Inhibitory action of endogenous sulfur on oxidative stress-induced TRPA1 activation

Naoko Oguma, Kenji Takahashi, Toshio Ohta

Dept. Vet. Pharmacol., Fac. Agri., Tottori Univ.

An endogenous sulfur, polysulfide (PS) is generated by oxidation of hydrogen sulfide. We previously reported that PS stimulated nociceptive transient receptor potential A1 (TRPA1) channel in sensory neurons. TRPA1 is also activated by reactive oxygen species (ROS). Here, we examined the effect of PS on responses to hydrogen peroxide (H_2O_2), one of ROS, using mouse sensory neurons and heterologously expressed mouse TRPA1 in HEK293 cells (mTRPA1-HEK). In mouse sensory neurons, H_2O_2 evoked two types of $[Ca^{2+}]_i$ responses, an early TRPA1-dependent and a late TRPA1-independent ones. Pretreatment with PS inhibited the H_2O_2-induced early responses in a dose-dependent manner. PS also suppressed $[Ca^{2+}]_i$ responses to PGJ_2, another endogenous TRPA1 agonist in mouse sensory neurons. In mTRPA1-HEK, PS inhibited $[Ca^{2+}]_i$ responses to not only H_2O_2 but also PS itself and PGJ_2. Simultaneous measurement of $[Ca^{2+}]_i$ and $[PS]_i$ showed that PS did not present in the period of the inhibiting effect of PS. The removal of extracellular Ca^{2+} and calmodulin inhibitor diminished the PS-induced suppression of $[Ca^{2+}]_i$ responses to H_2O_2. When PS was administrated intraplantary prior to H_2O_2, pain-related behaviors induced by H_2O_2 significantly decreased in mouse. The present data suggest that an endogenous sulfur desensitizes TRPA1 resulting in an inhibition of subsequent activation induced by oxidative stresses via Ca^{2+} influx through TRPA1. Calmodulin signaling may be involved in PS-induced TRPA1 desensitization.