Glucagon engagement is essential for the direct anti-inflammation and anti-fibrosis effect of efocipegtrutide in TAA-induced mouse model of liver injury and fibrosis

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ABSTRACT

Background/Aims: Nowadays, potential benefits of incretin such as GIP, and GLP-1 and glucagon (GCG) beyond metabolism have been proposed, particularly in inflammation and fibrosis. A long-acting GCG/GIP/GLP-1 triple agonist, efocipegtrutide (also known as HM15211), was developed for MASH and demonstrated consistent treatment benefits in various animal models of MASH and/or fibrosis. Considering its unique activity profile, GCG action of efocipegtrutide might play an important role in the improvement effect on inflammation and fibrosis. To demonstrate this hypothesis, potential effect of GCG engagement was investigated in a TAA (thioacetamide)-induced liver injury and fibrosis mouse model.

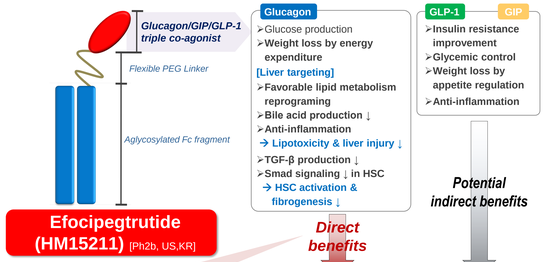
Methods: TAA was i.p. injected into mice for 12 weeks to induce liver injury and fibrosis, and efocipegtrutide was administered during the last 10 weeks. Tirzepatide (GLP-1/GIP) was included as comparative control. Efpegerglucagon, which has a same structure with efocipegtrutide but only exhibits GCG activity, was also included. At the end of the treatment, hepatic hydroxyproline content and pro-collagen 1α1 level were measured, and the liver tissues were subjected to H&E and Sirius Red staining followed by histological grading.

Results: Efocipegtrutide treatment significantly reduced hepatic hydroxyproline content (178.46 nmol/g; p<0.001) compared to the TAA vehicle group (243.73 nmol/g). Similar reduction was observed with efpegerglucagon (184.07 nmol/g; p<0.001), while tirzepatide (230.68 nmol/g) had only marginal effect. Similarly, efocipegtrutide significantly reduced pro-collagen 1α1 content (0.47 mg/g; p<0.001) compared to the TAA vehicle group (0.88 mg/g), and efpegerglucagon also showed a significant reduction (0.64 mg/g; p<0.05), whereas tirzepatide (0.89 mg/g) had no reduction effect. H&E and Sirius red staining demonstrated that efocipegtrutide exhibited greater reduction in portal inflammation and fibrosis scores (1.00; p<0.001, 0.86 ; p<0.001) compared to the TAA vehicle group (2.29, 3.29). Notably, efpegerglucagon showed similar histological improvement (1.00; p<0.001, 1.29 ; p<0.001). In contrast, tirzepatide had no improvement effects. Consistent with these histological findings, hepatic expression of collagen 1α1 and blood level of TIMP-1 were significantly reduced by efocipegtrutide or efpegerglucagon, but not by tirzepatide.

Conclusion: In TAA mice, efocipegtrutide (GCG/GIP/GLP-1 triple) and efpegerglucagon (GCG mono) showed similar anti-inflammatory and anti-fibrosis benefits while tirzepatide (GIP/GLP-1 dual) had relatively little effect. These result demonstrate that GCG engagement could play a crucial role in managing hepatic inflammation and fibrosis. P2b study in biopsy confirmed MASH patients is currently ongoing to assess the clinical relevance of these findings.

BACKGROUND

Efocipegtrutide is a long-acting Glucagon/GIP/GLP-1 triple agonist conjugated with human IgG_4 Fc fragment via a short PEG linker



Glucagon
- Glucose production
- Weight loss by energy expenditure

[Liver targeting]
- Favorable lipid metabolism reprograming
- Bile acid production ↓
- Anti-inflammation → Lipotoxicity & liver injury ↓
- TGF-β production ↓
- Smad signaling ↓ in HSC → HSC activation & fibrogenesis ↓

GLP-1 **GIP**
- Insulin resistance improvement
- Glycemic control
- Weight loss by appetite regulation
- Anti-inflammation

Direct benefits

Potential indirect benefits

"Expected pharmacologic outcomes"
- → **MASH resolution**
- → **Fibrosis improvement**
- → Off-set blood glucose elevation

Key outcome:
Beneficial effect on liver fibrosis by glucagon engagement.

- **Designed and optimized for liver specific distribution and effects**
- **Multiple MoAs in liver to manage inflammation and fibrosis in addition to steatosis resolution** (steatosis improvement confirmed both in animals and human)
- **The extended half life is sufficient for weekly dosing**
- **Upto 80% liver fat reduction was demonstrated w/o notable safety signal in P1b/P2a study (NAFLD pts for 12 weeks)**
- **Designated by US-FDA as a 'fast-track program in NASH' (Jul. 2020)**
- **On-going for P2b study in biopsy-confirmed NASH pts (NCT04505436)**

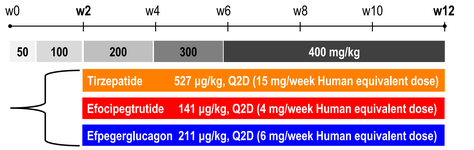
STUDY DESIGN

Study design

TAA mice
(C57BL/6 strain)
(n= 7/group)

TAA (i.p., 3 times/wk for 12 wks)

Drug treatment (for 10 wks)

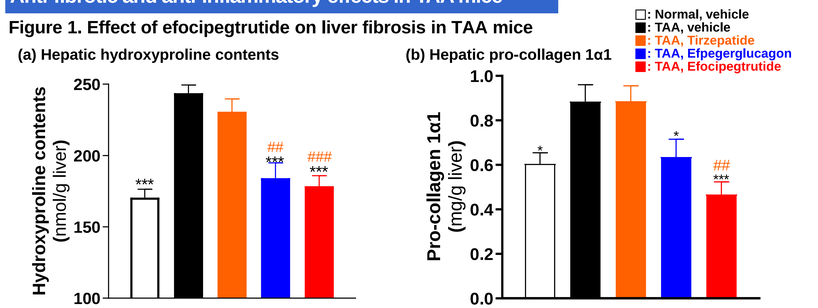


Glucagon receptor mono agonist (efpegerglucagon) was included to clarify the role of glucagon engagement.

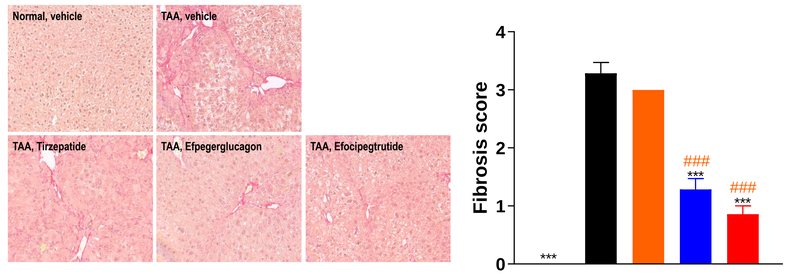
RESULTS

Anti-fibrotic and anti-inflammatory effects in TAA mice

Figure 1. Effect of efocipegtrutide on liver fibrosis in TAA mice

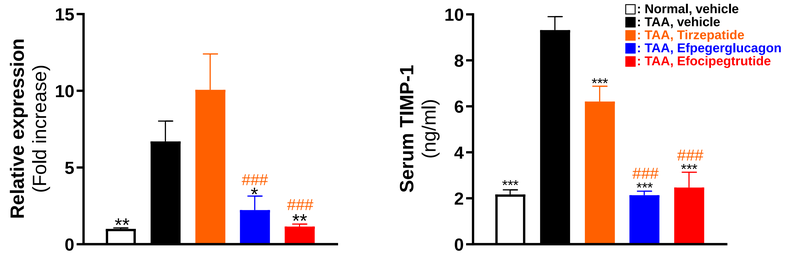


- Efocipegtrutide treatment significantly reduced hepatic hydroxyproline content and pro-collagen 1α1 compared to the TAA vehicle group. Similar reduction was observed with efpegerglucagon, while tirzepatide had only marginal effect.



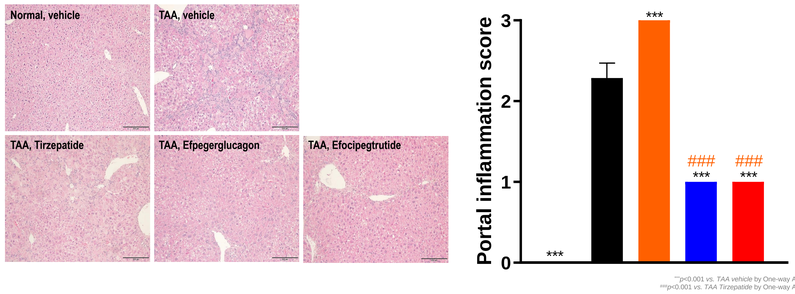
- Histological results demonstrated that efocipegtrutide and efpegerglucagon exhibited great reduction, whereas tirzepatide showed negligible effect. An additional therapeutic improvement could be derived from the glucagon engagement.

Figure 2. Anti-fibrosis effect of efocipegtrutide on marker gene and surrogate marker in TAA mice



- Consistent with the histological findings, hepatic expression of collagen 1α1 and blood level of TIMP-1 were significantly reduced by efocipegtrutide or efpegerglucagon, but not by tirzepatide.

Figure 3. Effect of efocipegtrutide on portal inflammation in TAA mice



- In portal inflammation exploration by H&E staining, glucagon engagement also could give more favorable anti-inflammatory efficacy than tirzepatide.

Conclusion

- **In TAA mice, efocipegtrutide** (GCG/GIP/GLP-1 triple agonist) **and efpegerglucagon** (GCG mono-agonist) **provide comparable anti-inflammatory and anti-fibrotic effects. In contrast, tirzepatide** (GIP/GLP-1 dual agonist) **exhibited relatively marginal efficacy. These results highlight the essential role of glucagon engagement in the treatment of hepatic inflammation and fibrosis.**
- **P2b study in biopsy confirmed MASH patients** (NCT04505436) **is currently ongoing to assess the clinical relevance of these findings.**

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