BMC Pharmacology

Poster presentation

Kinetics of NO-induced cyclic GMP responses in vascular smooth muscle

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from 2nd International Conference of cGMP Generators, Effectors and Therapeutic Implications
Potsdam, Germany, 10–12 June, 2005

Published: 16 June 2005

BMC Pharmacology 2005, **5**(Suppl 1):P8 doi:10.1186/1471-2210-5-S1-P8

Cyclic GMP is accepted to be the critical second messenger responsible for vasodilation of arterial smooth muscle, via the NO/GC/cGMP/PKG pathway. NO has been shown to increase the catalytic activity of the NO-sensitive Guanylate Cyclase (GC) from 200–400 fold as measured by cGMP production. However, the rapid fluctuations of cGMP in living cells remain elusive due to the transient nature of this molecule. Our goal is to examine the NO-induced kinetics of cGMP in primary vascular smooth muscle cells (VSMCs). We show that by utilizing our FRET-based and genetically encoded cGMP-indicator Cygnet-2.1, we can effectively monitor cGMP synthesis and breakdown. By employing dual-emission fluorescence microscopy, we have observed both sustained and rapid transients of NO-induced cGMP levels in dissociated rat aortic SMCs in response to various NO donors. These sustained elevations in cGMP can be further enhanced by Sildenafil™-mediated inhibition of phosphodiesterase 5. A current controversy is the regulation and mechanism of GC activation, which has important implications for the physiology of smooth muscle. In our live cell imaging studies of cGMP, we demonstrate that GC can be repeatedly activated by NO, and we do not observe global desensitization of GC in vascular smooth muscle. We show that VSMCs are able to differentially respond to various concentrations of nitric oxide, to rapidly downregulate cGMP levels, and are also able to maintain GC sensitivity to repeated applications of nitric oxide. Our results thus far have provided new insight into the mechanism of NO-induced GC activity in vascular smooth muscle.