Abstract-ID: SHC-425

THYROID HORMONE STIMULATES BROWN FAT BCAA METABOLISM WHEN GLUCOSE UPTAKE IS IMPAIRED

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Introduction: Thermogenesis occurs in brown adipose tissue (BAT) in response to cold exposure. BAT mitochondria are stimulated primarily by sympathetic innervation and thyroid hormone (T_3). This increase in mitochondrial activity and the induction of uncoupling protein leads to heat generation. Currently, little is known about the hormonal regulation of fuel utilization by BAT during thermogenesis.
Objective: We examined glycolysis and fatty acid b-oxidation in response to hormone treatment in primary brown adipocytes and thermogenesis when glucose uitilization was impaired *in vivo*.
Methods: We employed Seahorse XF Analyzer to measure extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) to analyze glycolysis and fatty acid b-oxidation in primary brown adipocytes. We then examined the effects of T_3 on thermogenesis and metabolism when glucose uptake was impaired by employing adipose tissue-specific Rictor-KO mice (RIKO) with reduced mTORC2/Akt-mediated glucose uptake.
Results*:* We found that norepinephrine (NE) preferentially increased glycolysis whereas T_3 or T_3 + NE increased fatty acid (FA) utilization in primary brown adipocytes. Interestingly, RIKO mice had lower baseline temperature than WT mice. They also were unable to maintain body temperature during prolonged (3 days) cold exposure despite markedly increasing FA b-oxidation in BAT. Surprisingly, T_3 treatment rescued body temperature over three days in RIKO mice; however, it did not further increase in FA b-oxidation. Instead, metabolic pathway analysis of BAT revealed that T_3 activated anaplerosis of branched-chain amino acids (BCAAs) that were metabolized to Succinyl-CoA to enter the TCA cycle. The conversion of Succinyl-CoA was coupled with conversion of acetoacetate to acetoacetyl-CoA by 3-oxoacid CoA-transferase 1 (Oxct1). Interestingly, siRNA knockdown of branched-chain keto acid dehydrogenase E1 subunit alpha (Bckdha), a key enzyme in BCAA metabolism, or Oxct1 partially blocked T_3's effects on oxygen consumption rate in Rictor KD brown adipocytes. Additionally T_3 stimulated $^{13}C_5$ valine incorporation into succinate and citrate of the TCA cycle in Rictor KD cells. These unexpected findings suggested that T_3 utilized branch chain amino acids as fuel when glucose uptake was impaired in BAT. We next examined whether T_3 also activated BCAA metabolism in BAT of insulin-resistant obese mice. Remarkably, T_3 also activated this same BCAA pathway in these mice as enzymes involved in BCAA and ketone metabolism were upregulated, and C3 and C4 acylcarnitines were increased after T_3 treatment.
Conclusions: Our findings showed that T_3 activated BCAA utilization to stimulate mitochondrial respiration in BAT during different metabolic conditions in which there were glucose deprivation.