iCase Project / AY 2023 -2024

Deciphering the molecular basis of amylin receptor-mediated satiation as an obesity treatment

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Department/Institute: Pharmacology

Industrial Partner: AstraZeneca

Research area: Receptor pharmacology and drug discovery

Project outline:

Amylin is secreted from pancreatic islet β-cells and has potent effects on gastric emptying and food intake. Pramlintide, a nonamyloidogenic analogue of human amylin is approved for the treatment of type-1 and type-2 diabetes in combination with insulin. However, amylin analogues have been shown to promote satiation leading to significant weight loss. Moreover, when co-administered with other weight losing agents (e.g. GLP-1) synergistic effects have been observed. Accordingly, there is significant interest in the development of new amylin analogues to treat obesity and co-morbidities. Amylin effects on satiation are localized to amylin receptors in the area postrema and involve the AMY3R, a heteromer of the calcitonin receptor (CTR) and receptor activity-modifying protein 3 (RAMP3).

Pharmaceutical company drug discovery programmes have previously identified novel agonistic peptides that showed both amylin peptide-like (significantly higher efficacy towards the AMY3R (RAMP3+CTR) over the CTR) and balanced dual agonist properties. These have been identified measuring peptide-induced cAMP accumulation (the AMY3R and CTR are both Gs-coupled GPCRs whose activation leads to increased intracellular cAMP). This studentship will determine the molecular determinates that govern AMY3R agonist selectivity. To achieve this, we will use a multidisciplinary approach combining in silico approaches like free energy calculations and molecular dynamic simulations, molecular pharmacology techniques (including fluorescent ligand binding, and G protein selectivity assays, and receptor isoform selectivity assays) supported by peptide synthesis and in vivo translation in models of acute food intake and obesity. Our data will provide a new rational for amylin receptor drug discovery.

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

BBSRC DTP secondary strategic theme: Understanding the rules of life