Reply to the Letter to the Editor

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To the Editor

We thank Dr. Herring et al. for their comments on our paper. In our recent report [1] we proposed that the postjunctional source of cardiac myocyte cGMP, from either soluble or particulate guanylyl cyclase, imposed directionality on the response to ligands. Such considerations also apply to stimulation of L-type calcium current (I_{Ca(L)}) by cyclic AMP [2]. Importantly, the muscarinic agonist carbachol (CCh) and atrial natriuretic peptide (ANP) inhibited IBMX-stimulated I_{Ca(L)} by an LY83583-sensitive process, presumably particulate guanylyl cyclase. Carbachol continued to inhibit isoproterenol-stimulated I_{Ca(L)} in the presence of LY83583 implying that suppression of adenyl cyclase activity, not a cGMP-mediated action, accounted for muscarinic inhibition under this condition. However, LY83583 prevented ANP from inhibiting isoproterenol-stimulated I_{Ca(L)}. A soluble guanylyl cyclase inhibitor, ODQ, had no effect against either CCh or ANP but prevented inhibition by the NO donor, SIN-1 (but see [3]). This underscores two features. First, cGMP is an important component of ANP action. Second, cGMP origin and concentration bear heavily on the outcome of experiments with CCh. Targeted disruption of cGMP-dependent protein kinase I not only illustrated its role in cardioinhibition by cGMP but also excluded its participation in muscarinic inhibition of forskolin-stimulated contractions [4]. This result is consistent with the dual pathway hypothesis for muscarinic inhibition [1] because forskolin activates adenyl cyclase as does isoproterenol.

Whether and how cGMP serves as a messenger for the cardiac actions of the vagus transmitter acetylcholine (ACh) has attracted critical attention since first reported [5]. Recently, Dr. DJ Paterson and colleagues reported that cGMP, from either soluble or particulate guanylyl cyclase, modulates prejunctional ACh release [6,7]. We concur that cGMP function appears site specific and we stress that the roles of guanylyl cyclases must be viewed carefully. The reports [8,9] cited by Dr. Herring, et al. gave evidence against the endothelial NO synthase hypothesis and NO in muscarinic inhibition of I_{Ca(L)}. Such experiments could not address completely the issue of guanylyl cyclase and muscarinic inhibition. Moreover, we consider that recent investigations have strengthened rather than diminished the importance of cGMP signaling, per se and in connection with ACh action. For example, CCh increased cardiac myocyte cGMP in the presence of NOS inhibitors indicating a NOS-independent path to regulate cGMP synthesis [10].

Several pathways promote cGMP synthesis pre- and postjunctionally yet cGMP-inhibited PDE (PDE 3) is the only cGMP effector identified in cardiac cholinergic nerves [6,7]. Postjunctonally, different cGMP effectors exist within the same cell. In cardiac myocytes derived from embryonic stem cells, ACh inhibited isoproterenol-stimulated I_{Ca(L)} by activating cGMP-stimulated PDE (PDE 2) in early-stage cells and by inhibiting adenyl cyclase in late-stage cells [11]. In human atrial cells, cGMP exerted opposite effects on I_{Ca(L)} by acting on PDE 3 and, at higher concentrations, through PDE 2 [12]. Further, cGMP may arise from muscarinic stimulation of soluble guanylyl cyclase to increase I_{Ca(L)} via PDE 3 [13] or activation of particulate guanylyl cyclase [1] to inhibit it via cGMP-dependent protein kinase [14]. These observations illustrate the complexity of this second messenger’s actions in modulating cardiac activity. The manifold patterns for synthesis and targeting of cGMP actions may well serve the homeostatic function of the autonomic nervous system and of hormones like ANP.

References


