A novel target for obesity treatment?

Characterisation of an appetite-modulating neuronal population in the mouse brain

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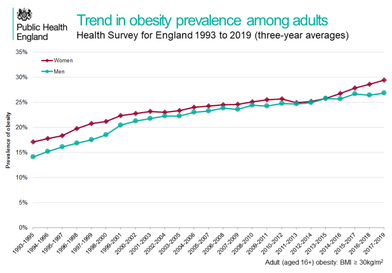
Why do we need treatments for obesity?

Obesity rates are rising in England and across the UK with serious implications for public health.



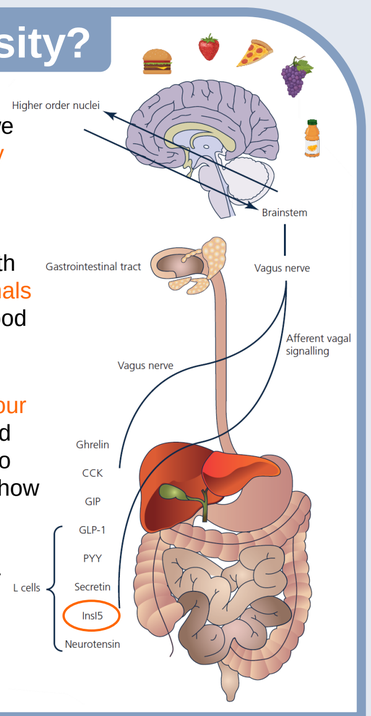
£ The wider cost to society is predicted to be **£50 billion** per year by 2050.

Obesity occurs when we consume more energy (food) than we use.

Our brains integrate environmental signals with nutrient and hormonal signals from the body to control food intake.

Hormones released from our guts act, both directly and indirectly, on our brains to determine what, when and how much we eat.

The gut hormone insulin-like peptide 5, Insl5, increases food intake in mice via the receptor RXFP4.



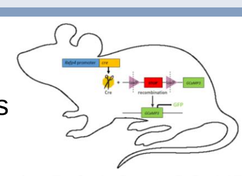
What do we want to know?

Research question: do cells that express *Rxfp4* in the brain influence food intake?

The main aims of this study were to characterise RXFP4 cells in terms of their: 1) location in the brain, 2) neural connections, 3) capacity to modulate food intake, and 4) involvement in food seeking behaviour.

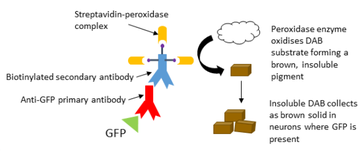
What did we do?

Reporter mouse models were created and combined with various techniques to identify and characterise RXFP4 cells in the brain.



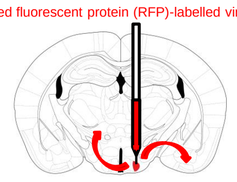
e.g. the Rxfp4-*Cre* x GCaMP3 mouse

1) Immunohistochemistry



2) Neuronal circuit mapping

Red fluorescent protein (RFP)-labelled viruses

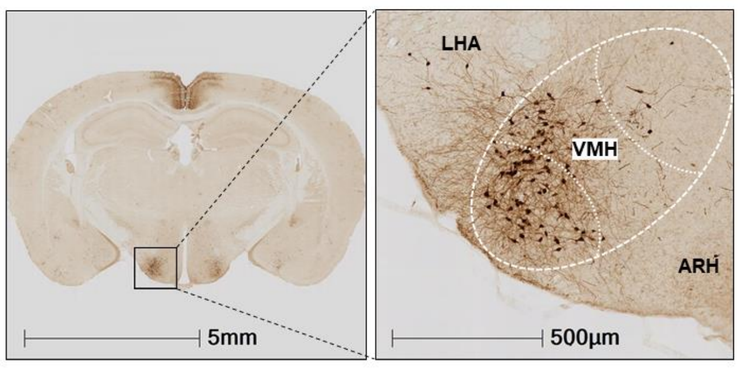


3) Food intake studies

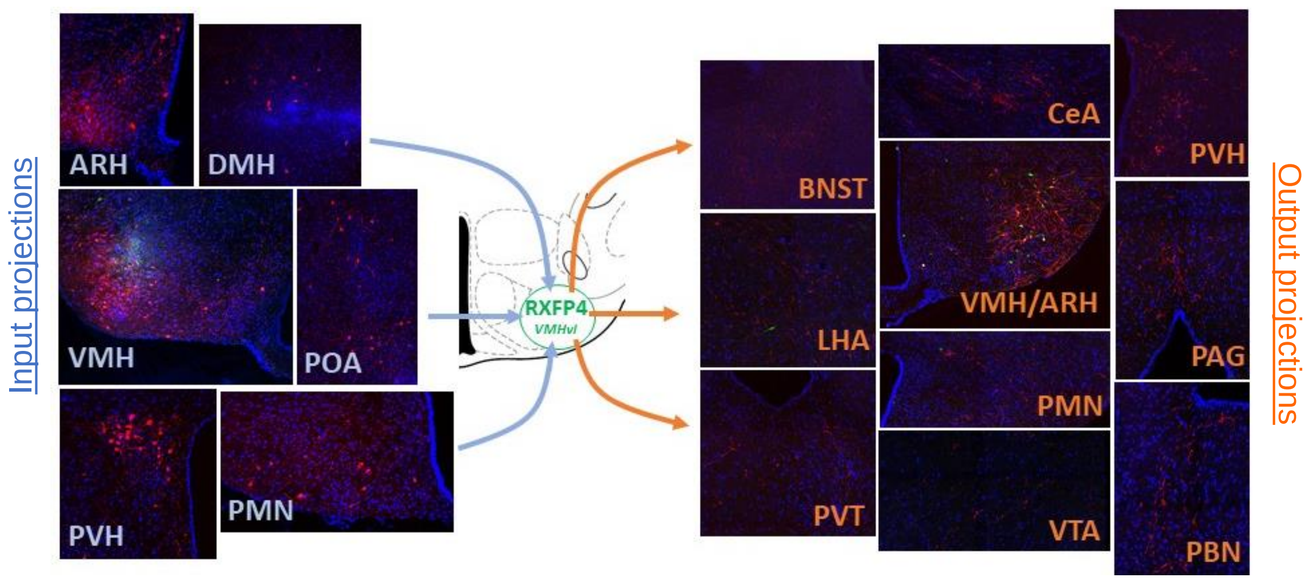
4) Operant conditioning studies

What did we find?

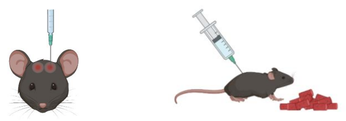
1) Neurons expressing *Rxfp4* were identified in a brain region known to regulate food intake, the ventromedial hypothalamus (VMH).



2) RXFP4 neurons in the VMH receive projections from brain regions associated with homeostatic food intake regulation and project to regions associated with reward-related food intake.



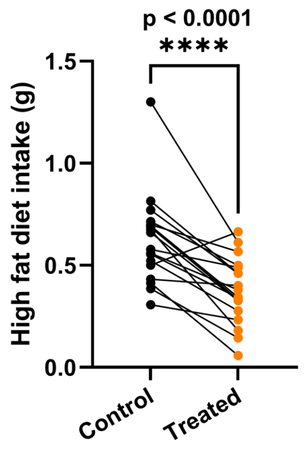
3) Activation of RXFP4 neurons in the VMH decreases intake of a high fat diet (HFD).



1. AAV-hM3Dq injected into VMH of Rxfp4-*Cre* mouse.

2. Post two-week recovery and exposure to the HFD, food is removed for 2 hours then returned and animal is injected with Veh (control) or CNO (treated).

3. Food intake recorded over 1 hour.

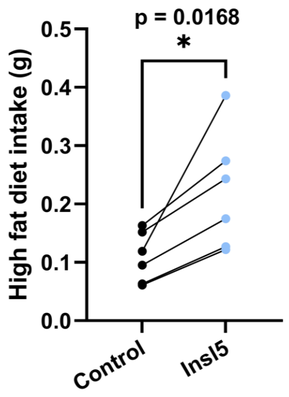


Inhibition of RXFP4 neurons in the VMH increases intake of a high fat diet (HFD).

1. Canula inserted into VMH of wildtype mouse.

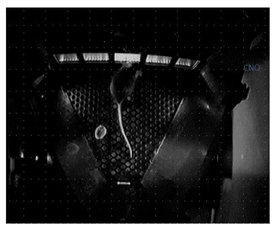
2. Post two-week recovery and exposure to the HFD, the mouse is infused with Veh (control) or Insl5.

3. Food intake recorded over 1 hour.

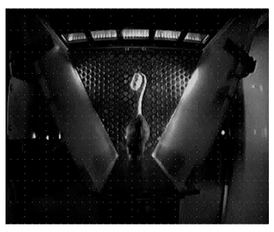


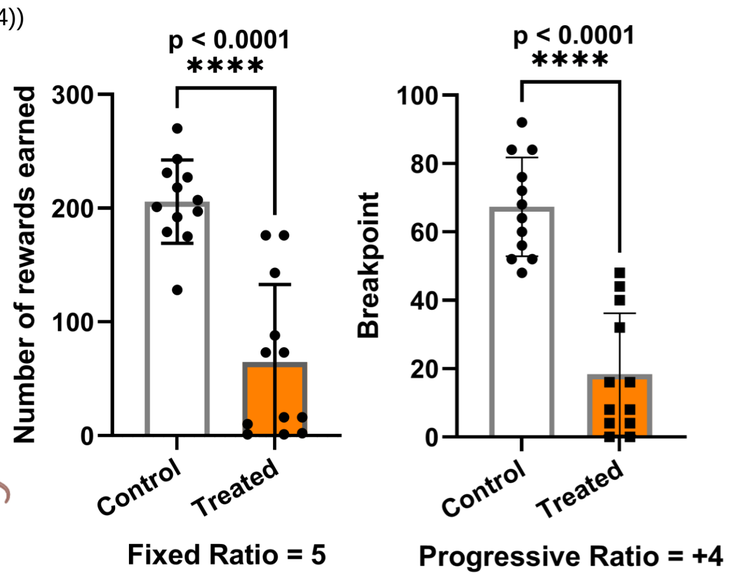
4) Activation of RXFP4 cells across the whole body decreases motivation to seek high fat, high sugar food.

1. Mouse touches screen (FR: x5 or PR: x(n+4))



2. Mouse receives food reward





Rxfp4-*Cre* x hM3Dq mice food restricted to 90% body weight were used in these studies. Mice were trained for 2 weeks then the number of rewards earned in 60 minutes following Veh or CNO injection was recorded.

Why is this research important?

Bariatric surgery is currently the only treatment for obesity that enables long term weight loss.

Drugs targeting gut hormone receptors have been shown to successfully reduce weight and improve health outcomes in patients with obesity in clinical trials.

New treatment strategies are essential if we want to improve the lives of the almost **2 million people living with obesity** in the UK.

We have identified a population of neurons expressing the gut hormone receptor RXFP4 in the VMH that modulates food intake and is a potential target for the development of obesity treatments.

Abbreviations

ARH: arcuate nucleus of the hypothalamus, BNST: bed nucleus of the stria terminalis, CeA: central amygdala, CNO: clozapine-N-oxide; DMH: dorsomedial hypothalamus, Insl5; insulin-like peptide 5; LHA: lateral hypothalamic area, LM: lateral mammillary body, MM: medial mammillary body, PAG: periaqueductal grey, PBN: parabrachial nucleus, PMN: premammillary nucleus, POA: preoptic area, PVH: paraventricular hypothalamus, PVT: paraventricular thalamus, RXFP4: relaxin/insulin-like family peptide receptor-4; SUM: supramammillary nucleus, TN: tuberal nucleus, VMH: ventromedial hypothalamus, Veh: vehicle; VTA: ventral tegmental area, 3V: third ventricle.

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