α- Adrenergic inhibition of the β-adrenoceptor-dependent chloride current in guinea-pig ventricular myocytes

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SUMMARY

1. α_1-Adrenoceptor-mediated inhibition of the β-adrenoceptor-dependent Cl^- current was investigated in guinea-pig ventricular myocytes with the patch clamp technique.
2. The Cl^- conductance activated by noradrenaline (0.1 to 10 μM) with an α_1-blocker (prazosin, 5 μM) was significantly greater than that activated by noradrenaline alone. Phenylephrine and methoxamine, α_1-agonists, exerted an inhibitory effect on the Cl^- conductance activated by isoprenaline. The dose-response relationship for isoprenaline and the Cl^- current activation, which was fitted to the Hill equation with a half-maximum concentration ($K_{1/2}$) of 28 nM in control, was shifted to higher doses in the presence of 30 μM phenylephrine; $K_{1/2}$ increased to 86 nM.
3. The interaction of α_1- and β-agonists on Cl^- current was also observed on the single channel level; in some of the outside-out membrane patches, phenylephrine (50 μM) depressed the activity of single Cl^- channel which was induced by 5 μM adrenaline.
4. Phenylephrine was ineffective on the Cl^- conductance induced by forskolin (0.5 to 5 μM), an activator of adenylate cyclase. The Cl^- conductance persistently activated by isoprenaline in GTPγS-loaded cells was also insensitive to phenylephrine.
5. The results suggest that the observed α_1-adrenergic attenuation of β-adrenergic response is not primarily due to inhibition of adenylate cyclase activity. The α_1-adrenergic action may interfere with the processes leading to the enzyme activation in the β-adrenergic pathway.
6. The phenylephrine action persisted when the capacity of intracellular Ca^{2+}-buffer was extremely increased with 20 mM BAPTA, indicating that Ca^{2+} ions are not involved in the observed α_1-action.