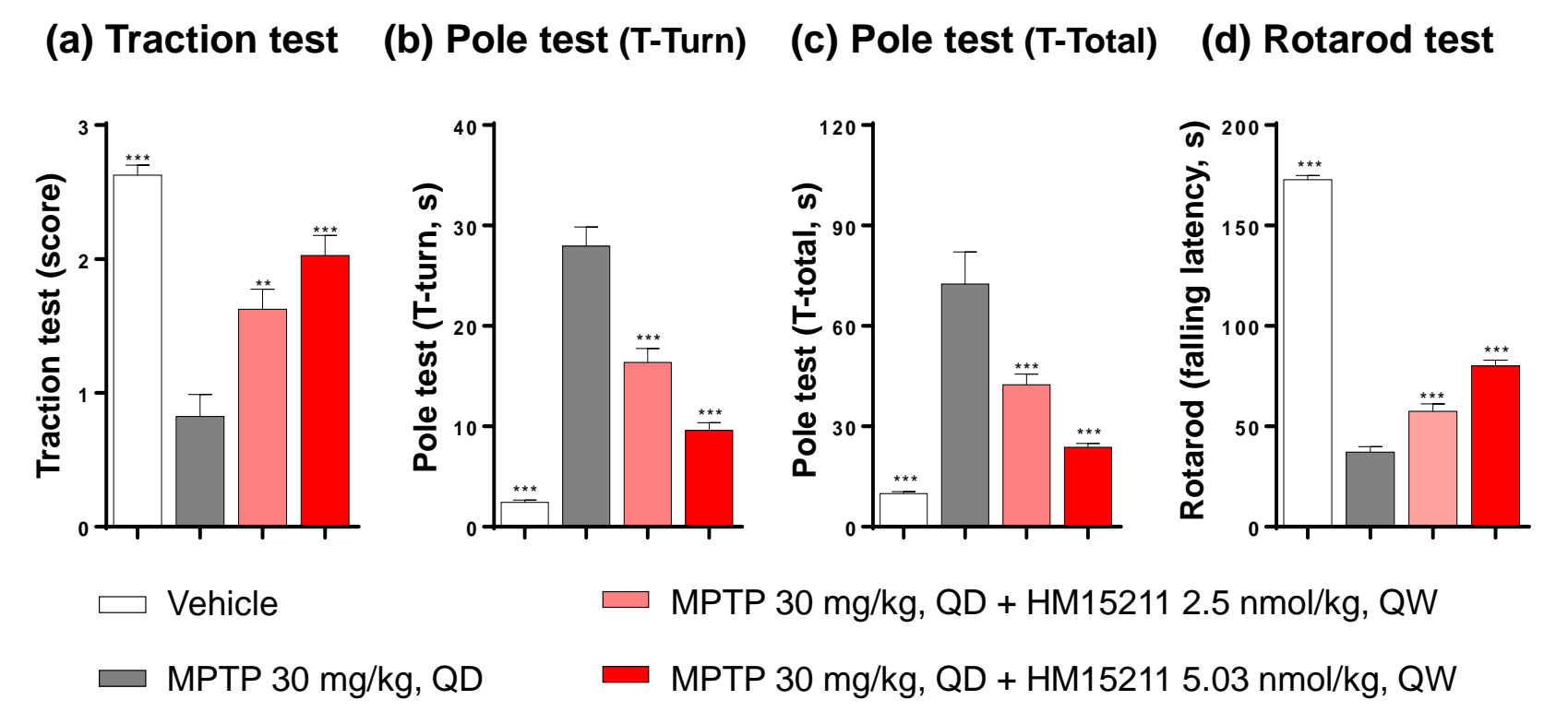
Motor function evaluation

Traction test
 Score 1: No gripping of the wire with either hind paws
 Score 2: Gripping of the wire with one hind paw
 Score 3: Gripping of the wire with both hind paws

Pole test
 T-turn: Time to turn their angle
 T-total: Time to land on all four paws

Rotarod: Falling latency

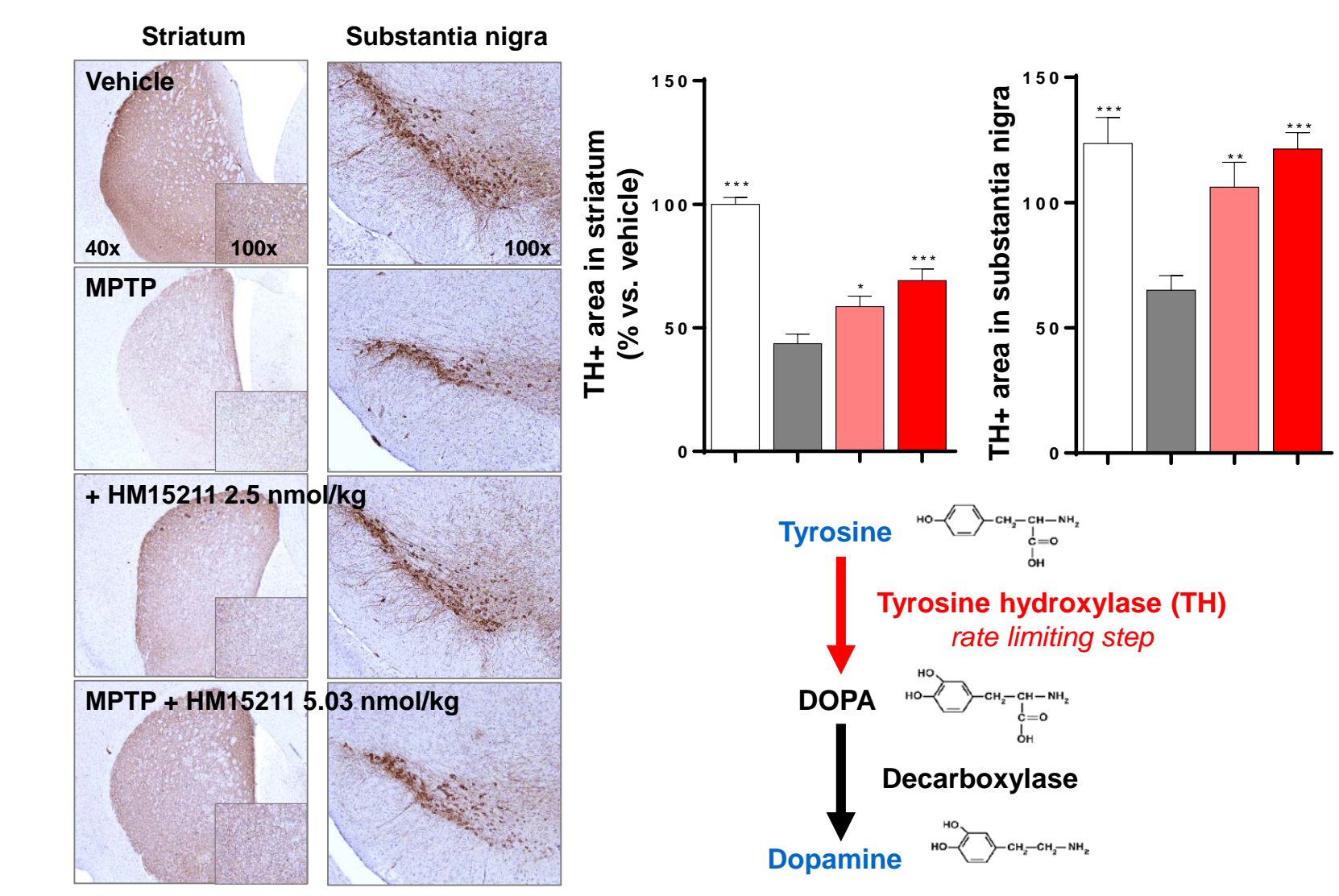
Figure 1. Motor function restoring effects of HM15211



HM15211 administration restored MPTP induced motor function impairment in (a) traction test, (b, c) pole test and (d) rotarod test.

Efficacy on dopaminergic neuroprotection

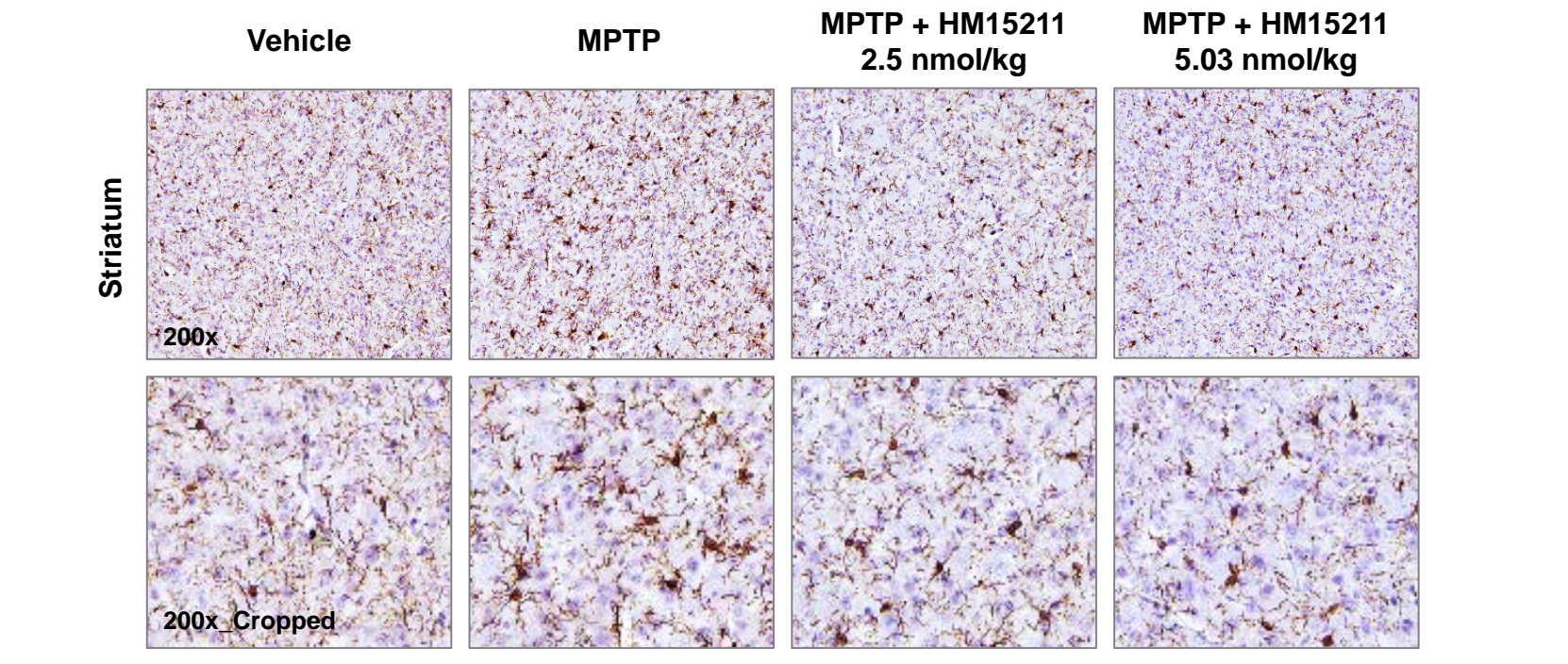
Figure 2. Neuroprotective effect of HM15211 against MPTP



HM15211 administration protected MPTP induced dopaminergic neuronal cell damage in the striatum and the substantia nigra.

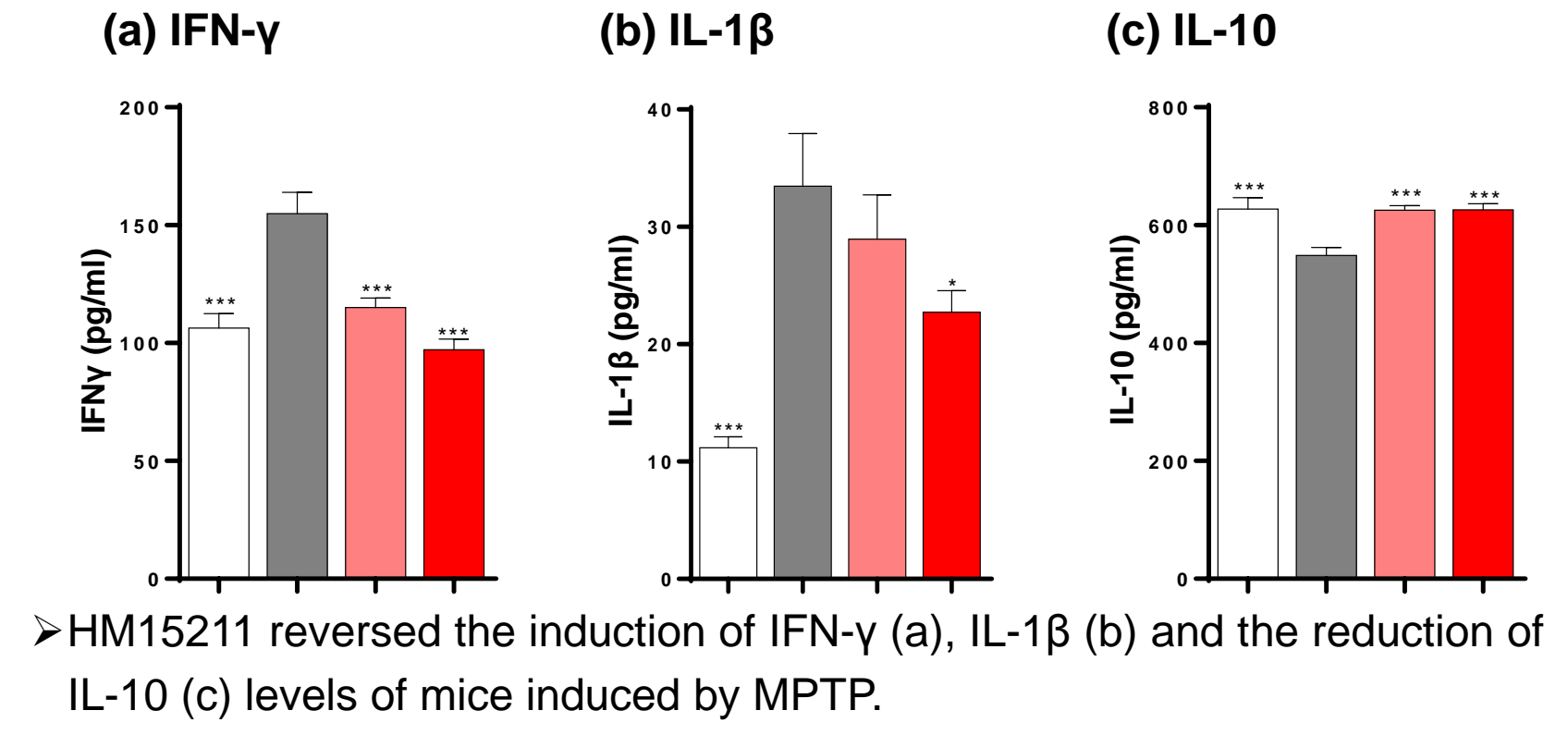
Effects on microglia activation and inflammatory cytokines

Figure 3. Activated microglia reduction by HM15211



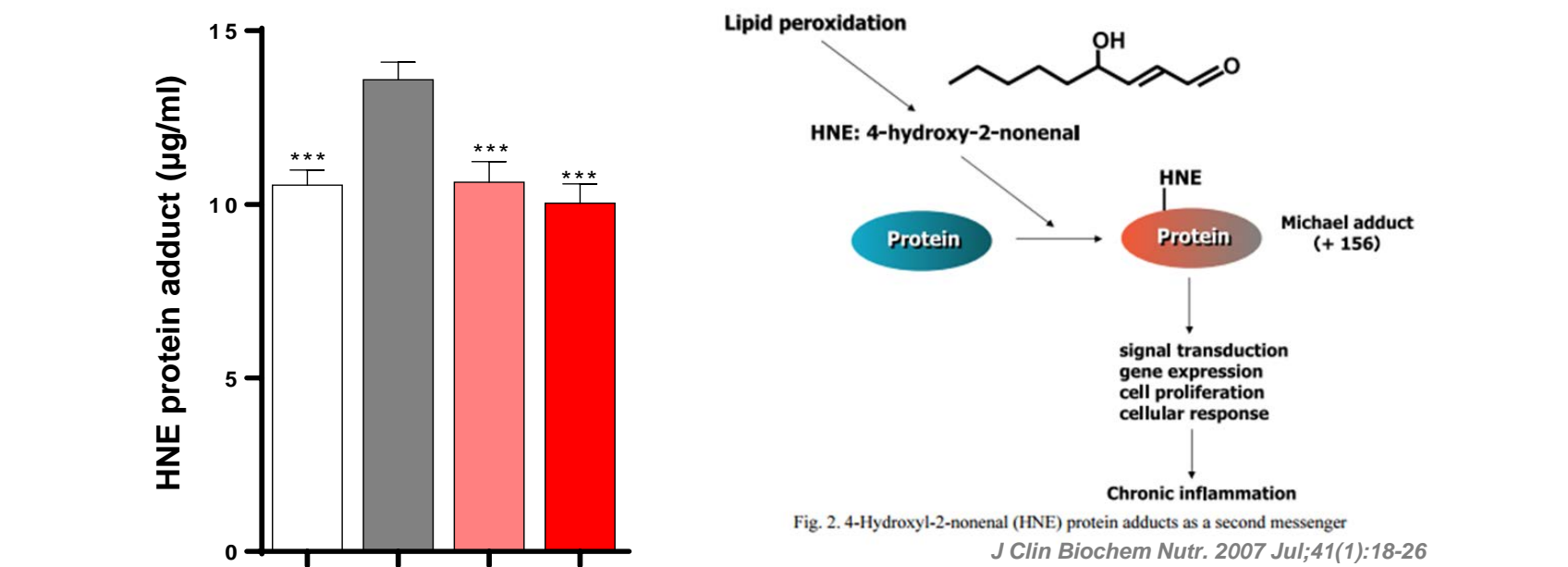
In striatum of MPTP PD mouse model, the area covered by microglia was increased and the morphology of microglia was activated. Administration of HM15211 leads to reduction of microglia activation.

Effects of HM15211 on the expression of pro- and anti-inflammatory cytokine



Effect on oxidative stress

Figure 5. Reduced lipid peroxidation by HM15211



In the striatum, HM15211 effectively decreased the HNE protein adduct (a byproduct of lipid peroxidation), which was induced by MPTP.

CONCLUSIONS

- HM15211 significantly improved MPTP induced motor impairments in three behavior tests in a dose-dependent manner.
- Histologically, the tyrosine hydroxylase (TH) positive neurons in substantia nigra and the staining density in striatum were reduced by MPTP. However, they were protected by HM15211.
- In addition, HM15211 changed inflammatory cytokine expression and reduced lipid peroxidation byproduct in the MPTP PD model.
- Even after a single injection of HM15211, neuroprotective effects were shown against 7 days repeated MPTP injection.
- Based on these results, the novel long-acting GLP-1/GIP/Glucagon tri-agonist, HM15211 could have therapeutic potential for PD.

REFERENCES

- Claudio Procaccini et al., *Metabolism*. 65(9):1376-90 (2016)
- Yazhou Li et al., *Proc Natl Acad Sci U S A*. Jan 27;106(4):1285-90 (2009)
- Rami Abu Fanne et al., *Am J Physiol Regul Integr Comp Physiol* 301: R668-R673 (2011)
- Yanwei Li et al., *Neuropharmacology*. 101, 255e263 (2016)