GLP-1 receptor agonists improve glycemia and lipidemia through changes in gut microbiota and the intestinal immune system.

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OBJECTIVES

Anti-diabetic drugs need to demonstrate benefits in addition to glucose control, in order to target niches of type 2 diabetic patients. To differentiate the GLP-1 receptor agonists liraglutide and exendin-4 (ex-4) from each other and to identify discriminant therapeutic features, we studied metabolic parameters, gut microbiota and the intestinal immune system in diet-induced obese (DIO) mice.

RESULTS

1. Liraglutide induces a more pronounced body weight loss as compared with exendin-4

2. Exendin-4 and liraglutide differentially alter glycemia and triglyceridemia

3. Liraglutide further inhibits intestinal cholesterol absorption and promotes cholesterol fecal excretion, as compared with exendin-4

CONCLUSION

- Ex-4 and liraglutide differentially alters gut microbiota and the intestinal adaptive immune system.
- The changes in gut microbiota improve the intestinal adaptive immune system and contribute to the amelioration of the metabolic disorders.
- The DIO mouse model, combined with in vivo phenotyping by microbiota sequencing and intestinal immune system analyses, represent useful tools to differentiate anti-diabetics and demonstrate their benefits beyond glucose control.

METHODS

DIO mice (60% high fat diet, D12492 from Research Diets) were treated i.p. with vehicle, ex-4 10µg/kg BID or liraglutide 100µg/kg QD (n=7 per group) and drug effects were evaluated after 14 days of treatment.

The intestinal immune system was studied by cell sorting analyses and the gut microbiota by 16S targeted metagenomic sequencing.

4. Exendin-4 and liraglutide differentially alter taxonomic profiling of gut microbiota

Generalized UniFrac distance based PCoA analysis of sequence data from the samples (A), LEfSe analysis of the fecal bacterial taxa correlated (red) or inversely correlated (green) with exendin-4 (B) and liraglutide (C) treatment, % of total reads for Lactobacillaceae (D), Bifidobacteriaceae (E) and Clostridiaceae (F) families detected in fecal samples from mice treated with vehicle, exendin-4 or liraglutide. **p<0.01 vs. vehicle

5. Liraglutide has an anti-inflammatory impact on the enteric immune system through a gut microbiota depending mechanism

Immune cells frequencies in the intestinal lamina propria from DIO mice (HFD), chow fed mice (NC), DIO mice treated with liraglutide (HFD Lira) or with liraglutide and antibiotic (HFD Lira Abx) by fluorescence-activated cell sorting (FACS) analysis: T helper cells (A), cytotoxic T cells (B), regulator T cells (C), T helper 17 cells (D) and T helper 1 cells (E). Data are presented as mean ± SEM. *p<0.05, HFD Lira vs. HFD.

6. Germ-free mice colonized with the microbiota from liraglutide-treated DIO mice become more glucose tolerant

Left panel: colonization of germ-free mice with the microbiota from DIO mice treated with saline or liraglutide. Right panel: glycemia during an oral glucose tolerance test in germ-free mice colonized with microbiome from DIO mice + saline (red line), DIO mice + liraglutide (green line) or chow fed mice (black line). Data are presented as mean ± SEM.