NEURODEGENERATIVE DISEASE

Dietary restriction exacerbates Alzheimer's features in miceLazic, D et al. *Neurobiol. Dis.* **136**, 104745 (2020)

A body of evidence from animal studies indicates that food restriction (FR) by caloric restriction or intermittent feeding can delay the onset of age-related disorders and extend lifespan. Studies in animal models of Alzheimer's disease (AD) show that FR can also slow cognitive decline associated with AD, but the effects of FR on AD pathological features such as amyloid- β deposition or neuronal loss require further investigation. A team from the Institute for Biological Research "Siniša Stanković in Serbia now shows that every-other-day feeding (EOD) does not affect amyloid- β accumulation but increases inflammation and neuronal deficits in the 5XFAD mouse model of AD.

"Our results provide first in vivo demonstration that EOD has harmful effects in the cortex of 5XFAD females, in contrast to the well accepted FR-induced protective effects on neurons and synapses during aging," explain the investigators in their report. Their findings contrast with previous

studies using different mouse models of AD, such as APP/PS1 mice in which EOD increased clearance of amyloid- β from the brain. Here, the investigators used 5XFAD mice carrying five human familial AD gene mutations which recapitulate several pathological features of AD including amyloid deposition and inflammation (as early as 2 months of age), synaptic changes (from 5 months of age), and progressive neuronal death.

5XFAD mice were fed ad libitum (AL) until 2 months of age. Mice were then randomly assigned to two differentially fed groups to either receive food AL every day (AL group) or every other day (EOD group) for 4 months. Tissues were collected at 6 months of age and analyzed by histochemical staining, Western blot and ELISA. The results revealed no changes in the degree of plaque deposition between 5XFAD-AL and 5XFAD-EOD mice, but 5XFAD-EOD showed an increase in cortical

inflammation and neuronal injury, and a downregulation in synaptic plasticity-related proteins. Behavioral performances were assessed at five and a half months of age, which indicated no significant differences between 5XFAD-AL and 5XFAD-EOD mice.

"Although causal relationship between intermittent fasting and the disease progression cannot be established based on this study, the results suggest that decision of using FR in AD patients should be carefully made," conclude the investigators. Futures studies will be needed to fully understand the effects of FR on AD, and determine whether applying a different regimen (such as caloric restriction) or initiating FR before the neuroinflammation onset would influence study outcomes.

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