Intestinal Consequences of SNAC-Enabled Oral Semaglutide Delivery

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Oral delivery of peptide drugs is hindered by poor intestinal permeability and enzymatic degradation. Oral semaglutide (SEMA), a GLP-1 receptor agonist for obesity and type 2 diabetes, incorporates salcaprozate sodium (SNAC) as a permeation enhancer to improve bioavailability[1]. However, SNAC's impact on intestinal and metabolic health remains underexplored. This study assessed the effects of SNAC and SEMA on intestinal barrier integrity, inflammation, and gut microbiota in healthy rats. In vitro, both compounds reduced CACO-2 monolayer TEER by up to 90% within two hours, similar to the disruption caused by a potent endotoxin, lipopolysaccharide (LPS) (**Fig. 1A**). In vivo, rats treated with SNAC (22 mg/kg BW), SEMA (0.74 mg/kg BW), or both for 21 days showed significant weight loss, elevated IL-6 and TNF-α levels, increased liver weight, and reduced caecum size (**Fig. 1B, C & D**). Short-chain fatty acid (SCFA) analysis revealed decreased butyrate and acetate, indicating impaired microbial function (data not shown)[2]. 16S rRNA sequencing of fecal samples at day 21 and subsequent PICRUSt2-assisted predictive metagenomics revealed functional shifts linked to dysbiosis and a disrupted bile acid and carbohydrate metabolism (**Fig. 1E & F**). These results raise safety concerns about SNAC-enabled oral delivery, suggesting its potential to damage gut barrier function and promote systemic inflammation. Further studies are needed to identify alternative oral GLP-1 analogue delivery strategies with reduced intestinal impacts.

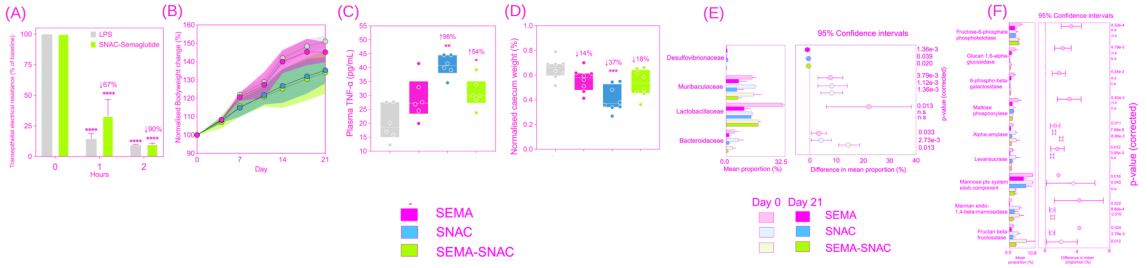

Figure 1: Summary of (A) in vitro barrier disruption, (B) rat bodyweight change, (C) systemic inflammation, (D) organ damage, and (E) gut microbiome species abundance and (F) predicted carbohydrate functional pathways derived from 16s sequenced samples.

References:

1. SELECT trial. Nat. Med. 2024, 30, 2049–2057.
2. Ariaee, A. et al. Foods 2024, 13, 1039.