学位論文要旨（博士（理学））

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論文題名：The roles of glucose metabolism in brain aging and
neurodegenerative diseases
（邦題）：脳の老化と加齢性神経変性疾患におけるグルコース代謝の役割（英文）

本文

　Aging causes progressive declines in the functional integrity of the brain and increases the risk of age-related neurodegenerative diseases such as Alzheimer's disease (AD). The brain is high in energy-demand, and most of the ATP in neurons is supplied by glucose metabolism. Aging induces changes in both glucose availability and energy production, including declines in glucose uptake, electron transport chain activity, and aerobic glycolysis in the brain. Low glucose uptake or reduction of glucose levels in the brain is also an early event in AD. This implies that strategies aimed at increasing glucose metabolism in neurons may protect against organismal aging. By contrast, dietary restriction (DR) has been reported to have an anti-aging effect. Since DR causes circulating glucose concentrations to fall, the pro-aging effects of reductions in brain glucose metabolism and the anti-aging effects of reducing insulin-stimulated glucose uptake are apparently contradictory. To resolve this discrepancy, it is necessary to elucidate how aging affects glucose metabolism in brain neurons and how such age-related changes in neurons interact with the anti-aging effects of DR.

　In this study, I show that aged brain neurons suffer from ATP deficits, and increased neuronal glucose uptake is sufficient to ameliorate age-dependent declines in ATP. I also demonstrate that increasing neuronal glucose metabolism optimizes the anti-aging effects of energetic challenges. Finally, I demonstrate that increasing neuronal uptake of glucose protects against neurodegeneration in a *Drosophila* model of AD.

　Using a genetically encoded fluorescent ATP biosensor, I found that decreased ATP in the neurons of aged flies. The lower ATP levels were correlated with decreased glucose levels, expression of glucose transporter and glycolytic enzymes, and mitochondrial quality. The age-associated reduction in ATP concentration did not occur in brain neurons with suppressed glycolysis or enhanced glucose uptake using the expression of glucose transporter*,* suggesting these pathways contribute to reductions in ATP. I also found that enhanced glucose uptake suppressed age-dependent locomotor deficits and extended life span. Furthermore, increasing neuronal glucose uptake during DR resulted in the longest lifespans, suggesting an additive effect of enhancing glucose availability during a bioenergetic challenge on aging.

Next, I analyzed the effect of enhancement of neuronal glucose uptake in neurodegeneration by using a fly model of AD. In this model, human tau, which accumulates in the diseased brain and causes neuronal death, is expressed in the retina. This model shows tau pathology such as abnormal tau phosphorylation and age-dependent neurodegeneration. I found that increased glucose uptake in neurons alleviates tau-induced necrosis despite tau pathology. These data suggest that neurons with enhanced glucose uptake are less susceptible to tau pathology.

In summary, I found that the enhancement of glucose metabolism in neurons is a critical regulator of organismal and brain aging as well as susceptibility to neurodegenerative conditions. Further studies of molecular mechanisms will lead to the identification of novel strategies for the extension of the healthy lifespan of an organism.