disease. The present experiment modelled whether the switch from SSB to NNS beverages described above conferred positive outcomes on behavioural and metabolic measures. Thus, in Stage 1, thirty adult female rats received *ad-libitum* access to 10% sucrose solution in addition to chow and water for 4 weeks. In Stage 2, rats were switched either to 0.1% Saccharin (*Suc-Sacch*) or to Water (*Suc-Water*) or remained on 10% Sucrose (*Suc-Suc*) for a further 4 weeks. Weight gain in Stage 2 was reduced for *Suc-Sacch* and *Suc-Water* groups relative to the *Suc-Suc* group. At cull, the *Suc-Suc* group showed poorer insulin sensitivity and greater g/kg fat than *Suc-Water* and *Suc-Sacch* groups. There were no group differences in either fasting glucose or liver and plasma triglyceride content. Short-term recognition memory, assessed using the place/object task, found no group differences but poorer performance overall on the hippocampal-dependent place task, consistent with all rats' access to sucrose in Stage 1. These results show beneficial effects on weight gain, insulin resistance and adiposity after switching from Sucrose to either Saccharin or Water. Our and others' past research suggests that Stage 2 may have been too short to observe group differences on other measures.

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IL-22 therapy reverses high fat diet induced colonic epithelial cell stress and inflammation

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In Type 2 diabetes β-cell dysfunction is accompanied by adverse cellular responses to high concentration of lipids and glucose, oxidative stress, endoplasmic reticulum (ER) stress and local inflammation. Furthermore, prolonged high fat diets (HFD) induce low-grade chronic intestinal inflammation in mice, and diets high in saturated fat are a risk factor for the development of human inflammatory bowel diseases. Previously we showed that IL-22 is a natural regulator of β-cell insulin biosynthesis and secretion, protecting the β-cell from stress, preventing hypersecretion of poor quality insulin, and suppressing innate islet inflammation [1]. To further investigate extra-pancreatic effects of IL-22 we hypothesized that HFD-induced endoplasmic reticulum (ER)/oxidative stress occur in intestinal secretory goblet cells, triggering inflammatory signalling and reducing synthesis/secretion of proteins that form the protective mucus barrier.

A prolonged HFD was accompanied by an increase in circulating triglyceride levels *in-vitro* in cultured intestinal goblet cells. Non-esterified long-chain saturated fatty acids directly increased oxidative/ER stress leading to protein misfolding. We noted an increase in the intestinal inflammatory cytokine signature, alongside compromised mucosal barrier integrity, loss in the tight junction protein, claudin-1 and increased serum endotoxin levels when mice were kept on HFD for 22 weeks. Obese mice treated with IL-22, not only had an improvement in hyperglycaemia but this was accompanied by reduced ER/oxidative stress in the intestine which overall led to an improvement in the integrity of the mucosal barrier. IL-22 treatment also reversed microbial changes associated with obesity and diabetes with an increase in *Akkermansia muciniphila* and decrease in *E. coli* and *Prevotella* spp. Consistent with epidemiological studies, our experiments suggest that HFDs are likely to impair intestinal barrier function, particularly in early life, which partially involves direct effects of free fatty acids on intestinal secretory cells, and this can be reversed by IL-22 therapy.

Reference

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