MONASH University

MONASH INNOVATION

MODULATING A HYPOTHALAMIC SWITCH TO TREAT OBESITY

A hypothalamic protein tyrosine phosphatase (PTP) 'switch', regulated by glucocorticoids, modulates insulin sensitivity and weight loss. Blocking glucocorticoid-receptor mediated expression of TCPTP or directly inhibiting TCPTP in diet-induced obesity re-sensitizes arcuate nucleus (ARC) neurons to insulin, leading to weight loss.

- **Potential target for developing centrally acting treatments to treat obesity**
- **Potential single agent and combination therapies**
- **'Proof of Mechanism' with *in vivo* efficacy for small molecule inhibitors**

THE CHALLENGE

Obesity is recognised as one of the world's fastest growing chronic conditions, costing more than $2 trillion of global health expenditure and greater than 6.5 million deaths globally each year. With the ever-increasing metabolic disease epidemic and the unsustainable treatment costs of associated co-morbidities (cancer, cardiovascular disease and stroke), there has never been a more desperate need to devise effective treatment strategies.

Stimulating white adipose tissue (WAT) browning increases energy expenditure and holds potential for combating obesity. WAT browning is regulated, in part, by insulin and leptin receptor signaling in hypothalamic neurons. Monash University researchers have previously shown that inactivating the phosphatases TCPTP and PTP1B in hypothalamic neurons increases insulin and leptin signaling, WAT browning, energy expenditure and prevents the development of diet-induced obesity.[1] This discovery raises the attractive potential of targeting these phosphatases to treat metabolic disease and obesity.

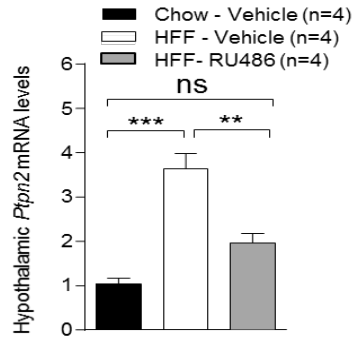

Figure 1: Central administration of the glucocorticoid antagonist RU486 attenuates high fat feeding (HFF)-induced increases in hypothalamic TCPTP expression.

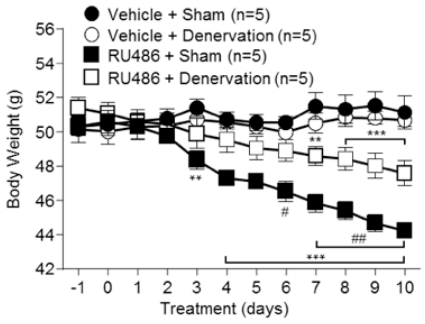

Figure 2: Central administration of the glucocorticoid antagonist RU486 reduces body weight in bi-laterally denervated (6-ODHA) obese mice by promoting WAT browning.

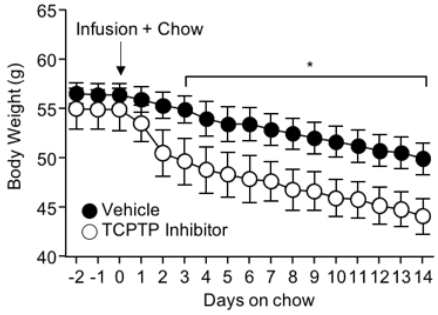

Figure 3. intraARC infusion of TCPTP inhibitor enhances diet-induced weight loss.

THE TECHNOLOGY

The Monash University research team, led by Prof. Tony Tiganis, have identified a novel hypothalamic phosphatase switch linking glucocorticoids to insulin receptor signaling.

- Hypothalamic TCPTP expression is regulated by physiological fluctuations in feeding and fasting.
- Glucocorticoids promote hypothalamic TCPTP expression in fasted mice.
- Increased TCPTP expression attenuates insulin signalling within ARC neurons, more specifically in agouti-related peptide (AgRP) neurons.
- Mice lacking TCPTP in ARC neurons are resistant to diet-induced obesity, as a consequence of enhanced WAT browning (PTP1B combined deletion has a synergistic action).
- Inhibiting TCPTP and/or PTP1B in ARC neurons may be highly efficacious in promoting weight loss in obesity and improving glucose metabolism (Figs. 1-3).

Intellectual property: A provisional patent application has been filed covering the use of target inhibitors for treating obesity.

THE OPPORTUNITY

We seek a partner to further develop novel compositions against this target. The Monash research team has extensive experience in the target, metabolic disease and obesity biology, with an array of in-house models and functional assays.

CONTACT US

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References

1. Dodd *et al*., (2015). Leptin and Insulin Act on POMC Neurons to Promote the Browning of White Fat. *Cell* 160:88-104.

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