論　文　要　旨
Thesis Abstract

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主論文題名　（Title）

Differential Effects of α-Tocotrienol on Oxidative Stress-Induced Tau Phosphorylation and MARKs Activation in N1E-115 Cells

内容の要旨　（Abstract）

With the rapid aging of the global population, the prevalence of Alzheimer's disease (AD) continues to increase, particularly in aging societies such as Japan, making AD a critical medical and social challenge worldwide. AD is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and neuronal degeneration; however, its precise molecular mechanisms remain incompletely understood. Among the pathological features of AD, abnormal accumulation of ß-amyloid and hyperphosphorylation of tau protein are considered central events, with tau hyperphosphorylation recognized as a hallmark of tauopathies.

Oxidative stress has been widely implicated in the onset and progression of aging-related diseases, including AD. Previous studies have reported a positive association between oxidative stress and abnormal tau phosphorylation; however, the molecular pathways linking oxidative stress to tau pathology have not been fully elucidated. Microtubule Affinity-Regulating Kinases (MARKs) are known to regulate microtubule stability, cell division, and neuronal survival, and to modulate tau–microtubule interactions. Therefore, MARKs have been proposed as potential mediators linking oxidative stress to tau hyperphosphorylation and subsequent axonal degeneration. Based on these findings, this study hypothesized that oxidative stress promotes tau phosphorylation, particularly at the Ser262 site, through activation of MARKs.

In addition, vitamin E is a naturally occurring lipid-soluble antioxidant, among which α-tocotrienol (α-T3) has attracted increasing attention due to its potent antioxidative and neuroprotective properties. Previous studies have suggested that α-T3 may exert protective effects against neuronal damage; however, its role in regulating tau phosphorylation under oxidative stress conditions remains unclear. Therefore, this study aimed to elucidate the mechanisms underlying oxidative stress-induced tau phosphorylation and to evaluate the neuroprotective effects of α-T3, with particular focus on its regulatory effects on tau multisite phosphorylation.

For this purpose, the mouse neuroblastoma cell line N1E-115 was employed as an in vitro neuronal model, allowing precise control of oxidative stress conditions and

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pharmacological interventions. Oxidative stress was induced by exposure to low concentrations of hydrogen peroxide, and tau phosphorylation, kinase activation, neurite degeneration, and cell viability were systematically analyzed.

This doctoral dissertation consists of two experimental chapters.

In Chapter 2, the expression of MARKs in N1E-115 cells was first confirmed by immunocytochemistry. Oxidative stress was then induced using hydrogen peroxide, and Western blot analysis was performed to evaluate changes in tau phosphorylation at the Ser262 site as well as phosphorylation of MARKs. The results demonstrated that oxidative stress activated MARKs and promoted tau hyperphosphorylation at Ser262, suggesting a mechanistic link between oxidative stress, MARK activation, and tau pathology.

In Chapter 3, the neuroprotective effects of α-T3 under oxidative stress conditions were investigated. Neurite degeneration and cell viability were assessed, and Western blot analyses were conducted to examine the effects of α-T3 on tau multisite phosphorylation and its potential regulatory mechanisms. The results showed that α-T3 markedly suppressed hydrogen peroxide–induced tau phosphorylation at Ser262 and exhibited a tendency to inhibit MARK activation. Furthermore, α-T3 significantly reduced tau phosphorylation at multiple sites, including Ser262, Ser404, and Thr181, while markedly improving cell viability. Although the inhibitory effect of α-T3 on MARK activation did not reach statistical significance, these findings suggest that α-T3 may suppress tau hyperphosphorylation through multiple mechanisms, including modulation of upstream kinase pathways and antioxidative effects.

Taken together, this study demonstrates that oxidative stress promotes tau hyperphosphorylation via kinase activation, including MARKs, and that α-T3 exerts a broad inhibitory effect on tau multisite phosphorylation while providing neuroprotection under oxidative stress conditions. These findings provide novel experimental evidence supporting α-T3 as a potential preventive and therapeutic candidate for Alzheimer's disease and related tauopathies.

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