Neuroprotective effects of HM15211, a novel long-acting GLP-1/glucagon/GIP triple agonist in the MPTP Parkinson’s disease mouse model

ABSTRACT

HM15211 is a novel long-acting GLP-1/glucagon/GIP triple agonist that is being developed for the treatment of obesity and related complications. Recent studies have shown that obesity, type 2 diabetes, and non-alcoholic fatty liver disease increase the risk of developing progressive neurodegenerative diseases such as Parkinson’s disease (PD) and Alzheimer’s disease (AD). Dysregulated metabolic pathways are shared in the metabolic syndrome (MS). To date, disease modeling has not yet been achieved through the use of MS mimics. In this study, we investigated the effects of HM15211 in an obesity model, and repeatedly positive increases in lipid hydroxylase and the hydroxylase addition, could be repeated in PD mice. In addition, glucagon also exerted neuroprotective effects in rats and brain-tissue injury model.

BACKGROUND

Obesity is one of the risk factors of neurological disorders such as Alzheimer’s disease (AD), multiple sclerosis (MS), and Huntington’s disease. Glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) have been shown to protect neurons in various disease models. Therefore, these results suggest HM15211 as a potential therapy for the treatment of PD.

METHODS

- **MPTP** 30 mg/kg was intraperitoneally injected once-daily for 7 days into 9-week-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 rotated test) were conducted before sacrifice. (n=10-15)
- To assess histological changes, hemispheres of all mice brain were dissected using cryoprobe and stained. (n=1-10)

RESULTS

Motor function evaluation

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Efficacy on dopaminergic neuroprotection

- **HM15211 administration reversed the induction of IFN-γ (a) and the reduction of IL-10 (c) levels of mice 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 substantia nigra 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/glucagon/GIPagonist, HM15211 could have therapeutic potential for PD.

REFERENCES

Potent body weight loss and efficacy in a NASH animal model by a novel long-acting GLP-1/Glucagon/GIP triple-agonist (HM15211)

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ABSTRACT

Obesity and related complications are an increasing threat to public health with existing therapies having only limited effectiveness. Therefore, additional therapeutic options are warranted. The role of glucagon is growing in the context of the human obesity paradigm where glucagon-like peptide-1 (GLP-1) and glucagon are both involved in the regulation of energy expenditure. HM15211 is a novel glucagon/glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide (GLP-1) receptor (GLP-1R) agonist with high glucagon (GCG) activity and balanced GLP-1/GIP action, optimal for next-generation antidiabetic therapies. In preclinical models, HM15211 showed potent body weight loss efficacy in rodent and humanized NASH models.

RESULTS

•Intravenous activity of HM15211

HM15211 possesses relatively high GCG activity and balanced GLP-1/GIP activity, which is well-reproduced in different batches of CHO cells (Figure 1). Treatment of CHO cells expressing either hGLP-1R, hGIPR or hGCGR with HM15211 showed dose-dependent increases in intracellular cAMP levels (Figure 2A). To evaluate therapeutic efficacy of HM15211 for obesity and related complications including NASH.

•In vitro activity of HM15211

HM15211 is a novel long-acting triple-agonist with high GCG & balanced GLP-1/GIP activity, which is well-reproduced in different batches of CHO cells (Figure 1). Treatment of CHO cells expressing either hGLP-1R, hGIPR or hGCGR with HM15211 showed dose-dependent increases in intracellular cAMP levels (Figure 2A). To evaluate therapeutic efficacy of HM15211 for obesity and related complications including NASH.

•Therapeutic potential of HM15211 in NASH was evaluated in MCD mice and HSD rats. Similarly, evaluation of therapeutic efficacy of HM15211 for obesity and related complications including NASH.

•HM15211 reduces hepatic TG, oxidative stress, and NAS in MCD mice. Therapeutic benefits in NASH was further confirmed in HSD rats (Figure 3 and Table 1). Our results suggest that GLP-1/GIP/GCG triple-agonists may have therapeutic potential in the treatment of obesity and related complications including NASH.

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