An autophagic role in Alzheimer's disease for intermittent dietary periods of very low-protein, high-carbohydrate intake

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Occasional periods of very low-protein, high-carbohydrate dietary intake may enhance lysosomal proteolysis in Alzheimer's disease (AD) by increasing activity of transcription factor EB (TFEB) via inhibition of glycogen synthase kinase 3 (GSK3).

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

Suitable AD therapies may therefore aim to reduce neuronal insulin resistance and increase activity of TFEB, a master gene regulator of lysosomal biogenesis. Upon cellular starvation and in response to inhibition of mammalian target of rapamycin (mTOR), TFEB translocates from the cytosol to the nucleus, whereupon it increases transcription of 291 genes, including many involved in autophagy. At least 20 of these genes participate in lysosomal biogenesis, acidification, and proteolysis.

The mTOR inhibitor rapamycin apparently cannot induce lysosomal biogenesis by TFEB, as rapamycin does not blunt mTORC1's nutrient-induced phosphorylation of TFEB at Serine 142, which keeps TFEB localized in the cytosol.

But GSK3 also phosphorylates TFEB at S142, and GSK3 inhibition results in translocation of unphosphorylated TFEB into the nucleus, increasing transcription of lysosomal genes and degradation of Aβ. GSK3 inhibition in AD may further be useful because GSK3 hyperphosphorylates tau, increases Aβ production, and impairs memory.

As recent proof of concept, treatment of mice expressing mutated amyloid precursor protein (APP) and presenilin-1 (PS1) with the selective GSK3 inhibitor L803-mts increased acidification of lysosomes, reduced Aβ deposits, and ameliorated cognitive deficits.

Insulin apparently exerts opposing actions with respect to TFEB, both (a) activating mTOR and thereby decreasing TFEB nuclear localization, and (b) inhibiting GSK3 and thereby increasing TFEB nuclear localization. If the effect of insulin's mTOR-mediated decrease in nuclear localization of TFEB could be lessened, while maintaining the effect of insulin's GSK3 inhibition-mediated increase in that localization, then insulin could be harnessed to augment lysosomal biogenesis.

Settembre et al. found that the constitutive activation of growth factor (e.g., insulin) inputs to mTORC1 occurring in TSC2 -/- cells could not suppress nuclear translocation of TFEB in response to amino acid starvation. This suggests that during intermittent periods of very low dietary protein intake, elevating serum insulin concentrations to inhibit GSK3, such as by a high dietary carbohydrate intake, may promote nuclear localization of TFEB and its consequent stimulation of lysosomal transcription. In other words, during autophagy induced by amino acid deprivation, high insulin signaling may stimulate more lysosomal biogenesis than does low insulin signaling, such as in starvation.

Moreover, there is evidence suggesting that intermittent dietary protein restriction may reduce insulin resistance in the AD brain. For example, elevated amino acid levels in humans induce insulin resistance in skeletal muscle via activation of mTOR and ribosomal protein S6 kinase 1 (S6K1). And severe protein restriction both decreases insulin requirements in type 1 diabetics and decreases fasting hepatic glucose output and basal insulin levels in normal subjects.

A dietary regime of intermittent very low-protein and high-carbohydrate intake may thus be effective in preventing

and treating AD.

A study implementing this strategy in a transgenic AD mouse model is proposed.