Targeted Project / AY 2025 -2026

Investigating the role of sodium-coupled glucose transporter-1 in glucose interoception using a new conditional knockout mouse model

Project Reference: TRG-IMS-FR

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BBSRC DTP main strategic theme: Understanding the rules of life

BBSRC DTP secondary strategic theme: Bioscience for an integrated understanding of health

Project outline:

SGLT1 is an electrogenic sodium-coupled glucose transporter (SGLT) responsible for glucose absorption across the intestinal brush border. Enteroendocrine cells (EECs) lie scattered through the gut epithelium, and a wealth of evidence has pointed towards the concept that SGLT1-mediated glucose absorption acts as the principal EEC glucose sensor underlying gut hormone responses to glucose ingestion, based on pharmacology, electrophysiology and studies on global Sglt1 knockout mice. A number of recent studies have pointed towards a role for SGLT1 in the triggering of afferent neuronal signals including those underlying learnt sugar preference and consumption, but the cell types responsible for this SGLT1-dependence remain unknown. To address the physiology of SGLT1-mediated interoception, the Reimann/Gribble lab has recently generated a conditional Sglt1 knockout (KO) mouse, which will be available for this project and which will allow selective Cre-dependent deletion of Sglt1 in cell types of interest using a range of Cre-driver strains developed in the group.

The studentship will investigate the cellular physiology underlying SGLT1-dependent glucose sensing in the gut-brain-pancreatic axis, and its role in the context of metabolic regulation using the new floxed Sglt-KO mouse model:

1. What is the metabolic effect of Sglt1-KO in either intestinal L or K cells (secreting GLP-1 and GIP, respectively)? Sglt-flox mice will be crossed with existing Glu-Cre and Gip-Cre strains established in the laboratory, and mice with cell-specific Sglt1-KO will be examined by oral glucose tolerance testing, to assess effects on plasma GIP/GLP-1, glucose and insulin. Recovery surgery will be performed to cannulate the small intestine, allowing region-specific infusion of SGLT1 substrates, to test the importance of SGLT-dependent glucose-sensing in EECs in different regions of the gut.

2. What is the feeding phenotype (e.g. body weight on different diets, intake of high sugar vs high fat diet, learned sugar preference) of mice with Sglt1-KO in L-cells or K-cells? This will test the idea that SGLT1 in EECs is important for (a) acute and learned sugar preference and (b) satiation. Different Cre-models will be tested to address which EEC population is most critical for post-ingestive glucose sensing.

3. Does L-cell specific Sglt1-KO impair glucose sensing in vitro? Intestinal organoids or primary intestinal cultures will be examined by live cell calcium imaging and secretion assays to determine the effect on glucose responsiveness.

4. Is there a role of SGLT1 in brain glucose sensing? Targeted intra-cerebral injections AAV-Cre into Sglt1-fl/fl mice will be performed to KO Sglt1 in the hypothalamus or brainstem. Mice will be metabolically phenotyped, potentially including feeding behaviour/body weight on high sugar diet, glucose tracer fluxes (to monitor glucose disposition and hepatic glucose output), glucose-dependent insulin secretion and hypoglycaemia responsiveness.