ALTERATIONS OF MEMBRANE PROTEINS IN CARDIAC HYPERTROPHY

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INTRODUCTION

Hypertrophy of the heart is an adaptive mechanism to an increase in hemodynamic work. During this process, development without multiplication of the cardiac myocytes occurs and new sarcomeres are added to improve the contractility. As shown by Anversa et al. in compensatory hypertrophy of the rat (1,2), the overall result of the membrane development is an increase of the surface area parallel to the degree of hypertrophy which maintains a constant surface/volume ratio. However, some specialized membrane structures undergo a preferential development like the T-tubules (a 107 % increase for the T-tubules as compared to a 33 % for the sarcolemma (SL)) and the sarcoplasmic reticulum (SR) (a two fold increase). In this review on the membrane proteins of the hypertrophied myocyte, we shall take this into account to estimate their density of the receptors and their total number per myocyte or per left ventricle. We report that three types of regulation occur with enhanced, unchanged or decreased density leading to increased or unchanged total number of membrane proteins.

Together with these quantitative modifications, we shall consider if a qualitative alteration of the expression of the genes coding for the cardiac membrane proteins might be assumed. In fact, the expression of new isoforms of proteins during cardiac hypertrophy is well documented particularly for myosin (3). In the rat heart, the myosin isoform shift from the fast V1 to the slow V3 is, at least in part, responsible for the decrease in Vmax and the improvement in the wall stiffness. However, transcriptional or pre-translational modifications of the expression of a gene coding for a membrane protein have not yet been clearly demonstrated in the hypertrophied heart but might not be totally discarded since the properties of the Na⁺/K⁺ ATPase (4,5) or the coupling of the β-receptors are altered (6).
This review is focused on the quantitative and/or qualitative alterations of Ca\textsuperscript{2+} channels, \(\beta\)-adrenergic system, Na\textsuperscript{+}/K\textsuperscript{+} ATPase and Ca\textsuperscript{2+}-ATPase from SR. These modifications which seem to develop with the severity and the stage of the heart failure account for the alteration in the inotropic response of the hypertrophied heart. Hence the use of inotropic agents in the treatment of cardiac failure has to adapt to these new parameters of the hypertrophied myocyte.

Ca\textsuperscript{2+} CHANNEL

In cardiac muscle, where Ca\textsuperscript{2+} influx is essential for contraction, the voltage-dependent L type calcium channel plays a key role in excitation-contraction coupling. Moreover, as described in skeletal muscle (7) it might also act as a voltage-sensor to induce the release of calcium from the SR. The \(\alpha_1\) subunit of the cardiac dihydropyridine (DHP) receptor has a molecular mass of 243,000 D. Its primary structure has recently been elucidated by cloning and sequencing its cDNA (8). Injection of the \(\alpha_1\) subunit mRNA into Xenopus oocytes led to the production of a functional calcium channel. However the \(\alpha_2\) subunit might cooperate with \(\alpha_1\) since the co-injection of \(\alpha_1\) and \(\alpha_2\) mRNA enhanced the Ca\textsuperscript{2+}-current activity. Regulation of the Ca\textsuperscript{2+} channel function also occurs through phosphorylation by cAMP dependent kinase (9) and coupling to \(\alpha\) Gs protein (10, 11). Binding of Ca\textsuperscript{2+} agonists or antagonists lengthens or shortens the open time of the Ca\textsuperscript{2+} channel (12).

Ca\textsuperscript{2+} channels in the hypertrophied heart

One of the ordinary features of the hypertrophied heart is a prolongation of the duration of action potential (AP), particularly of the phase II which is observed in ventricles or isolated myocytes (13). This occurs whatever the model (hypertrophy secondary to hypertension or mechanical overload) or the species. It has been suspected that the Ca\textsuperscript{2+} channel might be responsible for this increased duration of the AP and numerous studies have appeared over the past few years. The studies have been performed on isolated membranes to determine the characteristics of the DHP receptors and on isolated myocytes to measure the current.