ALPHA-1 ADRENERGIC RECEPTORS, PROTEIN KINASE C, AND REGULATION OF INTRACELLULAR pH IN CARDIAC PURKINJE FIBERS

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ABSTRACT

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ALPHA-1 ADRENERGIC RECEPTORS, PROTEIN KINASE C, AND REGULATION OF INTRACELLULAR pH IN CARDIAC PURKINJE FIBERS

Subtypes of the alpha-1 adrenergic receptor are found in many tissues including the myocardium. The cardiac conduction system has not been examined for the existence of alpha-1 receptor subtypes. The current study investigated three questions with respect to alpha-1 receptor subtypes in canine cardiac Purkinje fibers: 1.) do alpha-1 receptor subtypes exist in canine Purkinje fibers, 2.) are the functional responses of activation of alpha-1 receptor subtypes related to the responses of activation of protein kinase C, 3.) does activation of alpha-1 receptors affect intracellular pH. The results of this study support the conclusion that alpha-1 receptor subtypes exist in canine cardiac Purkinje fibers. The alpha-1 agonist phenylephrine in combination with the beta antagonist timolol maximally increased active tension at 1 μM and significantly reduced active tension at 1 mM. In addition, the alpha-1 antagonists prazosin, WB4101, and benoxathian competitively inhibited the positive inotropic effect of phenylephrine, but only prazosin and WB4101 blocked the negative inotropic effect. The negative inotropic effect of phenylephrine was not a result of activation of the alpha-2 adrenergic receptor as the alpha-2 antagonist yohimbine

did not inhibit either the positive or negative inotropy observed with phenylephrine. Chloroethylclonidine, a drug selective for only one alpha-1 receptor subtype, produced a decrease only in active tension. Radioligand saturation binding studies using [^{125}I]HEAT with purified ventricular sarcolemmal membranes was consistent with two alpha-1 binding sites. Activation of protein kinase C with phorbol-12,13-dibutyrate profoundly reduced active tension. The specificity of the action of phorbol 12,13-dibutyrate was verified with 4α-phorbol 12,13-didecanoate, an inactive phorbol ester. The cholinergic antagonist atropine potentiated the effect of lower doses of phorbol 12,13-dibutyrate. Protein kinase C was activated by enhancing the accumulation of diacylglycerol with the diacylglycerol kinase inhibitor R59022. R59022 decreased active tension in a manner similar to phorbol esters and inhibited the positive inotropic effect of phenylephrine. Phenylephrine and phorbol 12,13-dibutyrate increased intracellular pH. The alkalinization produced by phenylephrine was sensitive to amiloride, an antagonist of the Na^+/H^+ exchanger. The results of this study support the conclusion that one of the alpha-1 receptor subtypes produces the positive inotropic effect, while the other alpha-1 receptor subtype is responsible for the negative inotropic effect. Further, functional responses following activation of protein kinase C or alpha-1 receptors are similar for both active tension and intracellular pH.

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