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Original Contribution

α-Tocopherol suppresses lipid peroxidation and behavioral and cognitive impairments in the Ts65Dn mouse model of Down syndrome

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ABSTRACT

It is widely accepted that oxidative stress is involved in the pathogenesis of Down syndrome, but the effectiveness of antioxidant treatment remains inconclusive. We tested whether chronic administration of α-tocopherol ameliorates the cognitive deficits exhibited by Ts65Dn mice, a mouse model of Down syndrome. α-Tocopherol was administered to pregnant Ts65Dn females, from the day of conception throughout the pregnancy, and to pups over their entire lifetime, from birth to the end of the behavioral testing period. Cognitive deficits were confirmed for Ts65Dn mice fed a control diet, revealing reduced anxiety or regardlessness in the elevated-plus maze task test and spatial learning deficits in the Morris water maze test. However, supplementation with α-tocopherol attenuated both cognitive impairments. In addition, we found that levels of 8-iso-prostaglandin $F_{2\alpha}$ in brain tissue and hydroxyoctadecadienoic acid and 7-hydroxycholesterol in the plasma of Ts65Dn mice were higher than those of control mice. Supplementation with α-tocopherol decreased levels of lipid peroxidation products in Ts65Dn mice. Furthermore, we found out that α-tocopherol improved hypocellularity in the hippocampal dentate gyrus of Ts65Dn mice. These results imply that α-tocopherol supplementation from an early stage may be an effective treatment for the cognitive deficits associated with Down syndrome.

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Down syndrome is caused by a chromosomal aberration involving total or partial trisomy of chromosome 21 in humans. Down syndrome is considered to be the most common genetic cause of mental retardation. Mental retardation associated with Down syndrome is accompanied by learning and memory deficits, a high rate of repetitive behaviors, and impairments in adaptive behavior [1–3]. There is a high incidence of hyperactivity in children with Down syndrome, with accompanying attention deficits [4].

Ts65Dn mice are the most widely used animal model of Down syndrome. Ts65Dn mice carry a segmental trisomy of mouse chromosome 16 [5]. Many of the genes in human chromosome 21 are conserved in mouse chromosome 16. Although these mice do not present all the features associated with Down syndrome (such as congenital heart defects), they display many Down syndrome-like features, including significant performance deficits in specific behavioral tasks [6,7], motor dysfunction [8], craniofacial dysmorphogenesis [9], and age-related loss of cholinergic markers in the basal forebrain [10].

The brain abnormalities observed in Down syndrome have been linked to an inherent oxidative stress. Busciglio and Yankner reported that neurons of Down syndrome patients exhibited a three- to fourfold increase in intracellular reactive oxygen species (ROS)[1] and elevated levels of lipid peroxidation [11]. It has been suggested that one source of ROS in Down syndrome patients is the excessive production of hydrogen peroxide (H_2O_2) through the action of Cu, Zn superoxide dismutase (Cu,Zn-SOD) [12]. As a result of the overexpression of Cu,Zn-SOD in Down syndrome patients, there may be an imbalance between Cu,Zn-SOD and other antioxidant enzymes, such as catalase and glutathione peroxidase, which may induce oxidative damage. Some controlled clinical trials of various doses and combinations of antioxidant vitamins, including α-tocopherol, and mineral supplements given for 3 to 8 months have been conducted in children and young people with Down syndrome [13–18]. However, none of these trials have shown any significant effect of antioxidants on cognitive function. Several studies have reported that oxidative stress plays an important role in the pathology of Down syndrome, but there is currently no clear clinical evidence that antioxidant supplementation is an effective treatment for Down syndrome. On the

Abbreviations: ESI, electrospray ionization; GC–MS, gas chromatography–MS; HODE, hydroxyoctadecadienoic acid; IS, internal standard; 8-iso-$PGF_{2\alpha}$, 8-iso-prostaglandin $F_{2\alpha}$; LC–MS/MS, liquid chromatography–tandem MS; MS, mass spectrometry; 2*N*, control mice (diploid); 7-OHCh, 7-hydroxycholesterol; ROS, reactive oxygen species; tCh, total cholesterol; t18:2, total linoleic acid; DG, dentate gyrus; CA, cornu ammonis.

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other hand, Perrone et al. reported that the concentration of isoprostanes (a marker for lipid peroxidation) in the amniotic fluid of mothers who were pregnant with Down syndrome fetuses was ninefold greater than in pregnancies involving normal fetuses [19]. These results suggest that oxidative stress occurs early in pregnancy and support the idea that prenatal antioxidant therapy may prevent or delay the onset of oxidative stress in Down syndrome.

This study was designed to test whether chronic administration of α-tocopherol, the most biologically active form of vitamin E, could reverse the cognitive deficit found in Ts65Dn mice. α-Tocopherol was administered to pregnant Ts65Dn females from the day of conception throughout the pregnancy and to Ts65Dn and control pups over their entire life, from birth until the end of the behavioral testing period.

Materials and methods

Animals

All mice were a result of crossing B6EiC3Sn a/A-Ts(17<16>)65Dn (Ts65Dn) females (originally obtained from The Jackson Laboratory, Bar Harbor, ME, USA) to C57BL/6JEi × C3H/HeSnJ (B6EiC3Sn) F1 males (The Jackson Laboratory). Control mice (2*N*, diploid) for this experiment were normosomic littermates of the Ts65Dn mice with the same genetic background (B6EiC3Sn). Animals from the same litter were group-housed and maintained on a 12-h/12-h light/dark schedule. All mice were chromosomally genotyped. Because C3H/HeSnJ mice carry a recessive mutation producing retinal degeneration, all mice were preexamined by individual ophthalmoscopy, and only mice without signs of retinal disorder were used.

For the study of the effects of α-tocopherol treatment on Ts65Dn mice and 2*N* mice, female Ts65Dn mice were administered a controlled diet (0.002% (w/w) α-tocopherol acetate per kilogram of diet; Funabashi Farm, Chiba, Japan) or an α-tocopherol-supplemented diet (0.1% (w/w) α-tocopherol acetate per kilogram of diet) during the entire pregnancy and lactation period. The newborn mice were administered the same diet from the day of birth for 12 weeks (until the end of the behavioral characterization period). Mice were divided into four groups depending on the genotype and type of diet. Ten-week-old male 2*N* mice (controlled diet $n = 13$, α-tocopherol-supplemented diet $n = 16$) and male Ts65Dn mice (controlled diet $n = 12$, α-tocopherol-supplemented diet $n = 9$) were tested on the Morris water maze test and elevated-plus maze task. The experimental protocols were approved by the Institutional Animal Care and Use Committee of the National Institute of Advanced Industrial Science and Technology.

Materials

8-Iso-$PGF_{2\alpha}$, 8-iso-prostaglandin $F_{2\alpha}$-d4 (8-iso-$PGF_{2\alpha}$-d4), 13-hydroxy-9*Z*,11*E*-octadecadienoic acid (13-(*Z*,*E*)-HODE), 9-hydroxy-10*E*,12*Z*-octadecadienoic acid (9-(*E*,*Z*)-HODE), and 13*S*-hydroxy-10*E*,12*Z*-octadecadienoic-9,10,12,13-d4 acid (13-HODE-d4) were obtained from Cayman Chemical (Ann Arbor, MI, USA). 9-Hydroxy-10*E*,12*E*-octadecadienoic acid (9-(*E*,*E*)-HODE), 13-hydroxy-9*E*,11*E*-octadecadienoic acid (13-(*E*,*E*)-HODE), 10-hydroxy-8*E*,12*Z*-octadecadienoic acid (10-(*Z*,*E*)-HODE), and 12-hydroxy-9*Z*,13*E*-octadecadienoic acid (12-(*Z*,*E*)-HODE) were obtained from Larodan Fine Chemicals (Malmö, Sweden). 7α-Hydroxycholesterol (7α-OHCh) and 7β-hydroxycholesterol (7β-OHCh) were obtained from Steraloids (Newport, RI, USA), and their isotopes 7α-hydroxycholesterol-25,26,26,26,27,27,27-d7 (7α-OHCh-d7) and 7β-hydroxycholesterol-25,26,26,26,27,27,27-d7 (7β-OHCh-d7) were obtained from Medical Isotopes (Pelham, NH, USA). The standard for α-tocopherol was kindly supplied by Eisai Co., Ltd. (Tokyo, Japan). The standard for α-tocopherylquinone was prepared by oxidation of α-tocopherol with copper sulfate and the standard for α-tocopheryl hydroquinone was prepared by the reduction of α-tocopherylquinone with sodium borohydride. Other materials were of the highest grade available commercially.

Elevated-plus maze

The elevated-plus maze consisted of two opposing closed arms (10 × 50 cm, with 40-cm-high wall) and two opposing open arms (10 × 50 cm) extending from a common central region (10 × 10 cm) to form a "plus" shape. The arms were elevated 50 cm from the floor. In a single 5-min trial, a mouse was placed in the center of the maze, and the time spent in the open and closed arms was recorded. The number of entries to the open arms and the time spent in these arms are considered exploratory behaviors negatively correlated with anxiety. Data collection was automated by a computerized video tracking system, CompACT VAS (Muromachi Kikai, Tokyo, Japan). The open-arm ratio was calculated as shown below:

$$\text{open arm ratio} = (\text{time in the open arm}) / [(\text{time in the open arm}) + (\text{time in the closed arm})].$$

Morris water maze

Spatial learning was assessed using the hidden platform task of the Morris water maze [20] adapted for mice. The Morris water maze consists of a circular swim tank (150 cm in diameter and 20 cm deep) filled with water (22 °C). A small circular platform (10 cm in diameter) is placed into the tank in one of the four quadrants. The top of the platform was 1 cm below the surface of the water. Each mouse was allowed to swim for a maximum of 60 s and the time required to reach the platform (escape latency) was recorded in each trial. In total, this task consisted of four trials per day over 5 days. Data collection was automated by a computerized video tracking system, CompACT-VAS (Muromachi Kikai).

Spontaneous motor activity

Spontaneous motor activity was measured using the Supermex activity-monitoring system (Muromachi Kikai), as described previously [21]. A sensor box was mounted in the center of the ceiling of a sound-attenuating chamber (45 × 50 × 45 cm, internal width × depth × height). Mice were placed individually in a transparent plastic home cage (24 × 30 × 18 cm, width × depth × height) located in a sound-attenuating chamber illuminated according to a 12-h/12-h light/dark cycle (light from 07:00 to 19:00). The sensor detects any object with a temperature >5 °C higher than the background, such as a mouse. The signals were converted to the number of movements registered and analyzed using Compact AMS software (Muromachi Kikai).

Plasma, cortex, and hippocampus sample processing

One week after all tasks were finished, the mice were anesthetized with pentobarbital and blood samples were taken from the abdominal aorta and collected in heparin-containing tubes. The samples were placed on ice immediately after collection. Plasma was obtained by centrifugation at 830 *g* for 5 min at 4 °C and immediately subjected to analysis. After the mice had been perfused transcardially with saline the cortex and hippocampus were carefully dissected from the brain and homogenized with saline (cortex or hippocampus/saline 1/3, w/w). The plasma, cortex, and hippocampus samples were processed for analysis by a reduction and saponification using a previously reported method [22]. The plasma, cortex, and hippocampus (100 μl) were mixed with 400 μl of saline. Subsequently, 500 μl of methanol containing internal standards (ISs), 8-iso-$PGF_{2\alpha}$-d4 (50 ng), 13-

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