PO1.106

Targeting MC4R with Setmelanotide Improves Metabolic Parameters in DIO Mice

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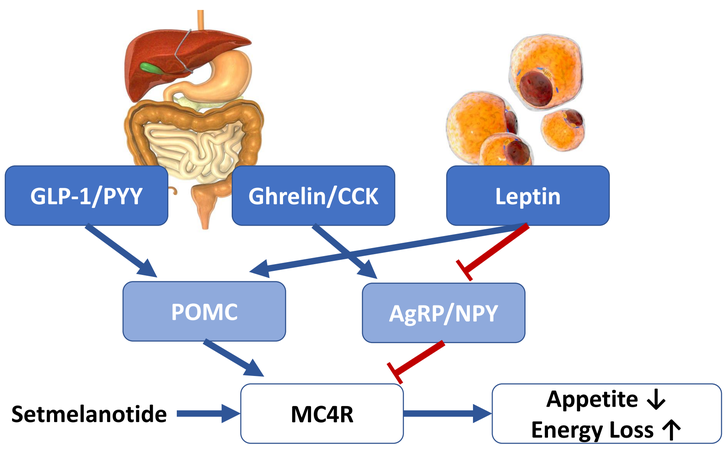
Introduction

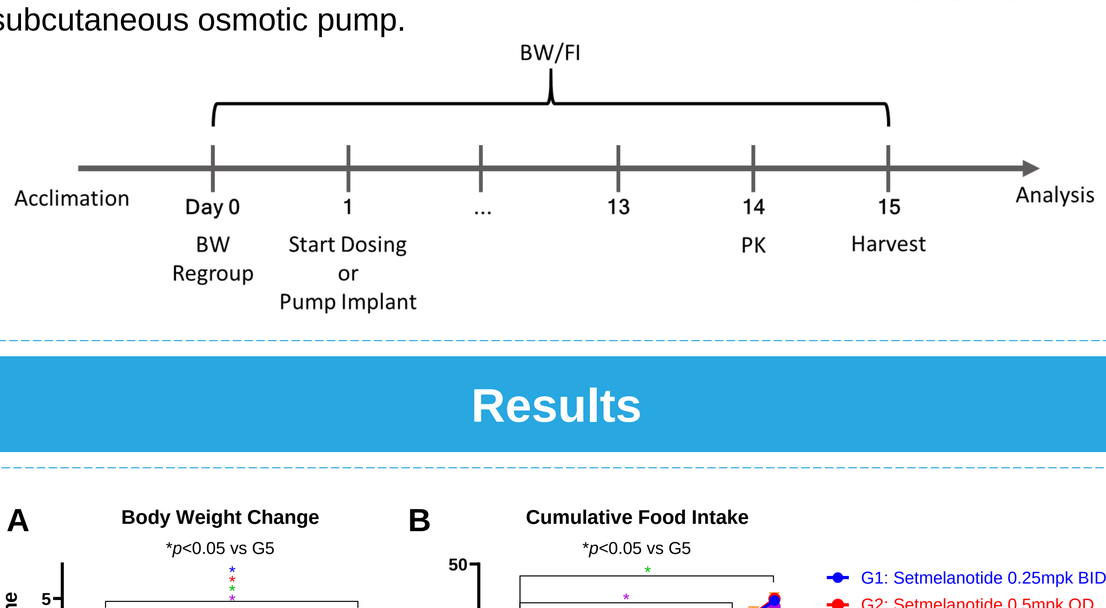
The global obesity epidemic has increased the risks of diabetes, cardiovascular diseases, cancers, and impaired health, reducing quality of life. Approximately 1-5% of severely obese patients harbor heterozygous mutations in the melanocortin-4 receptor (MC4R)[1]. MC4R can be activated by GLP-1 or leptin, and inhibited by ghrelin[2]. Targeting MC4R, which regulates appetite and energy in the brain, has become a promising approach to combating obesity.



This study aims to investigate the efficacy of setmelanotide, an MC4R agonist, in reducing body weight and improving metabolic parameters in a diet-induced obesity (DIO) mouse model using different dosing routes and dosages.

Method

Five-week-old male C57BL/6J mice were fed a high-fat diet (60% kcal, D12492) for 20 weeks to induce obesity. Afterward, they received either a vehicle or Setmelanotide at 0.25 or 5 mg/kg BID subcutaneously, 0.5 or 10 mg/kg QD subcutaneously, or continuously at 1.6, 0.4, 0.1, or 0.04 mg/kg/day via a subcutaneous osmotic pump.



Results

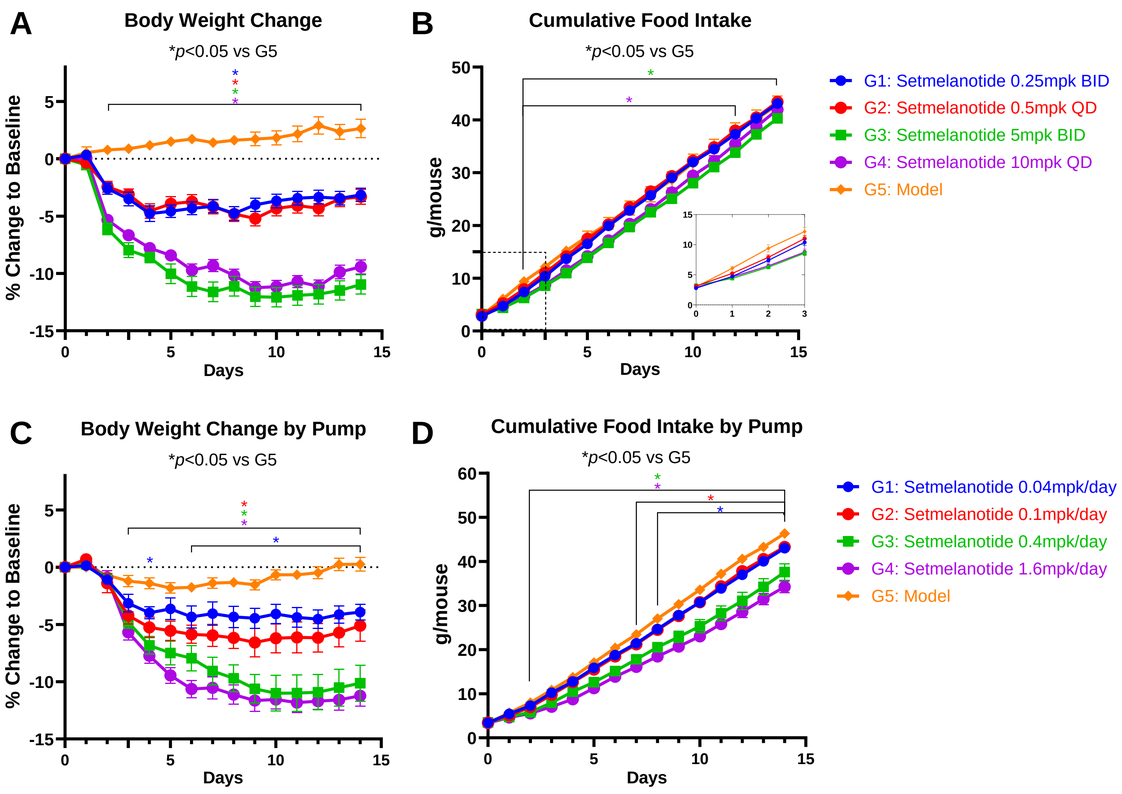


Figure 1. Body Weight Change and Cumulative Food Intake
Body weight change and cumulative food intake in DIO mice dosed with setmelanotide at (A, B) 0.25 or 5 mg/kg BID, or 0.5 or 10 mg/kg QD subcutaneously, or (C, D) continuously at 1.6, 0.4, 0.1, or 0.04 mg/kg/day via a subcutaneous osmotic pump.

Table 1. End Point Body Weight and Food Intake vs. Vehicle

End point Biomarker	0.25 mpk BID	0.5 mpk QD	5 mpk BID	10 mpk QD	Pump 0.04 mpk	Pump 0.1 mpk	Pump 0.4 mpk	Pump 1.6 mpk
Body Weight Change %	-3.16%*	-3.32%*	-10.97%*	-9.42%*	-1.36%*	-5.11%*	-10.14%*	-11.23%*
Food Intake Change %	+0.54%	+1.29%	-5.94%*	-2.09%	-7.22%*	-6.60%*	-18.83%*	-26.13%*

Setmelanotide administered QD or BID at the same daily dosage led to similar body weight loss (Figure 1A). However, setmelanotide administered via an osmotic pump resulted in significantly greater body weight loss at lower dosages (Figure 1C). Interestingly, the sustained release caused a significant reduction in food intake (Figure 1D), whereas QD or BID dosing only induced a mild decrease in food intake during the first few days after dosing (Figure 1B and the inset). For instance, 5 mg/kg BID resulted in similar body weight loss to 0.4 mg/kg/day via pump, while the latter achieved a food intake reduction three times that of 5 mg/kg BID (Table 1). These findings suggest that sustained release may improve drug efficacy and enhance the effect of appetite suppression.

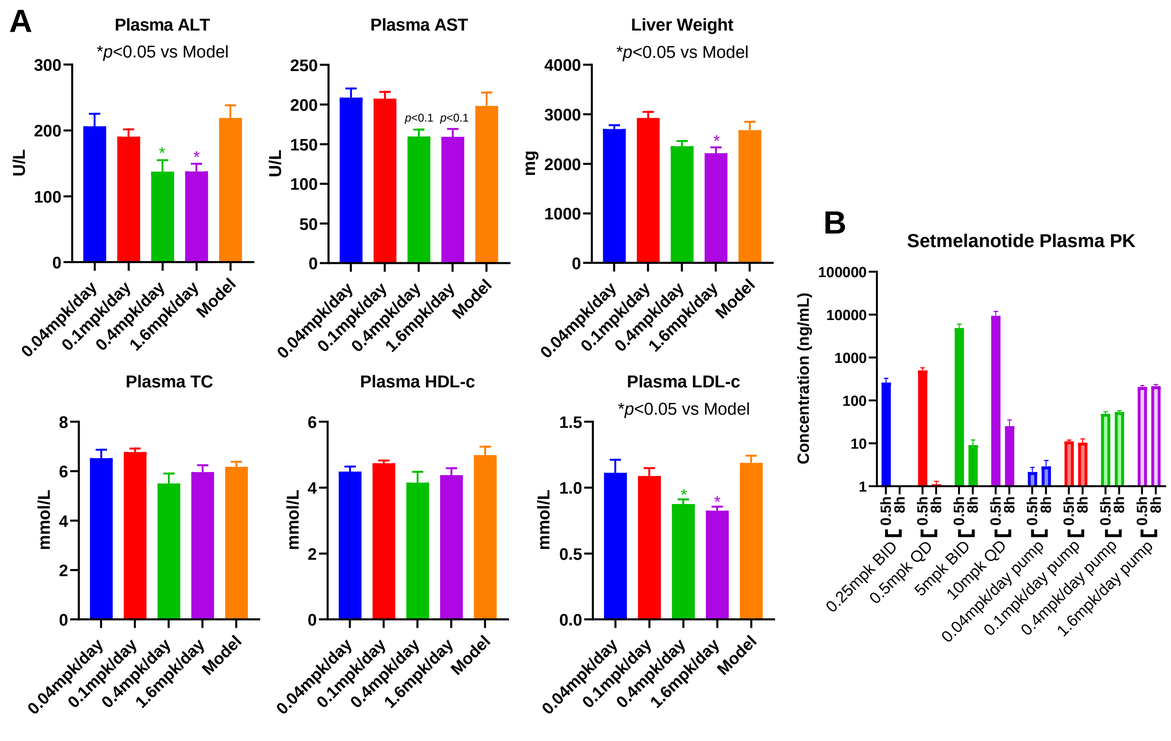


Figure 2. Plasma Biomarkers and Pharmacokinetics
(A) Biochemical analysis of plasma and liver collected after 14 days of osmotic pump treatment. (B) PK analysis of plasma samples collected at 0.5 hours and 8 hours after dosing, or at 7.5-hour intervals from pump-implanted mice.

Setmelanotide administration via osmotic pumps improved PK profiles (Figure 2B) and significantly reduced plasma ALT and LDL-c at 0.4 and 1.6 mg/kg/day (Figure 2A), indicating improvements in liver function and plasma lipid levels.

Summary

Targeting MC4R with Setmelanotide significantly reduces body weight and improves metabolic parameters in a diet-induced obesity mouse model. Setmelanotide, especially via subcutaneous infusion with an osmotic pump, effectively decreased body weight and food intake, and improved metabolic biomarkers. These findings highlight MC4R activation as a promising obesity treatment strategy.

References

1. Collet, Tinh-Hai et al. “Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency.” *Molecular metabolism* vol. 6,10 (2017): 1321-1329. doi:10.1016/j.molmet.2017.06.015
2. Chermon, Danyel, and Ruth Birk. “Predisposition of the Common MC4R rs17782313 Female Carriers to Elevated Obesity and Interaction with Eating Habits.” *Genes* vol. 14,11 1996. 25 Oct. 2023, doi:10.3390/genes14111996

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