Neuroprotective and Anti-Obesity Effects of Tocotrienols

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Summary Vitamin E is a natural lipophilic vitamin, and the most famous function of vitamin E is an antioxidant activity. Because we have α-tocopherol transfer protein, many vitamin E-related reports are about α-tocopherol. Recently, other vitamin E isomers, tocotrienols are focusing. Because tocotrienols have unique biological functions such as induction of apoptosis, neuroprotective and anti-obesity effects. Tocotrienols contain in annatto, palm, whole wheat and rice bran. Rice is a typical food in the East Asian countries and Japan. Recently, intake of whole rice is a popular in young women of Japan. Previously, we demonstrated that treatment with tocotrienols on the neuronal cells shows a strong antioxidant effect compared to the tocopherols. In this review, I introduce about neuroprotective and anti-obesity effects of tocotrienols. I would like to show daily intake of whole rice is very good for our health in this review.

Key Words tocotrienols, bran, neuron, anti-obesity, oxidative stress

1. Introduction of Tocotrienols

Vitamin E is a common natural lipophilic vitamin with an antioxidant activity as the most important function (1–3). Vitamin E plays a role in radical scavenger and attenuates oxidative stress from reactive oxygen species (ROS) in our living tissues. Because ROS produce constantly in our body, we cannot avoid from oxidative damage as long as we live (4). Especially, it is well known that mitochondria is a main source of ROS. Accumulation of oxidative damage accelerates senescence process (5, 6). Several severe diseases such as Alzheimer’s disease, cardiovascular disease and arteriosclerosis are deeply related to oxidative damage, and we called them “free radical diseases” (7, 8). To prevent oxidative damage, we need to take antioxidant substances chronically. In that respect, vitamin E is one best antioxidant substance. We can take easily vitamin E from natural plants, fruits and oils.

Vitamin E is classified two major forms, such as tocopherols and tocotrienols (Fig. 1). Each form includes four different isomers (α, β, γ and δ), and eight major isomers of vitamin E are existed. The major difference of chemical structure between tocopherols and tocotrienols is side chain. Tocotrienols have three unsaturated double bonds in their side chain. The highest level of vitamin E in our every organ is α-tocopherol (9). Alpha-tocopherol transfer proteins (α-TTP) exist in our body and α-tocopherol are selected (10). It has been reported that palm oil, whole wheat, annatto and rice bran and germ are containing relatively large amount of tocotrienols (11). Rice is the staple food in Japan and East Asian countries, and recently, intake of bran and whole wheat are popular as healthy foods all over the world. Tocotrienols contain relatively large volume in rice bran and germ (Fig. 2). The whole rice is a beneficial food in keep health. Recently, several kinds of evidence of biological functions of tocotrienols have been demonstrated, such as induction of apoptosis in cancer cells (12, 13), suppression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (14, 15), anti-obesity effect (16) and neuroprotection. It introduces neuroprotective and anti-obesity effects of tocotrienols in this review. We want to elucidate that chronic intake of rice germ and bran which are containing tocotrienols is a beneficial for our health and decrease risks of onset of several severe diseases.

2. Neuroprotective Effects of Tocotrienols

One famous crucial function of tocotrienols is neuroprotection. Previously, we examined that treatment with tocotrienols significantly inhibited cell death in hydrogen peroxide-treated cells in a concentration- and a time-dependent manner (17, 18). The ratio of cell survival on tocotrienols-treated samples was significantly higher than tocopherols-treated samples. Furthermore, we found that neurite and axonal degeneration have been occurred prior to induction of cell death. Treatment with tocotrienols significantly inhibited these alterations, and the protective ratio of tocotrienols were higher than that of tocopherols (4). Although, treatment with tocopherols also showed neuroprotective effect via their antioxidant function, the numbers of dendrite and neurite alteration areas such as beads formation, shrinkage and fragmentation in tocotrienols-treated cells were significantly lower than those of tocopherols-treated cells. These results indicate that antioxidant function of tocotrienols are stronger than that of tocopherols.

To clarify the mechanism of neuroprotective effect of tocotrienols, we have been studying many things. One mechanism of neuroprotective effects of tocotrienols may relate to maintenance of microtubules stabilization. It is well known that microtubules are one typical cytoskeletal protein and exist ubiquitously in...
every cell. The microtubules consist of α- and β-tubulin complexes. Treatment with a low concentration of hydrogen peroxide induced hyperphosphorylation of collapsing response mediator protein (CRMP)-2 (19). CRMP-2 is one microtubule-related protein and binds to tubulins (20). Phospho-CRMP-2 cannot bind tubulins and induces microtubule destabilization. Changes in the ratio of pCRMP-2/CRMP-2 has been reported in the early Alzheimer’s disease brains (21, 22). Protein modifications may also important event in neurite degeneration in hydrogen peroxide-treated cells. Acetylation, tyrosination and other modifications were occurred, and co-treatment with tocotrienols prevents microtubule-related protein modifications. Other mechanisms of neuroprotection of tocotrienols may relate to the autophagy (21) and maintenance of calcium homeostasis (23). Mitochondria have accumulated at the neurite beading regions. However, the relationship between microtubule destabilization and accumulation of oxidative damage has not yet elucidated and further investigation is to need. Sen et al. reported that α-tocotrienol is a low affinity against α-TTP compared to α-tocopherol (24). However, they explained very low volume of α-tocotrienol can reach brain through the blood brain barrier and plays a role in neuroprotective effect. Previously, we also detected α- and γ-tocotrienol in the mice brains by high-performance liquid chromatography with an electrochemical detection. However, the levels of both tocotrienols were very low compared to the tocopherols. The levels of tight junction-related proteins such as junctional adhesion molecule (jam)-1, occludin, and claudin-5 were low in normal aged mice and rats compared to the normal young animals. These results indicate that accumulation of oxidative damage during aging may attenuate blood brain barrier and can enter tocotrienols easily compared to the young controls. Resulting in, tocotrienols play neuroprotective effects in brains.

3. Anti-obesity Effect of Tocotrienols

The second famous function of tocotrienols is anti-obesity effect. The ratio of obesity is gradually increasing in the developed and the East Asian countries. Specifically, childhood obesity has been a severe problem in these countries. Intake of tocotrienols inhibits obesity. There are some reports the relationship between obesity and tocotrienols in rodents and human studies.

Zhao et al. reported that treatment with γ-tocotrienol for 4 wk attenuates high-fat diet-induced obesity, insulin resistance and inflammatory cytokines productions in C57BL/6 mice (16). Wong et al. reported the relationship between obesity-induced inflammatory cytokines productions and tocotrienols in high-carbohydrate high-fat (HCHF) diet-treated Wistar rats (25). They reported possibilities that treatment with tocotrienols attenuates the risks of onset of obesity-induced severe diseases such as diabetes, high blood pressure and hyperlipidemia. Furthermore, treatment with tocotrienols improved HCHF diet-induced osteoporosis. They have pointed out that the mechanism of anti-obesity effect of tocotrienols depends on leptin and adiponectin levels. Allen et al. reported that co-treatment with high-fat diet (HFD) (58% fat) and annatto-derived δ-tocotrienol decreased adiposity and insulin resistance, but not decrease weight volume in C57BL/6 mice (26). In our experiments showed that treatment with tocotrienols for 2 mo inhibited weight volume gain in HFD-treated mice (27).

However, these reports differed experimental condition, respectively. Because vitamin E, especially α-tocopherol contains in many natural plants or foods, it does not become vitamin E deficiency condition in our normal life. Some reports used annatto-derived tocotrienols in animal studies. They mixed annatto-derived tocotrienols with vitamin E-deficient diet. It cannot judge the biological effect of tocotrienols. Annatto-derived tocotrienols does not tocopherols and the ratio of δ-tocotrienol is very high. However, palm-derived vitamin E extracts contain not only tocotrienols but also tocopherols. Purification levels of palm-derived tocotrienols also different each experiment. There are some wheal-derived vitamin E in the normal or HFD pellets on the animal studies. The difference of staple food such as rice and bread, and intake volume of oil such as olive, rice, sesame and corn are also important problems in human studies. It is very difficult for us to clarify the anti-obesity effect of tocotrienols. For that reasons, it is very difficult to clarify the anti-obesity-effect of tocotrienols in animal and human studies. We need to focus on each experimental condition, deeply.

4. Conclusion

Tocotrienols are contained by rice germ bran, and
have a beneficial biological function for our health such as neuroprotective and anti-obesity effects. Rice germ and bran are relatively easy to intake in normal life. It is no doubtful that chronic intake of whole rice is beneficial for our health.

Disclosure of State of COI

The authors confirm that there are no conflicts of interest.

Animal ethics

All animal experiments in this review were performed with the approval of the Animal Protection and Ethics Committee of the Shibaura Institute of Technology (Tokyo, Japan) (Approval number is 18002).

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