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P-034 - THE BACE1 PRODUCT SAPP&BETA; INDUCES ER STRESS AND INFLAMMATION AND IMPAIRS INSULIN SIGNALING

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Resumen

Objectives: β-secretase/β-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) is a key enzyme involved in Alzheimer's disease that has recently been implicated in insulin-independent glucose uptake in myotubes. However, it is presently unknown whether BACE1 and the product of its activity, soluble APPβ (sAPPβ), contribute to lipid-induced inflammation and insulin resistance in skeletal muscle cells.

Material and methods: Studies were conducted in mouse C2C12 myotubes, skeletal muscle from *Bace1*$^{-/-}$mice and mice treated with sAPPβ and adipose tissue and plasma from obese and type 2 diabetic patients.

Results: We show that BACE1 inhibition or knockdown attenuates palmitate-induced endoplasmic reticulum (ER) stress, inflammation, and insulin resistance and prevents the reduction in Peroxisome Proliferator-Activated Receptor g Co-activator 1alpha (PGC-1alpha) and fatty acid oxidation caused by palmitate in myotubes. The effects of palmitate on ER stress, inflammation, insulin resistance, PGC-1alpha down-regulation, and fatty acid oxidation were mimicked by soluble APPβ *in vitro*. *BACE1* expression was increased in subcutaneous adipose tissue of obese and type 2 diabetic patients and this was accompanied by a decrease in *PGC-1alpha* mRNA levels and by an increase in sAPPβ plasma levels of obese type 2 diabetic patients compared to obese non-diabetic subjects. Acute sAPPβ administration to mice reduced PGC-1alpha levels and increased inflammation in skeletal muscle and decreased insulin sensitivity.

Conclusions: Collectively, these findings indicate that the BACE1 product sAPPβ is a key determinant in ER stress, inflammation and insulin resistance in skeletal muscle and gluconeogenesis in liver.

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