Investigating the interactions of incretin hormone mimetics with hypothalamo-neurohypophysial system arginine vasopressin and oxytocin release

Supervisory team:
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Host institution: University of Bristol

Project description:
Our research focus over decades has been the osmoregulatory function of a special collection of neurones in a part of the brain called the hypothalamus. Magnocellular neurones (MCNs) make the peptide hormones arginine vasopressin (AVP) and oxytocin (OXT) and release them peripherally into the blood circulation from nerve terminals in the pituitary gland. Once secreted, these peptides modulate physiological parameters such as blood osmolality, blood pressure and blood glucose by acting on specific receptors in the periphery to maintain homeostasis. There is a resurgence in interest in AVP and OXT, which stem from clinical associations with body mass index, and consequently diabetes, obesity, and metabolic syndrome.

When we eat a meal the gut releases hormones, aptly grouped as gut peptides, to control the amount of food and fluid we ingest by acting on specific receptors to promote a feeling of fullness. Interestingly, MCNs express receptors for gut peptides GLP-1 and GIP at the cell body and nerve terminals in the pituitary, so potentially integrate signals from endogenous gut peptides as well as new pharmacological circuits created by incretin mimetics. There is currently a dearth of information about how gut peptides and incretin mimetics interact with receptors expressed by this crucial axis. We will use viruses to deliver genetic tools to decrease production of gut peptide receptors in rat MCNs. We will then feed these rats meals at a specific time of day (schedule-feeding) to investigate roles in feeding. We will investigate hormone release from isolated MCN tissue preparations and pituitary glands using state-of-the-art biosensor cells. We will investigate the pharmacological actions of incretin hormone mimetics on AVP and OXT release mechanisms by phosphoproteomic analysis of the pituitary gland. We will use genome-wide association study (GWAS) data derived from various tissues and cell-types to guide proteomics target identification towards clinical significance. In all animal studies we will measure food and water intake, hormone release, and alterations to cell functions, to better understand the physiological and pharmacological roles mediated by gut peptide receptors in MCNs.

Understanding MCN gut peptide receptors is essential for our knowledge of current treatments of diabetes and obesity that use stable peptide analogues in humans. This data may inform about some of the many undesired side effects of GLP-1 receptor treatments and as a result, may help with design and development of new drugs for more targeted methods of activating receptors at specific sites, and thus influence current therapeutic strategies.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.