iCase Project / AY 2023 -2024

Study of the human hypothalamic circuitry regulating appetite

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Industrial Partner: AstraZeneca

Research area: Neuronal control of food intake

Project outline:

There is a powerful heritable component that underlies the large variation in body-weight between different people, with genetic studies pointing to the brain, in particular the hypothalamus, having a crucial role in controlling appetitive behaviour. To date, our understanding of circuitry controlling food intake has emerged primarily from murine studies. A recent collaboration with the MRC brain bank network, has allowed us access to fresh and fixed human donor brain samples. This, coupled with recent developments in droplet single-cell sequencing technologies and single-molecule fluorescent in situ hybridization (smFISH), provides us with a timely opportunity to map the functional architecture of the human hypothalamus underlying appetitive behaviour.

In this studentship, we propose to study two systems; the g-protein coupled receptor GPR75, and the calcitonin-amylin system. Genetic data emerging from UK BioBank point to both GPR75 and the calcitonin receptor playing a role in human control of body-weight. Predicted heterozygous loss-of-function variants in GPR75 are found in 4 of every 10,000 individuals, with carriers, on average, having a 1.9 kg/m2 lower BMI. Mutations in CALCR, the receptor for both calcitonin and amylin, was associated with higher adiposity in humans. This is notable as amylin analogues are known to reduce body weight in rodents and humans through actions on brain–expressed CALCR. Here we propose to characterize human neurons that express GPR75 and CALCR to uncover the heterogeneity of these neurons and to map where they reside in the human hypothalamus, in order to better understand their role in the control of appetite.

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