OBESITY

Adiposity and inflammation: a pathway to cognitive dysfunction

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Obesity is a growing problem worldwide and is associated with a range of comorbidities, such as diabetes mellitus and atherosclerosis. Several studies indicate that obesity might also alter cognition, but the mechanisms underlying this association remain unexplored. Using mouse models of diet-induced obesity and fat transplantation experiments, a group of investigators from Augusta University in Georgia demonstrates that visceral adipose tissue (VAT) impairs cognition by increasing the levels of proinflammatory cytokine IL-1 β in the brain, where it perturbs the properties of resident immune cells and their interactions with neurons. By adding to the growing evidence that excessive adipose tissue affects cognition, these findings support the development of lifestyle or surgical interventions to prevent neurological diseases.

Obesity is accompanied by chronic inflammation, which is increasingly recognized as an etiology for cardiovascular and metabolic diseases. Studies in rodents have shown that NOD-like receptor family pyrin domain-containing 3 (NLRP3), a core component of the inflammasome complex, is a culprit behind obesity-associated inflammation, as whole-body *Nlrp3*^{-/-} mice are protected against high-fat diet (HFD)-induced inflammation. NLRP3 deficiency also prevents age-related cognitive decline in mice, but the tissue-specific effects of NLRP3 induction on neuroplasticity and neuroinflammation have not yet been investigated.

“To our knowledge, the VAT transplantation studies in this report represent the first regionally selective manipulation of NLRP3 to examine tissue-specific regulation of synaptic plasticity and cognition,” explain the investigators in their report. The team performed a series of experiments in which lean mice were transplanted with VAT from wild-type (WT) or NLRP3-KO donor mice with dietary obesity. Two weeks after surgery, protein quantification revealed that mice transplanted with WT fat (TRANS_{WT}) showed increased IL-1 β levels in the

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hippocampus compared with sham mice, whereas mice transplanted with KO fat (TRANS_{KO}) had a similar IL-1 β level to that of sham mice. The mice were also submitted to a battery of behavioral tests (water maze, Y-maze, and novel object recognition tasks), which revealed that TRANS_{WT} mice but not TRANS_{KO} mice, showed memory deficits. Similar to HFD-induced obesity, these results indicate that VAT transplantation increases IL-1 β in the hippocampus and induces memory deficits, and that these effects require visceral adipose NLRP3.

Further experiments demonstrated that HFD-induced obesity and VAT transplantation activated microglia, a population of resident immune cells in the brain. Microglia also showed sensitization in response to IL-1 β , which primed the cells to amplify IL-1 β signal in the brain.

Hypothesizing that interleukin-1 receptor type 1 (IL-1R1) mediates the effects of IL-1 β on microglia, the investigators generated a mouse model in which IL-1R1 was specifically deleted in microglia. Analysis of the transgenic mice challenged with HFD or VAT transplantation confirmed that

microglial IL-1R1 mediated hippocampal IL-1 β increase, microglial activation, and learning impairments. In a previous report, the team had found that dietary obesity disrupts the organization of microglial processes around hippocampal synaptic terminals. In the present study, they showed that VAT transplantation produced similar perturbations of the microglia—synapse relationships and that these effects were IL-1R1 dependent. IL-1R1 deletion also prevented the reduction in synaptic plasticity observed in the hippocampus of mice after VAT transplantation.

Altogether, these findings identify a new pathway in which visceral adipose NLRP3 inflammasome activation affects cognition via IL-1-mediated microglial activation. This pathway might be responsible for the different associations reported between visceral adiposity and cognitive decline in human studies. These findings also support the development of lifestyle or surgical interventions to reduce body fat in order to prevent neurological diseases. Previous human studies have reported that adherence to Mediterranean diet in adults is associated with less brain atrophy, but long-term compliance to diet and exercise can be difficult to achieve. Surgical interventions such as bariatric surgery, which are performed to reduce the risk of comorbidities, have also been associated with improvements in mood and attention.

In the discussion, the investigators suggest that their study could also open new therapeutic avenues to prevent cognitive decline. “For mild to moderate obesity, surgical interventions will generate more risk than reward, even in the context of long-term vulnerability to age-related cognitive decline. However, studying brain circuits that respond to weight loss surgery could uncover novel targets for noninvasive modulation using transcranial magnetic stimulation and other emerging technologies.”

Alexandra Le Bras

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