The effects of kaempferol against mutant copper-zinc superoxide dismutase-mediated toxicity via autophagy

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Amyotrophic lateral sclerosis (ALS) is a neuromuscular degenerative disorder characterized by the selective and progressive loss of motor neurons. ALS patients experience motor weakness, which starts focally and spreads throughout the nervous system and dies within a few years of diagnosis. While the majority of clinical ALS is sporadic, mutation copper-zinc superoxide dismutase 1 (SOD1) cause about 20 % of familial ALS (FALS). ALS with mutant SOD1 is caused by a toxic gain of function associated with the propensity of misfolding SOD1. The motor neurons in ALS patients are known to be formation of intracellular protein aggregate that are caused by mutations in the SOD1 gene. Kaempferol is a phytoestrogen found in a variety of vegetables and fruits, such as tomatoes, hops, red grapes, and strawberries. Kaempferol has been used in traditional medicine and is believed to have various biological functions. The purpose of this study was to clarify effects of kaempferol against ALS-associated mutant SOD1-induced neurotoxicity. We examine whether kaempferol and kaempferide, a derivative of kaempferol, have neuroprotective effect against mutant SOD1-induced neurotoxicity in a cellular model. Kaempferol and kaempferide inhibited mutant SOD1-induced cell death and reduced the intracellular mutant SOD1 aggregates. Both kaempferol and kaempferide significantly suppressed mutant SOD1-induced superoxide in mitochondria. To examine the mechanism, which reducing the number of intracellular aggregate, we focused on autophagy, a major pathway for the elimination of aggregated-proteins and damaged-organelles. Western blot analysis showed that kaempferol, but not kaempferide, promote the formation of LC3-II, indicating the upregulation of autophagy. To identify the signal transduction pathway mediated by kaempferol, we examined the following pathways that regulate the mammalian target of rapamycin (mTOR) activity. Kaempferol induced autophagy via the AMP-activated protein kinase (AMPK)-mTOR pathway. These results suggest that kaempferol against mutant SOD1-mediated neurotoxicity will be an efficient source of new treatments and prevention for ALS.