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The Role of PLCβ1 in Desensitization of Acetycholine Activated K^+ Currents in Mouse Atrial Myocytes

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The negative chronotropic effect of ACh on heart fades in the continuous presence of ACh, which is known as a phenomenon called "vagal escape". The underlying mechanism of vagal escape is not entirely clear, but desensitization of acetylcholine-activated K^+ currents (K_{ACh}) was suggested, at least in part, to be responsible. It was recently shown that in PLCβ1 mutant mice, carbachol (CCh) induced a sustained membrane hyperpolarization, resulting in a complete cessation of spontaneous rhythm. From this result, it could be hypothesized that signal transduction pathways involving PLCβ1, such as PKC and PIP_2, may contribute to desensitization of K_{ACh}. In the present study, we have tested this hypothesis using isolated atrial myocytes of PLCβ1 mutant mice. Uisng nystatin perforated whole cell clamp technique, voltage ramps between -120 and +60 mV were applied, and K_{Ach} was obtained from the increase of currents induced by 10 μM CCh. The results are as follows:

1. Activation of K_{ACh} induced by CCh showed no difference between wild type and mutant mice. The extent of desensitization was significantly smaller in PLCβ1 mutant mice. The decrease of current measured at -120 mV after 4 min of CCh application was 20.5 $\pm$ 10.6 % (n=8) in wild type, and 8.3 $\pm$ 9.8 % (n=6) in mutant mice.

2. PKC specific activator, PDBU (100 nM) and TPA (1 μM), have no effect on K_{ACh} desensitization in wild mice, whereas they facilitated desensitization in mutant mice, resulting in further reduction by 22.7 $\pm$ 9.4 % (n=3). But PKC specific inhibitor, staurosporine(10 nM) have no effect on K_{ACh} desensitization both in wild mice and mutant mice.

3. K_{ACh} desensitization was accelerated by 100 μM phenylephrine which is known to hydrolyze PIP_2 via different PLC.

These results support the hypothesis that signal transduction pathways involving PLCβ1, such as PKC and PIP_2, contribute to desensitization of K_{ACh}, and thus modulate chronotropic response to CCh.