LBP4.012 Novel FGF1 analogue M43 reduces body weight and increases metabolic activity of brown adipose tissue in Zucker Diabetic Fatty (ZDF) rats

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OBJECTIVES

The aim of the study was to evaluate the effect of 56-day long administration of M43, a novel FGF1 analogue, on body weight, food intake and brown adipose tissue (BAT) thermogenesis under obesity conditions. BAT activity modulations were assessed using thermogenesis markers gene expression and protein level analysis

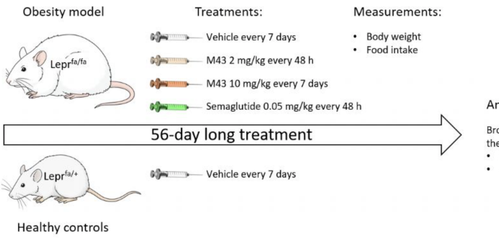
CASE

Fibroblast growth factor 1 (FGF1) is an autocrine/paracrine regulator with mitogenic activity, involved in broad spectrum of processes e.g. wound healing, anglogenesis, skeletal muscle regeneration and cardioprotection. FGF1 has also insulin-sensitizing properties, leading to decreased blood glucose level. However, due to its high affinity toward heparan sulfate proteoglycans, FGF1 region of action is highly restricted. In contrast FGF21, an endocrine peptide produced mainly by liver, has systemic effect and is also involved in glucose and lipid metabolism modulations. In rodent models of obesity FGF21 administration reduces body weight by increased energy expenditure, namely thermogenesis in BAT.

Recombinant FGF1 analogues have been developed to overcome FGF1's limited region of action and mitogenic hallmark, while retaining its beneficial metabolic effects. In the present study we investigated the effect of M43 protein, a novel FGF1 analogue (Q55P/S62I/H108G/S114A/L150D) with reduced proliferative properties and retained ability to control glucose metabolism, on body weight and BAT thermogenesis in obesity conditions.

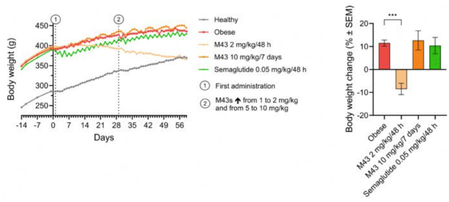
MATERIALS-METHODS

Experiment scheme



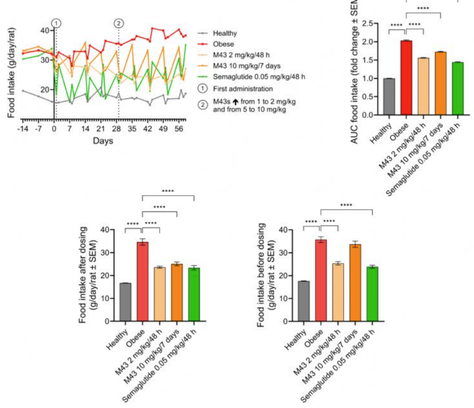
RESULTS

Body weight change



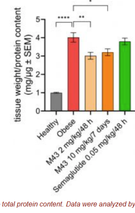
*Body weight was monitored every day and its post-administration fluctuations were noted in Semaglutide 0.05 mg/kg and M43 10 mg/kg/7 days groups. Anti-obesity effect showed only M43 administered at 2 mg/kg/48 h, at day 33 body weight was significantly lowered and by the end of experiment it was comparable to the Healthy controls. Body weight change (%) graph presents final vs. initial body weight. Data were analyzed by one-way ANOVA, followed by Dunnett's post hoc test; *** – p < 0.001 (n = 10). Error bars are omitted for clarity of body weight vs. time graph.*

Food intake



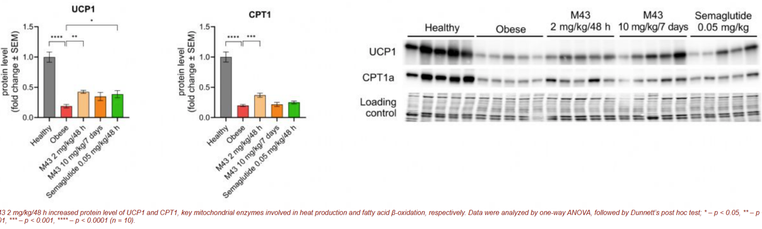
*Food intake was assessed in three twenty-four-hour periods regarding the time of administration: -24–0 h, 0–24 h and 24–48 h. Area under the curve (AUC) of food intake, demonstrating differences in total food consumption, was decreased in all drug-treated groups, especially in 24 h post-administration period. Mean food intake was assessed 0–24 h after/before dosing. Caloric restriction effect of M43 10 mg/kg/7 days was discontinued 7 days after administration (24 h before next administration). Data were analyzed by one-way ANOVA, followed by Dunnett's post hoc test; **** – p < 0.0001 (n = 10).*

BAT steatosis



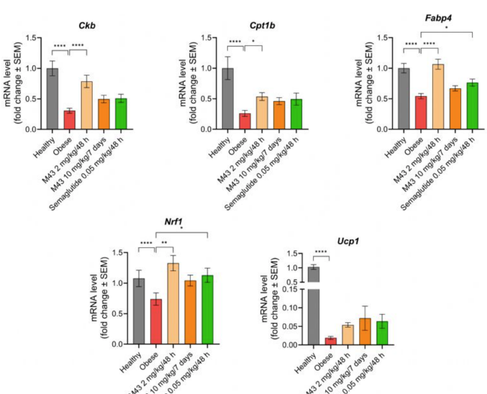
*BAT steatosis was diminished by M43 treatments, demonstrated by lower ratio of fat tissue weight to total protein content. Data were analyzed by one-way ANOVA, followed by Dunnett's post hoc test; * – p < 0.05, ** – p < 0.01, **** – p < 0.0001 (n = 10).*

Thermogenesis Western Blot analysis



*M43 2 mg/kg/48 h increased protein level of UCP1 and CPT1, key mitochondrial enzymes involved in heat production and fatty acid β-oxidation, respectively. Data were analyzed by one-way ANOVA, followed by Dunnett's post hoc test; * – p < 0.05, ** – p < 0.01, *** – p < 0.001, **** – p < 0.0001 (n = 10).*

Thermogenesis genes expression



*Real-time qPCR analysis confirmed upregulation of genes involved in BAT thermogenesis in group treated M43 2 mg/kg/48 h – Ckb, Cpt1b, Fabp4, Nrf1, however Ucp1 expression was unchanged. β-actin and Rpl32 were used as reference genes. Data were analyzed by one-way ANOVA, followed by Dunnett's post hoc test; * – p < 0.05, ** – p < 0.01, **** – p < 0.0001 (n = 10).*

CONCLUSIONS

Our results show that M43 administered 2 mg/kg every 48h exerts a robust anti-obesity effect in a rodent model through behavioral (reduced food intake) and molecular (enhanced BAT thermogenesis) mechanisms. The data suggest that M43 improves energy homeostasis by calorie restriction coupled with increased energy expenditure, making M43 a promising candidate for obesity treatment.

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