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Neuroprotective of S-allyl-L-cysteine against ischemic damage in *in vitro* and *in vivo* models

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Among five organosulfur compounds derived from garlic, S-allyl-L-cysteine (SAC) has been shown to reduce ischemic injury due to its antioxidant activity. However, the antioxidant property of SAC has been controversial. The present study investigated (i) the neuroprotective mechanism of SAC in cerebral ischemic insults; (ii) the effect of dietary SAC on stroke in stroke-prone spontaneously hypertensive (SHRSP) rats; (iii) charaterized the neuroprotective and antioxidative activities of five organosulfur compounds with a thioallyl structure ($-S-CH_2CH=CH_2$) in terms of structure-activity relationships (SAR). **I. Neuroprotective mechanism.** SAC decreased the size of infarction after transient or global ischemic insults. While it did not alter the NMDA excitotoxicity, SAC significantly scavenged the endogenously or exogenously produced $ONOO^-$ and reduced $ONOO^-$ cytotoxicity. In contrast, SAC has much lower scavenging activity against H_2O_2, $O_2^{\cdot-}$ or NO. Further, SAC inhibited the activity of extracellular signal-regulated kinase (ERK) increased in cultured neurons exposed to oxygen-glucose deprivation (OGD) or in rat brain tissue after transient middle cerebral artery occlusion. The neuroprotective effect of SAC was mimicked by the ERK inhibitor U0125. **II. Dietary effect in SHRSP.** SAC was found to reduce mortality with lesser incidence of stroke and also to lower the overall stroke-related behavioral score in SHRSP rats by dietary administration. **III. SAR.** Among five organosulfur compounds, only SAC having the alanyl group ($-CH_2CHNH_2-COOH$) and lacking the oxo (O=) group with in-between molecular properties, was effective in protecting cell death induced by both OGD and global cerebral ischemia. Furthermore, significant correlation was only found between *in vivo* neuroprotective activity and OH^- scavenging activity (r = 0.55, p = 0.032) among ROS scavenging activities. Therefore, the present results indicate that SAC exert its neuroprotective effect by scavenging $ONOO^-$ and inhibiting the ERK signaling pathway activated during initial hypoxic/ischemic insults. Also, the anti-stroke effect of dietary SAC was demonstrated in SHRSP rats. In terms of SAR, presence of the alanyl group and absence of the oxo group are essential for the manifestation of neuroprotective activity against ischemic insults and scavenging of OH radical, with SAC surfacing as a potent neuroprotectant.