Involvement of the cAMP-dependent pathway in the dextromethorphan-induced inhibition of spontaneous glutamate transmission in the nucleus tractus solitarius neurons of guinea pigs

Yoshiaki Ohi, Daisuke Kodama, Akira Haji

Lab. Neuropharmacol., Sch. Pharm., Aichi Gakuin Univ.

The second-order neurons in the nucleus tractus solitarius (NTS) receive excitatory inputs from the broncho-pulmonary afferents and serve as a gate in the cough reflex pathway. Although central antitussives are thought to inhibit the cough center including the NTS, their sites of action and mechanisms are not fully understood. In our previous study, dextromethorphan (DEX) inhibited tractus solitarius (TS)-evoked synchronous release of glutamate in the second-order NTS neurons independently of its agonistic effect on the sigma receptor. However, there is still limited knowledge of its cellular mechanisms. To clarify the inhibitory mechanism of DEX, the present study examined the interaction of DEX with cAMP. The effects of DEX on miniature and tractus solitarius-evoked excitatory postsynaptic currents (mEPSCs and eEPSCs) were recorded under activation of the cAMP-dependent pathway using the brainstem slices. An increase in cAMP by forskolin (adenylyl cyclase activator) counteracted the inhibitory effect of DEX on mEPSCs. 8-Bromo-cAMP (cAMP analog) and N-ethylmaleimide (Gi/o protein inhibitor) also attenuated the DEX effect. However, forskolin had negligible effects on the DEX-induced inhibition of eEPSCs. The present study demonstrates for the first time that the cAMP-dependent pathway regulates the excitatory synaptic transmission in the NTS neurons and the distinct mechanisms underlie the DEX-induced inhibition of spontaneous and synchronous release of glutamate in the second-order NTS neurons.