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Ginsenosides Regulate Ligand-Gated Ion channel at Extraceullular Side

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Treatment of ginsenosides, major active ingredients of *Panax* ginseng, produces a variety of physiological effects in central and peripheral nervous systems. Recent reports showed that ginsenosides inhibit various types of ligand-gated ion channel activity. However, it is not clear whether ginsenoside-induced regulation on ligand-gated ion channel activity could be achieved via extracellular or intracellular side, since they are also a kind of saponins with membrane-permeable property. Although it needs to identify the action side of ginsenosides, it is not yet determined. In the present study, we investigated the action side of ginsenoside Rg_3 or M4, a ginsenoside metabolite, in the regulation of ligand-gated ion channel activity using *Xenopus* oocyte gene expression system. The ligand-gated ion currents were measured using two-electrode voltage clamp techniques. Extracellular treatment but not intacellular injection of ginsenoside Rg_3 or M4 inhibited 5-HT_{3A} and $\alpha 3\beta 4$ nACh receptor-mediated ion currents. In oocytes expressing gustatory cGMP-gated ion channel, which is known to have cGMP binding site at intracellular side of plasma membrane and is only activated by cytosolic cGMP, extracellular treatment/excised outside-out patch clamp but not cytosolic injection/excised inside-out patch clamp of ginsenoside Rg_3 inhibited cGMP-gated ion currents. These results indicate that ginsenoside Rg_3 and M4 regulate ligand-gated ion channel activity at extracellular side.