Original Article

Tocotrienols reach the brain and play roles in the attenuation of body weight gain and improvement of cognitive function in high-fat diet-treated mice

Yugo Kato,[1] Hayami Uchiumi,[2] Ryo Usami,[2] Hirokatsu Takatsu,[3] Yoshinori Aoki,[4] Shuichi Yanai,[5] Shogo Endo,[5] and Koji Fukui[1,2,*]

[1]Molecular Cell Biology Laboratory, Department of Functional Control Systems, Graduate School of Engineering and Science and [2]Molecular Cell Biology Laboratory, Department of Bioscience and Engineering, College of Systems Engineering and Science, Shibaura Institute of Technology, Fukasaku 307, Minuma-ku, Saitama 337-8570, Japan
[3]Department of Medical Technology, Faculty of Health Sciences, Kyorin University, Shimorenjaku 5-4-1, Mitaka, Tokyo 181-8612, Japan
[4]Mitsubishi-Chemical Foods Corporation, Marunouchi 1-1-1, Chiyoda-ku, Tokyo 100-8251, Japan
[5]Aging Neuroscience Research Team, Tokyo Metropolitan Institute of Gerontology, Sakae-cho 35-2, Itabashi-ku, Tokyo 173-0015, Japan

(Received 19 January, 2021; Accepted 30 March, 2021)

Obesity induces severe disorders such as type 2 diabetes and cardiovascular events, and the number of people with obesity is increasing all over the world. Furthermore, it is possible that obesity increases the risk of cognitive dysfunction via the acceleration of oxidative damage. Tocotrienols, which are part of the vitamin E family, have antioxidant and anti-obesity effects. However, the effects of Tocotrienols on high-fat diet-treated mice have not been completely elucidated. In this study, we assessed changes in body weight, spatial reference memory acquisition, liver lipid droplet size, blood brain barrier-related protein expressions and antioxidative defense systems in high-fat diet-treated mice in the presence or absence of Tocotrienols. The results showed that Tocotrienols significantly inhibited body weight gain and lipid droplet synthesis. Although the amount was very small, it was confirmed that Tocotrienols surely reached the brain in the perfused brain. Treatment with Tocotrienols was tended to improve cognitive function in the control mice. However, Tocotrienols did not modulate blood brain barrier-related protein expressions or antioxidative defense systems. These results indicate that treatment with Tocotrienols could be effective for the prevention of obesity and cognitive dysfunction. Further extended research is needed to elucidate the relationship between anti-obesity and antioxidant effects of Tocotrienols, especially in the brain.

***Key Words*: vitamin E, anti-obesity effects, blood brain barrier, antioxidative defense systems, fatty liver**

Obesity is a major medical problem all over the world and causes many severe secondary diseases such as type 2 diabetes and cardiovascular disease.[1,2] Because these diseases increase medical costs and the caregiver burden, public attention is focused on obesity prevention. One possible mechanism of obesity is oxidative damage by reactive oxygen species (ROS).[3] The ROS production and the accumulation of oxidative damage associated with obesity are deeply involved in the onset of many diseases such as type 2 diabetes, cardiovascular disease, and non-alcoholic steathepatitis.[4–6] Oxidative damage in the brain has been shown to attenuate cognitive function in rodent models.[7,8] Numerous studies have reported a relationship between obesity and an increased risk of Alzheimer's disease (AD).[9,10] However, the relationship between oxidation and cognitive dysfunction in obesity has not been elucidated in detail.

Several lines of evidence have been demonstrated that natural compounds such as caffeine and ginger have strong anti-obesity effects.[11,12] We are also interested in the anti-obesity effects of natural compounds, and have therefore been focusing on tocotrienols (T3s), which are part of the vitamin E (VE) family.

VE is classified into tocopherols (TOCs) and T3s based on the presence or absence of double bonds on the phytyl side chain, respectively. There are four isoforms (α-, β-, γ-, δ-) in TOCs and T3s according to differences in the number and position of the methyl group on the chroman ring.[13] It is well known that VE exhibits strong antioxidant function both *in vivo* and *in vitro*,[14,15] and T3s have specific beneficial functions not found in TOCs. For example, T3s have neuroprotective, anti-obesity and anti-cancer effects.[16–18] However, a few contradictions were found in an anti-obesity studies on T3s.[17,19] As for the reasons for the contradictory results regarding the anti-obesity effects of T3s, we think that the experimental conditions (e.g., type of diet, compositional balance of T3s isoforms, treatment period, volume of T3s) differed between each research group. We previously reported that T3s significantly inhibited body weight gain in high-fat diet (HFD)-treated mice.[20,21] Although we recognized the anti-obesity effects of T3s, no change was seen in antioxidative enzyme activities or cognitive and motor functions using several maze apparatuses. On the other hands, other our previous study demonstrated that T3s prevented cognitive dysfunction by attenuating oxidative stress in the rat brain.[14] T3s need to cross the blood brain barrier (BBB) to exert a neuroprotective effect; however, some reports have indicated that T3s cannot cross the BBB,[14] which regulates the exchange of substances between capillary blood vessels and neurons in the brain.[22] It is well known that tight junction is a complex of BBB system, and is composed of the specific proteins such as Occludin, Claudin 5, and Junctional adhesion molecule (JAM) 1.[23–25] These tight junction-related proteins are injured by oxidative damage and during aging. As a result, neurons are more likely to be attacked by oxidative stress and other factors. However, to our knowledge, no evidence of obesity-induced oxidative damage in the brain or

*To whom correspondence should be addressed.
E-mail: koji@sic.shibaura-it.ac.jp
He received "SFRR Japan Scientific Excellence Award" in 2020 in recognition of his outstanding work.

doi: 10.3164/jcbn.21-10