Body-weight lowering agents and their comparative metabolic and hepatic effects in obese mouse models of non-alcoholic fatty liver disease and steatohepatitis

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Introduction and Aim
The GLP-1 analogue liraglutide is an established treatment for obesity and type-2 diabetes. Here we aimed to compare the body weight lowering effects of liraglutide and the peroxisome proliferator activated receptor (PPAR) α/δ agonist, elafibranor, in diet-induced obese (DIO) and genetically obese mouse models of non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH).

Methods
Male wildtype C57BL/6J and leptin-deficient Lep-/-mice (5 weeks of age) were fed a diet high in trans-fat, fructose and cholate for a total of 26 weeks and 12 weeks, respectively, for induction of NASH. All mice were exposed to high fat chow ad libitum and were subjected to diet-induced obesity (DIO) or wildtype diet (Chow) for 8 weeks. In both models, mice were randomly assigned to the two intervention groups: vehicle (control) or one of the two drugs: elafibranor (10 mg/kg) or liraglutide (1.2 mg/kg). Diet-induced liver steatosis, inflammation, ballooning degeneration and fibrosis were evaluated by histological and biochemical analyses. Finally, a blinded histological evaluation of NAFLD Activity Score (NAS) was performed and compared to morphometric analyses of relative and total steatosis and fibrosis levels.

Study Design

The liver biopsy procedure

Figure 1

Animals were included based on a pre-study (week -1) histological assessment of steatosis stage (minimum 2) and fibrosis score (minimum 1). Animals were assigned based on NAS score 0-100 to the experimental groups and subsequently randomized to receive vehicle or one of the treatment regimens

Figure 3

Summary of histopathological scoring of the pre- and post-study biopsies for steatosis (Upper panel) and fibrosis (Lower panel) in DIO-NASH and ob/ob-NASH mice. Whereas liraglutide and elafibranor reduced steatosis score in DIO-NASH mice, only elafibranor reduced steatosis in ob/ob-NASH mice. Elafibranor also reduced fibrosis stage in both models. For each compound group, significance of number of animals with a lower score versus respective vehicle was assessed using Fisher’s exact test followed by adjustment for multiple comparison using the Bonferroni method (p<0.05). Ratings presented as mean ± SEM. 

4

Figure 2

Metabolic parameters in DIO-NASH and ob/ob-NASH animals. Liraglutide and elafibranor induced a significant body weight reduction of approximately 30% in both NASH models (upper panel). Liver weight and plasma ALT, AST and TC in both models, whereas elafibranor reduced ALT, AST and TC in ob/ob mice only (lower panel). Data presented as mean ± SEM. 

4

Figure 4

Schematic illustration demonstrating the inherent challenges in presenting relative data. A normal liver with relative fibrosis levels (left), being increased (relatively) due to fat depletion and subsequent shrinkage of total liver size (liraglutide, middle) or reduced (relatively) by liver hypertrophy due to peroxisome proliferation (elafibranor, right). The total amount of fibrosis is unchanged.

Conclusion
- Pharmacological intervention with liraglutide and elafibranor induced distinct metabolic and liver histological effects, despite having similar efficacy on body weight loss in wildtype diet-induced and genetically obese mouse models of NASH.
- Elafibranor improved steatohepatitis and fibrosis in DIO-NASH and ob/ob-NASH mice when assessed by histopathology, as well as relative steatosis and fibrosis ratios.
- Liraglutide improved hallmark of NASH in both models when incorporating effects on total liver size.
- The finding suggest that both weight-loss inducing agents have beneficial effects on hallmarks of NAFLD/NASH – but that different mechanism of action on liver size may impact conclusions drawn.