NEGATIVE INOTROPIC EFFECT OF CYSTEINYL-LEUKOTRIENES IN THE RABBIT HEART: POSSIBLE INVOLVEMENT OF THE CYS-LT_2 RECEPTOR

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Leukotrienes C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4) are involved in a variety of diseases, including myocardial ischemia. In the cardiovascular system they cause coronary artery constriction and rhythm abnormalities. In addition to the effects on the microvasculature, cysteinyl-leukotrienes (cys-LTs) are also able to affect directly the activity of myocardium, but the mechanisms underlying the negative inotropic effect on the ventricle have never been clarified. After the recent cloning and characterization of the cys-LT receptor cys-LT_2, as well as the demonstration that it is highly expressed in cardiac tissue, aim of our work has been to clarify the role of cys-LTs in cardiac tissues and isolated cells.
In rabbit Purkinje fibers, neither LTC_4, D_4 or E_4 were able to affect the shape, amplitude or duration of the action potential.
We examined also the effect of cys-LTs on the L-type Ca^{2+} current (I_{Ca}) in isolated ventricular myocytes of the rabbit.
LTC_4 did not show a significant effect on basal I_{Ca} but inhibited the I_{Ca} prestimulated by isoproterenol (Iso, 300 nM). Similar results were obtained for LTD_4 and LTE_4. This inhibition showed a concentration-dependance, with a maximum effect at 5 microM.
The selective cys-LT_1 antagonist MK 571 (1microM) did not affect the decrease in I_{Ca} induced by LTE_4, while the cys-LT_2 partial agonist BayU 9773 (1 microM), in a limited set of experiments, was able to reverse the cys-LT effect (in the presence of Iso).
In conclusion, we propose an antiadrenergic effect for cys-LTs in the rabbit heart and suggest a possible involvement of the cys-LT_2 receptor subtype.
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