Cytoprotective effects of vitamin E homologues against glutamate-induced cell death in immature primary cortical neuron cultures: Tocopherols and tocotrienols exert similar effects by antioxidant function. Y. Saito, K. Nishio, Y. O. Akazawa, K. Yamanaka, A. Miyama, Y. Yoshida, N. Noguchi, and E. Niki, *Free Radic. Biol. Med.*, **49**, 1542-1549 (2010).

Glutamate plays a critical role in pathological cell death within the nervous system. Vitamin E is known to protect cells from glutamate cytotoxicity, either by direct antioxidant action or by indirect nonantioxidant action. Further, α-tocotrienol (α-T3) has been reported to be more effective against glutamate-induced cytotoxicity than α-tocopherol (α-T). To shed more light on the function of vitamin E against glutamate toxicity, the protective effects of eight vitamin E homologues and related compounds, 2,2,5,7,8-pentamethyl-6-chromanol (PMC) and 2-carboxy-2,5,7,8-pentamethyl-6-chromanol (Trolox), against glutamate-induced cytotoxicity on immature primary cortical neurons were examined using different protocols. Glutamate induced the depletion of glutathione and generation of reactive oxygen species and lipid hydroperoxides, leading to cell death. α-, β-, γ-, and δ-T and -T3; PMC; and Trolox all exerted cytoprotective effects against glutamate-induced cytotoxicity, and a longer preincubation time increased both the cellular content and the cytoprotective effects of T more significantly than those of T3, the effect of preincubation being relatively small for T3 and PMC. The protective effect of Trolox was less potent than that of PMC. The cytoprotective effects of α-T and α-T3 corresponded to their intracellular content. Further, lipid peroxidation products were measured after reduction with triphenylphosphine followed by saponification with potassium hydroxide. It was found that glutamate treatment increased the formation of hydroxyeicosatetraenoic acid, hydroxyoctadecadienoic acid, and 8-F2-isoprostane 2α, which was suppressed by α-T. This study shows that vitamin E protects cells from glutamate-induced toxicity primarily by direct antioxidant action and that the apparent higher capacity of T3 compared to T is ascribed to the faster uptake of T3 compared to T into the cells. It is suggested that, considering the bioavailability, α-T should be more effective than α-T3 against glutamate toxicity in vivo.