Investigation into the Role of Astrocyte Insulin Mechanisms in the Onset of Cognitive Impairment

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Impaired glucose metabolism is a risk factor for dementia, therefore, it has been suggested that insulin signaling—a pathway involved in glucose metabolism regulation—plays a role in regulating cognitive function. Indeed, previous studies including our research have shown alterations in Insulin Receptor Substrate 1 (IRS1), a key regulatory molecule of this signaling pathway, in postmortem brains of patients with Alzheimer's disease (AD); however, the molecular mechanisms by which IRS1 contributes to the onset of AD remain unclear. Our study has revealed that IRS1 in glial cells, rather than in brain neurons, is involved in the astroglial-neuronal lactate shuttle (ANLS) and plays a crucial role in the regulation of cognitive function. Interestingly, we found that in old age, cognitive function is maintained because the function of the IRS1-related pathway is compensated for by the age-related increase and activation of its family member, IRS2. On the other hand, we found that malnutrition, particularly insufficient protein intake, further exacerbates cognitive decline caused by the functional deficiency of astroglial IRS1. Our study suggests that astroglial IRS1 is involved in the molecular basis of cognitive function regulation.