

**Mechanisms of thrifty protein-energy metabolism cross-linked with insulin
resistance during Catch-Up Growth - *a risk factor for later obesity and
cardiometabolic diseases***

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Catch-up growth during infancy and childhood (after earlier poor growth) is a major risk factor for type 2 diabetes and cardiovascular diseases later in life. This phase of accelerated growth, which is characterized by hyperinsulinemia and a high rate of fat deposition with lean tissue lagging behind (i.e. preferential catch-up fat) has been linked to a thrifty (efficient) metabolism resulting from suppressed thermogenesis and insulin resistance in skeletal muscle.

Using a validated rat model of catch-up fat driven by suppressed thermogenesis, the primary aims of this thesis work were to investigate whether thrifty energy metabolism driving catch-up fat could reside in (i) diminished skeletal muscle protein turnover (an energy costly substrate cycle), (ii) altered local thyroid hormone metabolism in skeletal muscle, and (iii) a lower core body temperature underlying a lower energy cost for homeothermy. Another aim was also to gain insights into the mechanisms by which diets high in polyunsaturated fatty acids (PUFA) improve glucose homeostasis during catch-up fat on high fat diets.

By assessing (i) *in-vivo* rates of protein synthesis in hindlimb skeletal muscles using the stable isotope technique (ii) *ex-vivo* muscle assay of net formation of thyroid hormone tri-iodothyronine (T3) from precursor hormone, thyroxine (T4), and (iii) protein expression of muscle deiodinases (type 1, 2 and 3) using validated antibodies, evidence is presented that diminished skeletal muscle protein turnover, associated with decreased local thyroid hormone T3 availability contribute to the adaptive thermogenesis that facilitates body fat recovery during weight regain.

Using an abdominally implanted telemetry system for continuous monitoring of core body temperature (T_c), together with monitoring of locomotor activity by infrared diode system, it is shown that 24h T_c was reduced during semistarvation (-0.77°C, p<0.001), and remained significantly lower than in controls during refeeding at 22°C (-0.27°C, p<0.001); the latter persisting during refeeding at thermoneutrality (29°C), during refeeding on diets low or high in fat, and was not associated with altered locomotor activity. Thus, the reduced energy cost of homeothermy in response to caloric restriction persists during the dynamic phase of weight recovery.

Using the hyperinsulinemic-euglycemic clamp, it is shown that while refeeding on a diet high in PUFA did not impact upon insulin-stimulated glucose utilization in skeletal muscle, it did improve insulin-stimulated glucose utilization in adipose tissue, associated with enhanced *de-novo* lipogenesis. An integration of these findings, together with the known effects of PUFA on lean-fat tissue partitioning and thermogenesis in this rat model suggests that the improvement in whole-body glucose disposal during refeeding on a high PUFA diet resides in the combined effects of (i) increased lean mass and hence increased glucose buffering capacity, (ii) increased glucose flux into *de-novo* lipogenic pathways which thus acts as a glucose sink, and (iii) increased glucose oxidation to fuel thermogenesis.

This thesis work provides evidence that diminished protein turnover in skeletal muscle associated with altered thyroid hormone availability, as well as diminished energy cost of homeothermy, constitute thrifty mechanisms that operate to enhance catch-up fat. It also provides insights into the mechanisms by which diets high in PUFA alter glucose and fatty acid metabolism in insulin-sensitive organs/tissues to limit impaired glucose homeostasis during catch-up growth.

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