Alpha-melanocyte Stimulatory Hormone (α-MSH): A Novel Player in Post-prandial Glucose Disposal in Skeletal Muscle in Humans

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BACKGROUND

- Studies in rodents demonstrate that increases in circulating pituitary-derived melanocortin receptor agonist alpha-melanocyte stimulatory hormone (α-MSH) contribute to post-prandial glycaemic control via melanocortin receptor 5 (MC5R) in skeletal muscle
- Intravenous administration of exogenous α-MSH lowers glucose excursions during oral glucose tolerance testing (OGTT) in mice.
- We set out to interrogate whether this action translated to human physiology both in vivo and in vitro. These studies represent the first time the role of α-MSH in glucose homeostasis has been investigated in humans.

METHODS

Six healthy volunteers underwent muscle biopsies of the *vastus lateralis* with myoblasts isolated from samples and used to establish primary cell lines. Melanocortin receptor profile of each cell line was assessed by qRT-PCR and glucose uptake in response to α-MSH measured by liquid scintillation counting of tritiated 2-deoxy-glucose.

In a separate randomized double-blinded cross-over study, fifteen healthy volunteers received infusions of saline, 15, 150 and 1500 ng/kg/hr α-MSH initiated 30 minutes prior to an OGTT. Plasma glucose and insulin was measured throughout. The same subjects then underwent hyperinsulinaemic-euglycaemic clamps while being infused with saline of 150 ng/kg/hr α-MSH. Peripheral glucose disposal was measured by the glucose infusion rate (GIR) needed to maintain euglycaemia.

RESULTS

Effect of α-MSH on Glucose Uptake Primary Human Myoblasts

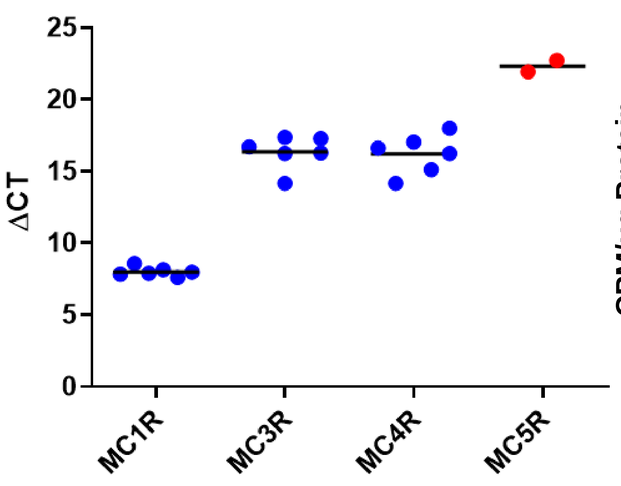

Figure 1.ΔCT values of myotube melanocortin receptor mRNA expression with GAPDH used as a reference gene. Each data point represents a discrete cell line (n=6)

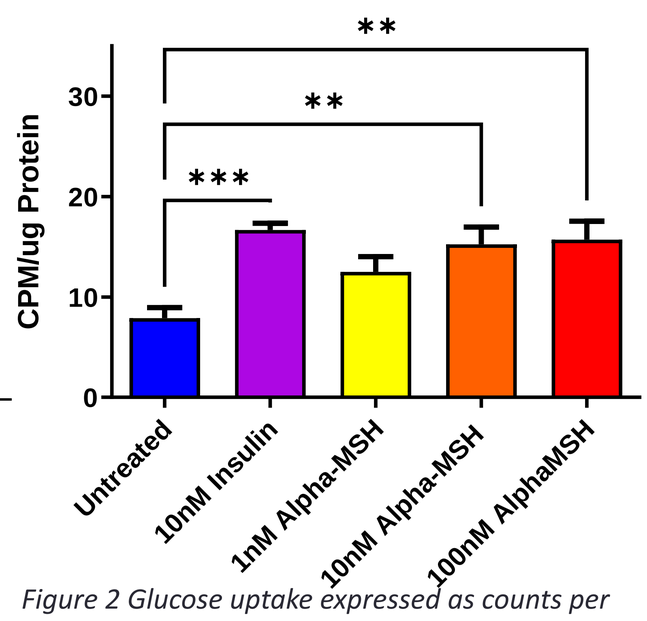

Figure 2 Glucose uptake expressed as counts per minute (CPM) of radiolabelled 2-deoxy-glucose per µg protein (n=6, one-way ANOVA p=0.01)

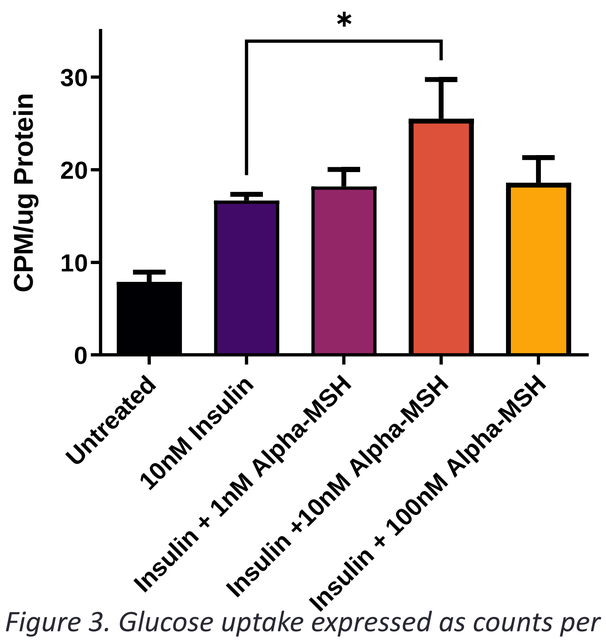

Figure 3. Glucose uptake expressed as counts per minute (CPM) of radiolabelled 2-deoxy-glucose per µg protein (n=5, one-way ANOVA p=0.005)

Differentiated human primary myotubes express melanocortin receptors 1, 3, 4 and 5 (MC1R>MC3R≈MC4R>MC5R). MC5R was only faintly detected in 2/6 established cell lines (Fig. 1)

α-MSH alone at both 10nM and 100nM increased glucose uptake by two-fold versus untreated control (Fig. 2)

Co-incubation of 10nM insulin and 10nM α-MSH significantly increased glucose uptake over insulin alone, and three-fold over untreated control (Fig. 3)

α-MSH Infusions in Healthy Volunteers

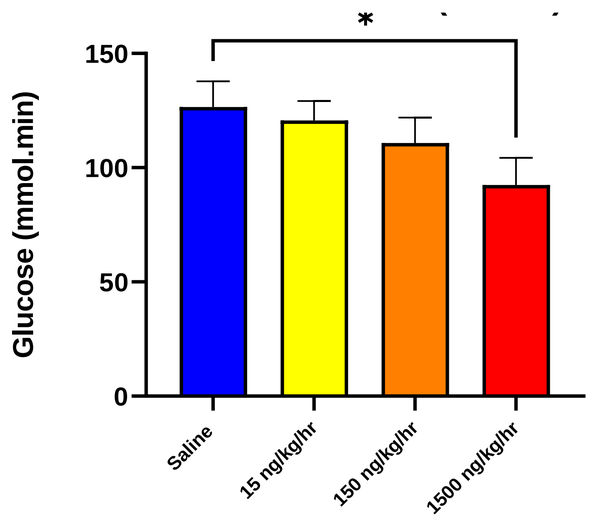

Figure 4. Baseline-adjusted area under the curve for plasma glucose during OGTTs (n=15) (one-way ANOVA p=0.02)

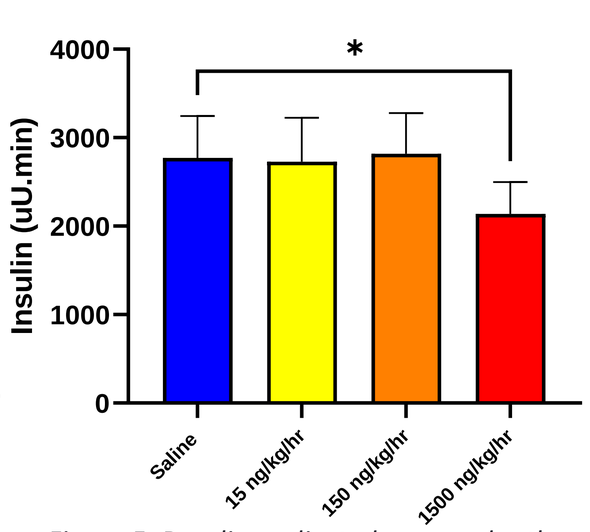

Figure 5. Baseline-adjusted area under the curve for plasma insulin during OGTTs (n=15) (one-way ANOVA p=0.006)

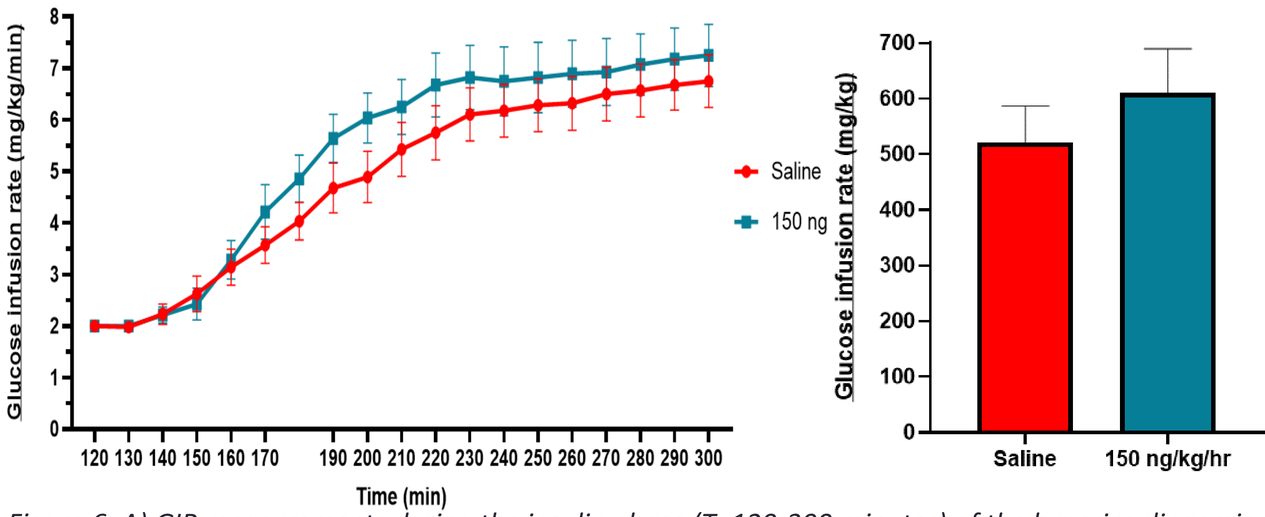

Figure 6. A) GIR measurements during the insulin phase (T=120-300 minutes) of the hyperinsulinaemic-euglycaemic clamp B) Baseline-adjusted area under the curve of GIR (n=14) (one-way ANOVA p=0.13)

Infusion of 150 ng/kg/hr α-MSH initiated 30 minutes prior to commencing OGTTs decrease both plasma glucose (Fig. 4) and insulin (Fig. 5) during the first 60 minutes compared to saline.
Continuous α-MSH infusion initiated 120 minutes prior prior to the insulin phase of the clamp (1 uU/kg/hr insulin) increases glucose requirements to maintain euglycaemia compared to saline.

CONCLUSIONS

- Primary human myotubes expressing melanocortin receptors respond to direct stimulation of α-MSH resulting in increased glucose uptake in a similar response to insulin. The scarcity of MC5R in human skeletal muscle suggests the possibility of MCR's 1, 3 or 4 being responsible.
- Co-incubating α-MSH with insulin resulted in a greater glucose uptake response than either treatment alone, pointing to an insulin independent, or sensitising, role in skeletal muscle glucose uptake.
- In healthy volunteers, infusion of α-MSH improves glucose tolerance by blunting the hyperglycaemic peak normally observed during an OGTT. A concomitant reduction in insulin levels is observed. Increased glucose disposal in peripheral tissue in response to α-MSH as seen during the clamps further support the *in vitro* data demonstrating a direct effect on skeletal muscle.
- These findings substantiate a previously undescribed role of peripherally acting α-MSH on the endocrine control of glycaemia in human physiology. Further experiments intend to elucidate the intracellular mechanism of this pathway and assess it's impact on glycaemic control in the pathophysiological states of Type I and II diabetes.