**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 alpha-melanocyte stimulatory hormone (α-MSH) contribute to post-prandial glycaemic control. Moreover, 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*

**Methods:** Using a randomized double-blinded cross-over design, fifteen healthy volunteers received infusions of physiological saline, 15, 150 and 1500 ng/kg/hr α-MSH initiated 30 minutes prior to the administration of a standard OGTT. Plasma glucose and insulin was measured during the OGTT. To assess the effect of α-MSH on glucose disposal into skeletal muscle disposal, 15 subjects underwent sequential hyperinsulinaemic-euglycaemic clamp, concomitant to either saline or 150ng/kg/hr α-MSH infusion. In a separate cohort of healthy volunteers (n=6), *vastus lateralis* muscle biopsies were obtained and used to establish cultures of primary human myotubes. Tritiated 2-deoxy-D-glucose was used to monitor glucose uptake in response to α-MSH.

**Results:** Infusion of α-MSH (1500ng/kg/hr) reduced the incremental area under the curve (iAUC) for plasma glucose (*p*=0.02), and plasma insulin (*p*=0.006) by approximately 20%. At high steady state insulin concentrations in clamp studies, α-MSH increased glucose requirements for the maintenance of euglycaemia. Primary human myotube cultures expressed melanocortin receptor subtypes (MC1R>MC3R≈MC4R) and both 10nM and 100nM α-MSH increased glucose uptake by two-fold versus vehicle (*p*=0.001).

**Conclusions:** These findings substantiate a role for peripheral α-MSH as a hitherto undescribed component of the endocrine control of glycaemia in human physiology.