An Autophagic Role in Alzheimer's Disease for Intermittent Dietary Periods of Very Low-protein, High-carbohydrate Intake

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Hypothesis:

Intermittent periods of very low-protein, high-carbohydrate dietary intake may enhance autolysosomal proteolysis in Alzheimer's disease (AD) by increasing activity of transcription factor EB (TFEB).

Background:

AD is characterized by 1) activation of neuronal autophagy with defective autolysosomal degradation,[1] and 2) neuronal insulin resistance, characterized by increased amyloid-β (Aβ) production in autophagosomes and reduced neuronal internalization of extracellular Aβ oligomers.[2]

Translocation of TFEB from cytosol to nucleus increases transcription of 291 genes and thereby induces autophagy,[3] lysosomal biogenesis, acidification, and proteolysis.[4]

Phosphorylation of TFEB by mammalian target of rapamycin complex 1 (mTORC1)[5] and by glycogen synthase kinase 3 (GSK3)[6] inhibits TFEB nuclear translocation.

GSK3 inhibition in transgenic AD mice increases acidification of lysosomes, reduces Aβ deposits, and ameliorates cognitive deficits.[7]

Why very low protein intake?

mTORC1 phosphorylation of TFEB is inhibited by amino acid starvation, even in the presence of strong insulin signaling.[8] Very low protein intake, combined with GSK3 inhibition, is therefore expected to promote TFEB nuclear translocation.

Why high carbohydrate intake?

High carbohydrate intake raises postprandial serum insulin, which inhibits GSK3[9] and presumably therefore reduces GSK3's phosphorylation of TFEB. Combined with mTORC1 inhibition, enhanced insulin signaling should thereby promote TFEB nuclear translocation.

This hypothesis awaits testing, e.g., in a transgenic AD mouse model.

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