FAD012, a ferulic acid derivative, protects against middle cerebral artery occlusion (MCAO)-induced ischemic stroke by preserving cerebral blood flow in rats

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Stroke including ischemic cerebrovascular diseases is the major leading cause of death worldwide, which causes various sequelae and increases the medical expenses. Recently, ferulic acid (FA), which is a phenolic antioxidative compound commonly found in fruits and vegetables, has been reported to exert antioxidative activities and improve ischemic brain injury in rodent models. In the present study, we investigated the effects of FAD012, a synthetic derivative of FA, against ischemic brain damage induced by middle cerebral artery occlusion following reperfusion (MCAO/Re) in rats.

Male adult Sprague-Dawley rats (11 weeks old) were orally treated with FAD012 or FA (10 or 30 mg/kg) for 1 week before MCAO/Re. MCAO with an intraluminal filament was performed under isoflurane anesthesia. After 2 h of MCAO, the filament was withdrawn to enable Re. Cerebral blood flow (CBF) during MCAO was quantified using 2D laser blood imager (OZ-2, Omegawave, Inc.). After 24 h of Re, neurological deficits and cerebral infarct volumes were evaluated in the rats.

In vehicle-control rats, the level of CBF was decreased to 61.9±4.2% of the baseline by MCAO. After 24 h of Re, severe neurological deficits and infarction developed in the corpus striatum and cortex (infarct volume: 29.5±2.3%) were observed in the rats. Pretreatment with FAD012 (30 mg/kg) suppressed the MCAO-induced decrease in CBF (72.8±2.8%) especially in the cortex of the ischemic hemisphere. FAD012 significantly improved neurological deficits and decreased the infarct volume (6.3±3.5%). To elucidate the mechanisms of CBF-preserving effect of FAD012 during MCAO, expression of endothelial NO synthase (eNOS) in the cerebral cortex after 2 h of MCAO was assessed by immunohistochemical staining. In control rats, the expression of eNOS localized in cerebral endothelial cells was decreased in the ischemic hemisphere, whereas it was sustained to the same extent as the non-ischemic contralateral hemisphere in FAD012-treated rats. These results suggest that FAD012 preserves CBF by maintaining eNOS expression in endothelial cells during cerebral ischemia and improves brain injury in rats.