Alpha-melanocyte stimulatory hormone (αMSH): A novel and potent regulator of glucose tolerance in humans.

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Abstract:
Background and aims: Intravenous administration of exogenous αMSH lowers glucose excursions during oral glucose tolerance testing (OGTT) in pre-clinical studies. We interrogate whether this action is preserved in human physiology, both in vivo and in vitro.

Materials and methods: Two cohorts, each of fifteen healthy volunteers received infusions of physiological saline, 15, 150, and 1500 ng/kg/hr αMSH initiated 30 minutes following the administration of a standard OGTT. Plasma glucose and insulin were measured during the OGTT. To assess the effect of αMSH on skeletal muscle glucose disposal, subjeqt sequential hyperinsulinaemic-euglycaemic clamp studies with saline and 150ng/kg/hr αMSH infusion. In a separate cohort of healthy volunteers (n=6), primary human skeletal muscle generated from vastus lateralis muscle biopsies and used to directly assess glucose uptake in response to αMSH.

Results: Infusion of αMSH (1500ng/kg/hr) led to a 45% reduction in the 2-hour incremental area under the curve (iAUC) for plasma glucose (p<0.001). Accordingly plasma insulin was reduced by 20% (p=0.006). In clamp studies, αMSH increased glucose requirements for the maintenance of euglycaemia. Primary human myotube melanocortin receptor subtypes (MC1R>MC3R≈MC4R). A sixty-minute incubation of myotube cultures with 10nM αMSH increased glucose uptake by two-fold versus v equipotent to the effect obtained with insulin. The glucose uptake promoting effects of insulin and α-MSH in myotubes were additive.

Conclusion: These findings substantiate a role for peripheral αMSH as a hitherto undescribed component of the endocrine control of glycaemia in human physiology. This axis offers a novel target for the development of diabetes pharmacotherapy.

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