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Potential mechanisms of skeletal muscle insulin resistance in women with PCOS: a pilot study



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Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting metabolic, reproductive and mental health. It has a prevalence of 12–21% in Australian women and is associated with increased risk of insulin resistance (IR), gestational diabetes, early onset type 2 diabetes (T2D), cardiovascular disease, stroke and obesity. IR is present in 85% of women with PCOS and is mechanistically linked to dysfunctional skeletal muscle, a major contributor to whole body glucose uptake. However, unlike in other obesity related diseases, little is known about which molecular mechanisms in skeletal muscle contribute to the aetiology of PCOS. Transforming Growth Factor (TGF β) ligand has been linked to an impaired improvement of skeletal muscle insulin sensitivity in T2D patients following an exercise intervention. Furthermore, TGF β has also been associated with increased fibrosis in reproductive tissue of women with PCOS, predisposing them to metabolic and reproductive dysfunction. In this pilot study, we have investigated the effects of TGF β and the Anti-Müllerian hormone (AMH), a novel TGF β superfamily ligand elevated in serum of women with PCOS, on cultured myotubes from 20 overweight women with PCOS and 10 lean healthy controls, as a causal factor of skeletal muscle IR in PCOS. Our preliminary data show that the treatment with TGF β and especially with high levels of AMH (30 ng/ml) on myotubes from overweight women with PCOS negatively affects insulin signalling and glucose uptake via TGF β signalling pathway compared to healthy lean controls. This suggests that these TGF β superfamily ligands may play a role in the skeletal muscle IR in PCOS. These results contribute to a better understanding of the aetiology of IR in PCOS but still further investigation is warranted to determine how these factors interact with other clinical markers.

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Expression of nutrient sensing mechanisms in the mouse stomach



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Background and aim: The ability of the gastrointestinal tract to detect nutrients is critical for the regulation of a range of physiological responses, including digestion and food intake. The detection of nutrients typically involves the interaction of a nutrient with a particular chemosensor. Limited information is available on the nutrient sensing capability of the stomach, with most of the studies primarily focusing the small intestine. Therefore, we investigated expression of nutrient sensors in the mouse stomach.

Methods: QRT-PCR was performed to investigate expression of nutrient sensors within the glandular regions (corpus and antrum)

of the stomach of 8 week old male C57BL/6 mice. Duodenal samples were included as reference tissue. Target genes included sensors for the detection of protein digestion products (GPR93, CaSR and MGLuR4), fatty acids (FFAR2, FFAR4 and CD36), the sweet and umami taste receptor subunit (T1R3), and cellular components involved in the transduction of the nutrient sensing signal (GNAT2, GNAT3 and TRPM5). Housekeeper genes were β 2-microglobulin, peptidylprolyl isomerase A and hypoxanthine guanine phosphoribosyltransferase.

Results: Within the stomach, CaSR, GPR93, FFAR2, FFAR4, T1R3, TRPM5, and GNAT3 were identified with higher mRNA expression observed in the antrum than corpus. CD36 and GNAT2 were also present, with comparable expression in the antrum and corpus. No significant differences were observed between the antrum and duodenum for GPR93, MGLuR4, FFAR4, T1R3 and TRPM5. Moreover, the expression of CaSR, FFAR2, GNAT3 and CD36 was higher in the corpus and antrum compared with the duodenum.

Conclusion: The mouse stomach expresses the genetic tools for the detection of nutrients, especially the digestion products of protein and fat. Furthermore, the level of expression is region-specific, with most targets presenting higher mRNA expression in the antrum than corpus. These gastric chemosensors may play a role in the modulation of gastrointestinal motility, digestive secretions and food intake.

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The impact of acute and chronic L-isoleucine supplementation on body weight and glucose tolerance in standard and high fat diet induced-obese mice



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Background: Dietary consumption of branched chain amino acids, including L-isoleucine, has been inversely associated with obesity in humans [1]. Acute L-isoleucine supplementation in standard laboratory diet (SLD) and high fat diet (HFD) fed rodents has been demonstrated to improve glucose tolerance, however, the effect of chronic isoleucine supplementation on glucose tolerance is unknown [2]. Therefore, we aimed to investigate the effect of chronic L-isoleucine supplementation on body weight and glucose tolerance in SLD and HFD-induced obese mice.

Methods: Male C57BL/6 mice ($n = 60$, 8wks old) housed in a 12 h light-dark cycle were allocated into 2 groups and fed either a SLD (14%kJ from fat) or a HFD (60%kJ from fat) for 17 wks. After 12 wks, mice were allocated into 3 groups/diet ($n = 10$ /group) and provided either normal drinking water (Control(C) & Acute(A)) or drinking water supplemented with 1.5% L-isoleucine (Chronic(Ch)) for the remaining 4 wks. At 17 wks, fasted mice received an oral gavage (0.1 ml/10 g body weight (BW)) of either normal water (C&Ch) or 300 mg/kg L-isoleucine (A) 30 min prior to an oral glucose tolerance test (OGTT; 1 g/kg BW).

Results: At 12 wks, HFD mice had gained more weight than SLD mice (SLD: 7.99 ± 0.34 g, HFD: 15.55 ± 1.67 g; unpaired- t -test ($P = 0.0002$). Between 13&16 wks, HFD mice gained more weight than SLD mice but there was no difference in weight gain within