Effects of lobeline, a nicotinic receptor ligand, on the cloned cardiac K^+ channels, Kv1.5, Kv3.1 and Kv4.3

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The effects of lobeline, an agonist at nicotinic receptors, on Kv1.5, Kv3.1 and Kv4.3 stably expressed in CHO cells were examined using the whole-cell patch-clamp methods. Lobeline accelerated the decay rate of Kv1.5 inactivation, decreasing the current amplitude at the end of the pulse in a concentration-dependent manner with a half maximal inhibitory concentration (IC_{50}) value of 15.1 μM. Using a time constant for the time course of drug-channel interaction, the apparent association (k_{+1}) and dissociation rate (k_{-1}) constants were 2.4 ± 0.2 $\mu M^{-1}s^{-1}$ and 40.9 ± 11.5 s^{-1}, respectively. The calculated K_D value derived by k_{-1}/k_{+1} was 17.0 μM. Lobeline slowed the rate of decay of the tail current, resulting in a tail crossover phenomenon. The inhibition of Kv1.5 by lobeline steeply decreased at potentials between −20 and +10 mV, which corresponds to the voltage range of channel activation. At more depolarized potential, a weaker voltage-dependence was observed with a value of electrical distance (δ) of 0.26. The voltage dependence of steady-state activation curve was not affected by lobeline, but lobeline shifted the steady-state inactivation curves of Kv1.5 in the hyperpolarizing direction. Lobeline produced use-dependent inhibition of Kv1.5 at a frequency of 1 Hz and 2 Hz and slowed the recovery from inactivation. Lobeline also inhibited Kv3.1 and Kv4.3 in a concentration-dependent manner with an IC_{50} value of 21.7 μM and 28.2 μM, respectively. These results indicate that lobeline blocks Kv1.5 by binding to the open state of the channels.