Calcium Signalling: A novel platform for screening anti-obesity therapeutics

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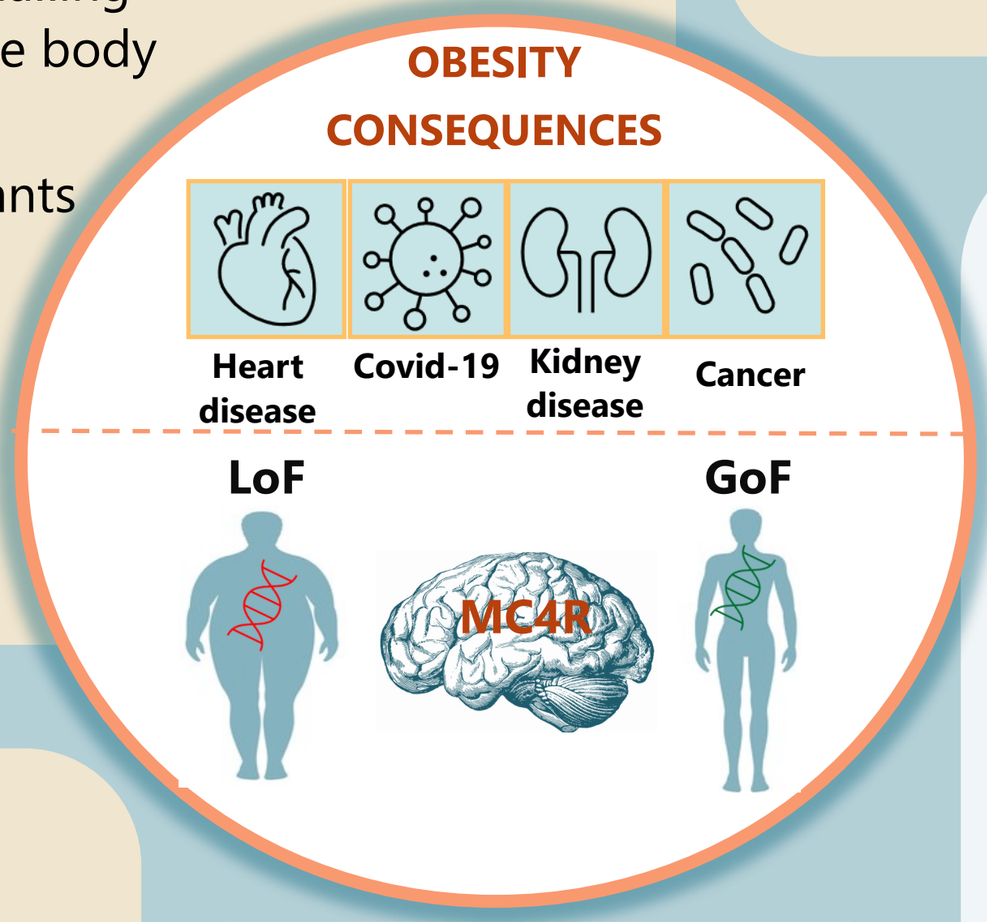
WHAT WE KNOW

- 1 in 3 people in NZ are <u>obese</u> with increasing prevalence for Māori and Pasifika.
- **Human melanocortin-4-receptor (hMC4R)** expressed in the brain is a prime target for anti-obesity therapeutics.
- Development of anti-obesity drugs is hindered because the hMC4R-signalling mechanisms that regulate body weight are unknown.
- Natural MC4R gene variants found in humans either <u>cause</u> (**Loss of function; LoF**) or <u>protect</u> (**Gain of function; GoF**) from obesity.



HOW WE DID

- HEK293 cells expressing hMC4R WT, LoF and GoF were loaded with <u>fluorescent Fura-2</u> molecule[(1)].
- Fura-2 entered the cell to bind the calcium released by MC4R.
- Fura-2 bound calcium emitted a fluorescent signal which was measured.

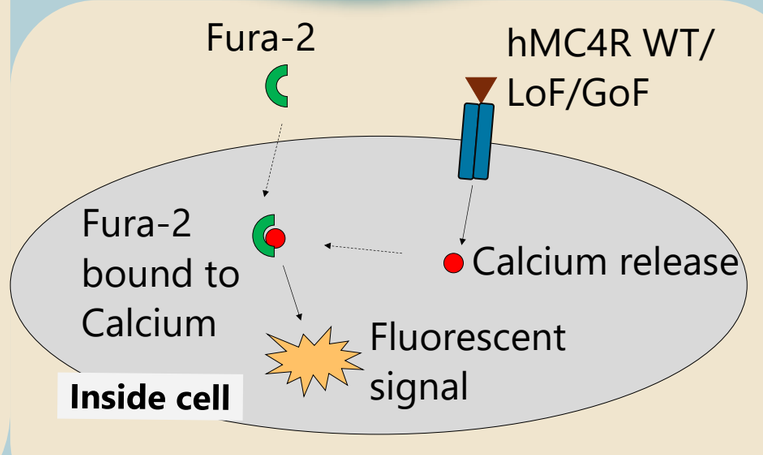


Figure 1: Fura-2 fluorescent assay

WHAT WE DID

Hypothesis: If hMC4R activated calcium signaling is required for body weight regulation, then calcium signalling will <u>differ</u> between LoF and GoF variants.

Objective: Compare the calcium signalling between hMC4R **Wildtype (WT)**, LoF and GOF variants.

RESULTS

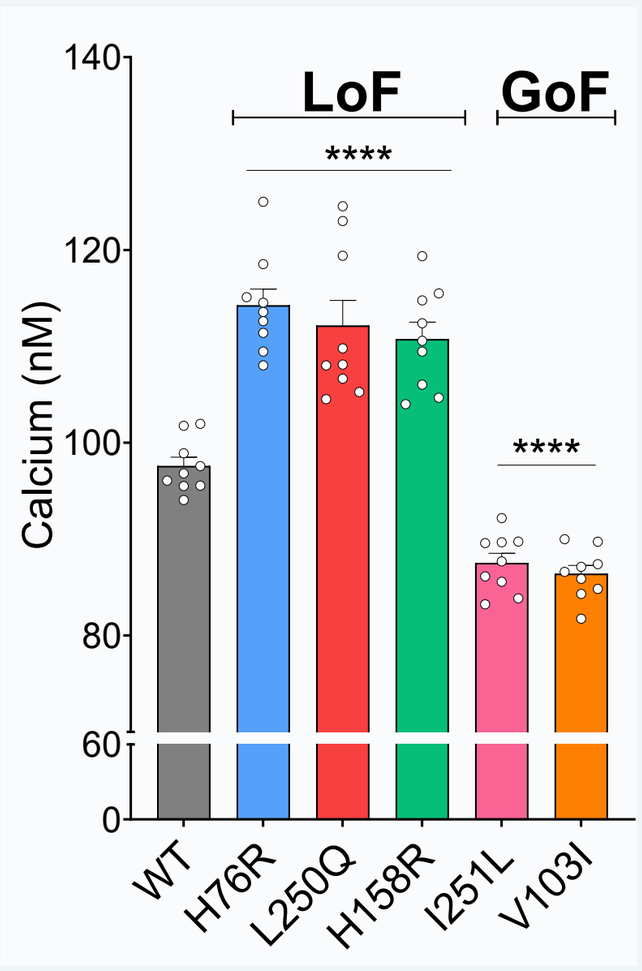


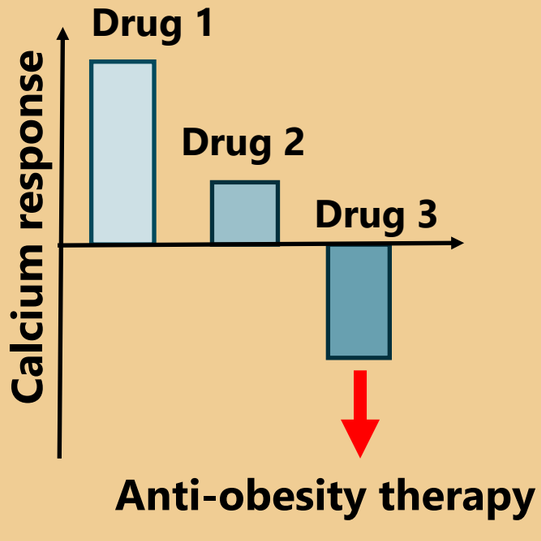
Figure 2: Calcium for wildtype and variant hMC4R. Data pooled from three independent experiments (n=9) and analysed using One-way ANOVA. ****p≤0.0001.

KEY MESSAGES

- LoF variants have increased calcium compared to WT.
- GoF variants have decreased calcium compared to WT.
- Therefore, we have confirmed our hypothesis that **hMC4R activation of calcium signalling plays a critical role in body weight regulation.**
- Manipulation of calcium signalling in animal models in the future is required to understand the effects on body weight (i.e. cause obesity or protect from obesity).

FUTURE IMPLICATIONS

MC4R DRUG SCREEN



- Unique calcium response between obesity-causing (LoF) and obesity-protecting (GoF) MC4R can be exploited to screen anti-obesity therapeutics against MC4R.
- In future drug screen, e.g. Drug 3 with reduced calcium could be explored further as an anti-obesity therapy in animal models compared to Drugs 1 and 2.
- **Rapid MC4R drug screen to narrow down drug of interest cost-effectively.**

References: 1. Kumar SS et al (2021). *J Mol Endocrinol, 66*(4), 285-297.

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