Short-term fasting in healthy human subjects: assessment of intrahepatic lipid content, GH signaling in peripheral tissues, and impact of GH blockade

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This PhD dissertation was accepted by the faculty of health Sciences at Aarhus University, and defended on Marts 26, 2009.

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Dan Med Bull 2009;56:100

ABSTRACT

Growth hormone (GH) is not only essential for promoting longitudinal growth and somatic maturation, but is also an important regulator of substrate metabolism and body composition.

Fasting is associated with a pronounced increase in GH production and in the lipolytic responsiveness to GH. The subsequent rise in free fatty acids (FFA) contributes to the observed impairment of insulin sensitivity, which may constitute a favorable protein sparing adaptation. However, despite the increase in circulating GH the level of IGF-I declines after 2-3 days of fasting. The mechanism subserving the switch in the actions of GH from IGF-I production to augmented lipolysis has not yet been elucidated.

The PhD dissertation consists of three original papers based on two randomized clinical protocols comprising healthy young men.

The objectives of the first protocol were to investigate the impact of fasting on GH-mediated effects on substrate metabolism and insulin sensitivity, and at the same time to assess the effects of fasting on GH-stimulated signaling pathways in peripheral tissues. In addition, we aimed to study the impact of fasting on intrahepatic lipid content. The objectives of the second protocol were to investigate the impact of GH receptor (GHR) blockade on substrate metabolism, insulin sensitivity and ghrelin levels during fasting.

In the first study protocol, we found increased metabolic clearance rate and prolonged $T^{1}/_{2}$ of exogenous GH in the fasting state as compared to the postabsorptive state, in addition to elevated basal GH levels, whereas IGF-I bioactivity was reduced. The lipolytic responsiveness to GH was enhanced in the fasting state and the insulin stimulated glucose uptake was suppressed during fasting. We recorded reduced phosphorylation of signal transducers and activators of transcription (STAT5b) in skeletal muscle and fat tissue in the fasting state. Moreover, fasting was associated with a ~156% increase in intrahepatic lipid content, which correlated positively with the level of circulating ketone bodies.

In the second study, partial GHR blockade with a GH antagonist during fasting suppressed lipolysis, FFA uptake in muscle, and lipid oxidation at the whole body level. GHR blockade did not affect protein metabolism. More surprisingly, insulin stimulated glucose uptake was also not affected and basal glucose level was even enhanced during GHR blockade. The impact on glucose metabolism may be related to the observed concomitant increase in the fraction of acyl ghrelin, as acyl ghrelin previously has been reported to augment circulating basal glucose levels and to reduce peripheral insulin sensitivity.