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Stereospecificity of ginsenoside Rg_3 in ion channel regulation

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Recent studies showed that ginsenosides, active ingredients of *Panax* ginseng, exist as a stereoisomer depending on the position of hydroxyl group at the carbon-20; i.e. 20(R)-ginsenoside and 20(S)-ginsenoside are epimers for each other. In previous reports we demonstrated that the mixture of 20(R)- and 20(S)-ginsenosides regulates ion channel activity. However, it is not yet determined precisely on ginsenoside stereospecificity in ion channel regulation. We investigated the structure-activity relationship using ginsenoside Rg_3 stereoisomers, (20-R-protopanaxatriol-3-[O-β-D-glucopyranosyl (1→2)-β-glucopyranoside]), 20(R)-Rg_3 and (20-S-protopanaxatriol-3-[O-β-D-glucopyranosyl (1→2)-β-glucopyranoside]), 20(S)-Rg_3 in regulation of voltage-dependent Ca^{2+}, K^+ or Na^+ channel current and 5-HT_{3A} or α3β4 nicotinic acetylcholine (nACh) receptor channel current expressed in Xenopus oocytes. 20(S)-Rg3 but not 20(R)-Rg_3 inhibited Ca^{2+}, K^+ or Na^+ channel current with dose- and voltage-dependent manner. The difference between Rg_3 epimers in voltage-dependent ion channel regulation indicate that the hydroxyl group of 20(S)-Rg_3 may be geometrically better aligned than that of 20(R)-Rg_3 with the hydroxyl acceptor group in ion channels. However, both Rg_3 stereoisomers inhibited 5-HT_{3A} and α3β4 nACh receptor channel currents with dose- and voltage-dependent manner. These results indicate that Rg_3 stereoisomers have a differential stereoselectivity in regulation of voltage-dependent ion channel and ligand-gated ion channel activity.