

cGMP inhibition of heart phosphodiesterase: is it clinically relevant?

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Editorial

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cAMP modulates cardiac function by activation of cAMP-dependent protein kinase and subsequent phosphorylation of several cardiac proteins including Ca^{2+} channels (1). Although cGMP also has been suggested to modulate cardiac function (2), most reported effects of cGMP were not robust and differed among species and preparations. Moreover, cGMP response to nitrovasodilators often did not correlate well with contractility (3). As the pathways of acetylcholine (ACh) activation of K^+ channels, phospholipase C, and of heterotrimeric GTP binding protein (Gi) inhibition of adenylyl cyclase were elucidated (1), any involvement of cGMP was considered by many to be "academic." More recently, however, the discovery that nitric oxide (NO)/cGMP mediates ACh effects in peripheral tissues has revived interest in cGMP function in the heart.

In this issue of *The Journal*, Kirstein et al. (4) suggest one mechanism by which NO and cGMP may affect human cardiac function. They show that SIN-1, an agent that chemically produces NO, increases Ca^{2+} current (I_{Ca}) in isolated human atrial myocytes. They show that this effect is probably mediated via cGMP effects on a cGMP-inhibited phosphodiesterase (PDE3A). As expected from such a mechanism, the effects of cGMP are mimicked by milrinone, a cardiotonic agent that selectively inhibits PDE3. In the presence of milrinone, cGMP no longer increases I_{Ca} .

The use of human cardiac tissue in this study is important because earlier work by the authors showed different effects of cGMP among species. For example, cGMP inhibition of I_{Ca} in frog ventricular cardiocytes was attributed to effects on a cGMP-stimulated PDE (PDE2). Subsequent studies in rat ventricular cardiocytes indicated that most effects of cGMP were mediated via stimulation of cGMP-dependent protein kinase (5). More recently, in rabbit pacemaker tissue, an obligatory role for NO in ACh function has been proposed (6). Taken together, these data suggest large differences between species and possibly between different regions of the heart in the mechanism(s) by which ACh and cGMP influence function.

Somewhat surprising in the present work is the observation that SIN-1 stimulates basal I_{Ca} . In other systems where PDE3 mediates hormonal responses, large effects of PDE3 inhibitors are not seen unless cAMP synthesis has first been raised. This is consistent with the fact that PDE inhibitors potentiate activation of adenylyl cyclase. Presumably, the basal activity of adenylyl cyclase is higher in human atrial tissue than in many other cell types.

Nitrovasodilators, as well as PDE3 selective inhibitors like milrinone (7), are known to affect cardiac Ca^{2+} handling.

Therefore, the effects of cGMP and milrinone to increase basal I_{Ca} may have important clinical implications. For example, the PROMISE study for milrinone as a treatment of congestive heart failure was halted before completion because of an increased incidence of fatalities in the treatment group (8). In retrospect, this might have been predicted given the known synergistic effects of PDE inhibitors with adenylyl cyclase agonists. Apparently, the single dose of drug chosen was based on concentrations that give a modest effect in healthy individuals. Patients with compromised cardiac performance should have an increased sympathetic tone and therefore an exaggerated response to a PDE inhibitor. The concurrent administration of digoxin and converting enzyme inhibitors would only exaggerate effects on cardiac Ca^{2+} . More recent analyses of patients receiving lower doses of milrinone (9), enoximone (10), or vesnarinone (11) all suggest positive therapeutic effects of PDE3 inhibitors at lower doses. The observations reported in this study may underlie these clinical effects.

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