

Carbon monoxide modulates electrical activity of murine myocardium via cGMP-dependent mechanisms

Abramochkin D., Konovalova O., Kamkin A., Sitdikova G.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2015, University of Navarra. Carbon monoxide (CO) is critical in cell signaling, and inhalation of gaseous CO can impact cardiovascular physiology. We have investigated electrophysiological effects of CO and their potential cGMP-dependent mechanism in isolated preparations of murine myocardium. The standard microelectrode technique was used to record myocardial action potentials (APs). Exogenous CO (0.96×10^{-4} – 4.8×10^{-4} M) decreased AP duration in atrial and ventricular tissue and accelerated pacemaking activity in sinoatrial node. Inhibitors of heme oxygenases (zinc and tin protoporphyrin IX), which are responsible for endogenous CO production, induced the opposite effects. Inhibitor of soluble guanylate cyclase (sGC), ODQ (10^{-5} M) halved CO-induced AP shortening, while sGC activator azosidnone (10^{-5} M– 3×10^{-4} M) and cGMP analog BrcGMP (3×10^{-4} M) induced the same effects as CO. To see if CO effects are attributed to differential regulation of phosphodiesterase 2 (PDE2) and 3 (PDE3), we used inhibitors of these enzymes. Milrinone (2×10^{-6} M), selective inhibitor of cGMP-downregulated PDE3, blocked CO-induced rhythm acceleration. EHNA (2×10^{-6} M), which inhibits cGMP-upregulated PDE2, attenuated CO-induced AP shortening, but failed to induce any positive chronotropic effect. Our findings indicate that PDE2 activity prevails in working myocardium, while PDE3 is more active in sinoatrial node. The results suggest that cardiac effects of CO are at least partly attributed to activation of sGC and subsequent elevation of cGMP intracellular content. In sinoatrial node, this leads to PDE3 inhibition, increased cAMP content, and positive chronotropy, while it also causes PDE2 stimulation in working myocardium, thereby enhancing cAMP degradation and producing AP shortening. Thus, CO induces significant alterations of cardiac electrical activity via cGMP-dependent mechanism and should be considered as a novel regulator of cardiac electrophysiology.

<http://dx.doi.org/10.1007/s13105-015-0387-y>

Keywords

Action potential, cAMP, Carbon monoxide, cGMP, Guanylate cyclase, Heart