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ARRHYTHMOGENIC MECHANISMS IN HEART FAILURE: FROM CELL CULTURES AND ANIMAL MODELS TO HUMAN CARDIOMYOPATHIES

De Paoli P., 3° anno di corso del Dottorato in Farmacologia e Tossicologia, XV° ciclo. Durata del Dottorato in anni: 3. Sede di servizio: Università degli Studi di Firenze, Dipartimento di Farmacologia Preclinica e Clinica

Sudden cardiac death in patients with cardiac hypertrophy and failure is associated with myocardial remodeling. A better knowledge of electrophysiological alterations in human cardiomyopathies may help to prevent and treat the arrhythmogenic hazard in this setting. Two arrhythmogenic mechanisms have been consistently reported; a prolongation of action potential, due to a reduction of repolarizing potassium currents [3] and the expression of the hyperpolarization-activated current, I_f [4].

Animal models of cardiac hypertrophy may be helpful for understanding events occurring in the diseased human heart. In fact, we have consistently observed that similar electrical abnormalities occur in severely hypertrophied (from old spontaneously hypertensive rats, SHR) and failing (from post myocardial infarction rats, PMI) rat hearts and in patients undergoing cardiac transplantation [4;5;6]. In these years, our work has been aimed at the study of the hyperpolarization-activated current I_f in ventricular myocytes, namely its occurrence, pharmacological modulation and the molecular basis of its expression. I_f is a cation time-dependent inward current normally present in pacemaker cardiac cells [7] and absent or poorly expressed in adult ventricular myocytes. However, both in rats [5;] and in humans [9] the functional expression of I_f is upregulated in cardiac disease, being significantly higher in cardiomiopathy than in controls. In rat and human ventricular cardiomyocytes (VCM), I_f activation occurs at voltages near the physiological resting potential [4;], and might contribute to arrhythmogenesis, especially in the presence of an increased adrenergic (AR) activity; in fact, βAR stimulation is able to positively modulate I_f [10]. Moreover, the animal models used for these studies (SHR and PMI) have allowed a deeper understanding of alterations occurring at the level of the βAR pathway. In fact, we observed a specific downregulation of β_1AR stimulation – possibly related to G_i proteins overactivity [10;12] – a feature which has been typically reported in cardiac hypertrophy and failure.

I_f over- or re-expression likely represents an example of a general phenomenon, i.e. cell re-entry into a fetal program [13]. Switching on/off the gene(s) encoding for I_f may depend on several neurotransmitters and hormones (e.g, catecholamines, angiotensin II) acting during physiological growth or pathological hypertrophy. The role of angiotensin II is further supported by the observation that a regression of cardiac hypertrophy (even in the absence of significant lowering of blood pressure has been observed for both ACE-inhibitors and AT_1 receptor blockers (ARBs). A recovery of electrophysiological cell properties has been demonstrated in hypertensive rats treated with losartan [14]. A more recent study, aimed to verify the effect of chronic treatment of old SHR with the ARB irbesartan, demonstrated a recovery of both electrophysiological and contractile properties of VCM [15,16].

A crucial point of all these observations is the possibility to investigate the mechanisms underlying the occurrence of arrhythmogenic alterations and their molecular identification. Cultured adult rat VCM can be a predictive *in vitro* model to this purpose: thus, we studied the consequences of hypertrophy and dedifferentiation in cultured VCM incubated with well-known growth factors (angiotensin-II, endothelin-1, α_1-agonists) in terms of changes in electrophysiological properties and particularly I_f expression [17].

On the whole, the evaluation of alterations spontaneously occurring in VCM from human and animal diseased hearts and those induced *in vitro* (cell cultures) may help to get deeper insight into the mechanisms involved in the electrophysiological remodeling of the hypertrophied and failing myocardium and to promote the development of novel therapeutic strategies.

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