396

Evaluation of the effects of GLP1R agonists on MC4R KO hyperphagic obesity model mice

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Introduction

POMC-MC4R pathway in hypothalamus controls food intake and body weight[1]. Patients with POMC mutation causes severe early phase obesity, increase of food intake[2]. However, there is no approved drugs treatment for POMC-MC4R pathway deficient diseases such as Prader–Willi syndrome.

The aim of this study was to evaluate the efficacy of GLP-1R agonists in obesity caused by MC4R-POMC pathway deficiency. We also evaluated and compared the efficacy of Semaglutide (GLP-1R monoagonist), Tirzepatide (GLP-1R, GIPR dual agonist), and Retatrutide (GLP-1R, GIPR, GCGR triple agonist), recently developed as anti-obesity agents.

Method

35-week-old male MC4R KO[3] and C57BL/6J mice were kept on a normal diet. Then, Saline, 0.1 mg/kg Semaglutide, 0.05 mg/kg Tirzepatide or 0.05 mg/kg Retatrutide administered subcutaneously to mice daily for 3 weeks. Body weight, food intake, body composition, and energy expenditure were measured.

Highlight of this study

- All GLP-1R agonists decreased body weight, food intake and fat weight.
- The reduction in visceral fat mass was more pronounced than in subcutaneous fat mass.
- All GLP-1R agonists decreased lean body mass and energy expenditure.

Results

All GLP-1R agonists showed significant food intake and weight reduction.

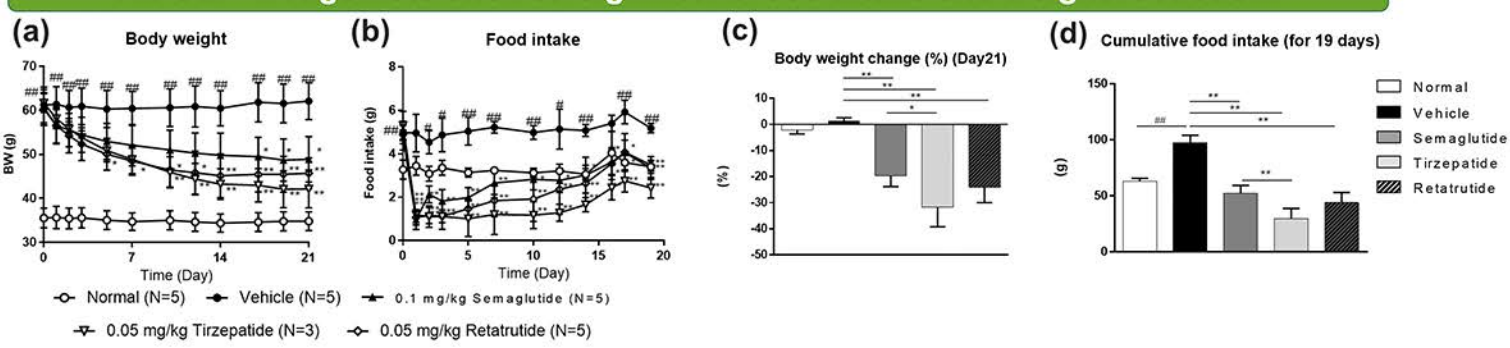
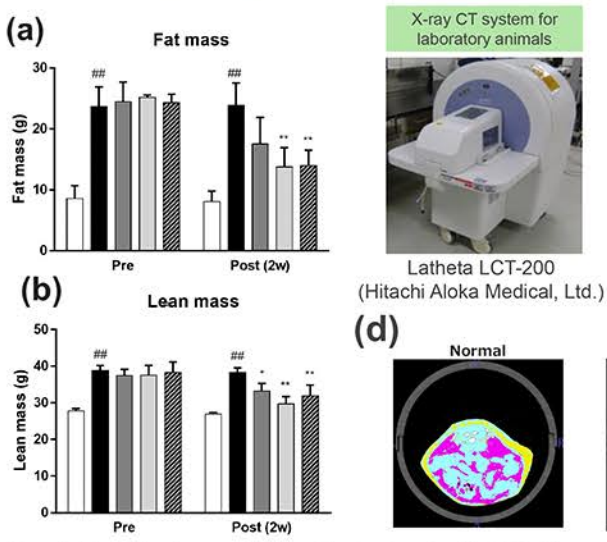


Fig.1 Effects of GLP-1R agonists on body weight, food intake. (a) Body weight change for 21 days. (b) Food intake change for 19 days. (c) Percentage change in body weight from before to after 21 days of treatment. (d) Cumulative food intake over a 19-day period. Data are represented as the mean ± SD. Statistical analysis in (a), (b) were done using Student's *t*-test or Tukey test followed by Bonferroni correction. Statistical analysis for (c)-(d) was done using Student's t-test or Tukey test. # p<0.05, ## p<0.01, vs Normal group by Student's *t*-test, * p<0.05, ** p<0.01, vs Vehicle or Semaglutide group by Tukey test

GLP-1R agonists reduced fat mass as well as lean mass.

Non-invasive body composition measuring instruments

EchoMRI-900
(Hitachi Aloka Medical, Ltd.)



X-ray CT system for laboratory animals

Latheta LCT-200
(Hitachi Aloka Medical, Ltd.)

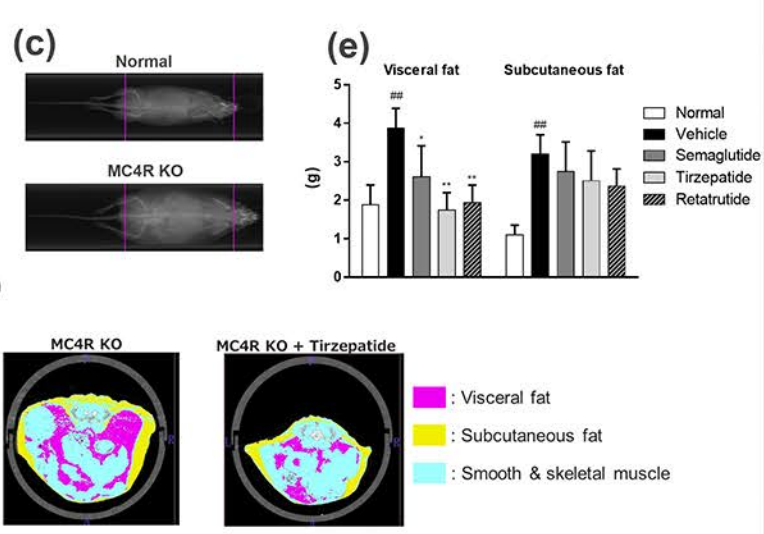


Fig.2 Changes in body weight and body composition after treatment with GLP-1R agonists (a) Fat mass before and after treatment. (b) Lean mass before and after treatment. (c) Scout image of mice whole body scanned by X-ray CT. (d) Cross-sectional image of the peri-abdominal area imaged by X-ray CT. (e) Quantitative evaluation value of visceral and subcutaneous fat from segmental CT images. Data are represented as the mean ± SD. Statistical analysis was done using Student's *t*-test or Tukey test. # p<0.05, ## p<0.01, vs Normal group by Student's *t*-test, * p<0.05, ** p<0.01, vs Vehicle group by Tukey test.

All GLP-1R agonists reduced energy expenditure.

System for measuring respiratory metabolism

Oxymax system
(Columbus Instructions)

※RQ values indicate which nutrients (carbohydrates, fats, etc.) are used as the main source of energy

Fig. 3 Measurement of energy expenditure and respiratory quotient in mice after treatment with GLP-1R agonists. Time course of the metabolic rates was monitored continuously for 18 hours by using an Oxymax system. Energy expenditure (a) and respiratory quotient (RQ) (b). Shaded regions represent the dark phase of 12-hour light-dark cycle. The average of energy expenditure (c) and RQ (d) per light and dark period. Data are represented as the mean ± SD. Statistical analysis for (c), (d) was done using Tukey test. * p<0.05, ** p<0.01, vs Vehicle group by Tukey test.

Conclusion

The present study confirms that all GLP-1R agonists have significant anti-obesity effects in MC4R KO mice. Comparison of the effects of weight loss and suppression of food intake showed that Tirzepatide had a stronger effect than Semaglutide. On the other hand, all GLP-1R agonists showed to decrease lean mass and energy expenditure, suggesting decreased lean mass may contribute to decreased energy expenditure. The muscle loss effect of GLP-1R agonists has been reported in clinical trials[4] and may be an issue in the development of future obesity drugs.

These results mimic the previously reported clinical effects of GLP1R agonists and indicate that MC4R KO mice are a suitable animal model of obesity for preclinical evaluation of anti-obesity drugs. The study also confirmed the efficacy of GLP1R agonists in the MC4R-deficient condition, suggesting that GLP1R agonists may be a good therapeutic option for patients with MC4R-POMC pathway deficiency.

Reference

1) M J Krashes, *et al*., *Nat Neurosci*. 2016 Feb;19(2):206-19.
2) H Krude, *et al*., *Nat Genet*. 1998 Jun;19(2):155-7.
3) M Matsumoto, *et al*., *PLoS One*. 2020 Jan 28;15(1).
4) I J Neeland, *et al*., *Diabetes Obes Metab*. 2024 Sep:26 Suppl 4:16-27.

COI disclosure information:
We have no financial relationship to disclose for our presentation contents.