Neuronal protective role of ginsenoside Rg3 against homocysteine-induced degeneration of brain hippocampus in rat; Therapeutic strategies for neuronal diseases

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We previously demonstrated that ginsenoside Rg(3) (Rg(3)), one of the active ingredients in Panax ginseng, attenuates NMDA receptor-mediated currents and NMDA-induced neurotoxicity. Ginsenoside Rg(3) antagonizes NMDA receptors through a glycine modulatory site in rat cultured hippocampal neurons. Accumulating evidence suggests that homocysteine (HC), a metabolite of methionine, exerts its excitotoxicity through NMDA receptor activation. In the present study, we examined the neuroprotective effects of Rg(3) on HC-induced hippocampal excitotoxicity in vitro and in vivo. Our in vitro studies using rat cultured hippocampal neurons revealed that Rg(3) treatment significantly and dose-dependently inhibited HC-induced hippocampal cell death, with an EC(50) value of 28.7+/-7.5 muM. Rg(3) treatment not only significantly reduced HC-induced DNA damage, but also dose-dependently attenuated HC-induced caspase-3 activity in vitro. Our in vivo studies revealed that intracerebroventricular (i.c.v.) pre-administration of Rg(3) significantly and dose-dependently reduced i.c.v. HC-induced hippocampal damage in rats. To examine the mechanisms underlying the in vitro and in vivo neuroprotective effects of Rg(3) against HC-induced hippocampal excitotoxicity, we examined the effect of Rg(3) on HC-induced intracellular Ca(2+) elevations in cultured hippocampal cells and found that Rg(3) treatment dose-dependently inhibited HC-induced intracellular Ca(2+) elevation, with an IC(50) value of 41.5+/-17.5 muM. In addition, Rg(3) treatment dose-dependently inhibited HC-induced currents in Xenopus oocytes expressing the NMDA receptor, with an IC(50) of 47.3+/-14.2 muM. These results collectively indicate that Rg(3)-induced neuroprotection against HC in rat hippocampus might be achieved via inhibition of HC-mediated NMDA receptor activation.