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Review

Calcium signaling in diabetic cardiomyocytes

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ABSTRACT

Diabetes mellitus is one of the most common medical conditions. It is associated to medical complications in numerous organs and tissues, of which the heart is one of the most important and most prevalent organs affected by this disease. In fact, cardiovascular complications are the most common cause of death among diabetic patients. At the end of the 19th century, the weakness of the heart in diabetes was noted as part of the general muscular weakness that exists in that disease. However, it was only in the eighties that diabetic cardiomyopathy was recognized, which comprises structural and functional abnormalities in the myocardium in diabetic patients even in the absence of coronary artery disease or hypertension. This disorder has been associated with both type 1 and type 2 diabetes, and is characterized by early-onset diastolic dysfunction and late-onset systolic dysfunction, in which alteration in Ca^{2+} signaling is of major importance, since it controls not only contraction, but also excitability (and therefore is involved in rhythmic disorder), enzymatic activity, and gene transcription. Here we attempt to give a brief overview of Ca^{2+} fluxes alteration reported on diabetes, and provide some new data on differential modulation of Ca^{2+} handling alteration in males and females type 2 diabetic mice to promote further research. Due to space limitations, we apologize for those authors whose important work is not cited.

1. Introduction: diabetic cardiomyopathy

Diabetes mellitus is a chronic disease by which the impossibility to maintain normal glucose homeostasis leads to chronic hyperglycemia. Two main very different pathophysiological mechanisms lead to this inability to maintain normal plasma glucose concentration. In type 1 diabetes (T1D), also called juvenile diabetes or insulin-dependent diabetes, an autoimmune process directed against insulin-secreting β cells of pancreatic islets, probably triggered by environmental factors such as a viral infection occurring on a favoring genetic background, leads to decreased insulin secretion when 80–90% of β cells are destroyed. Due to the overall increase in autoimmune diseases, its incidence increases by 3 to 4% each year [1]. Pathophysiology of type 2 diabetes (T2D) is more complex and comprises itself two main mechanisms: a resistance of the peripheral tissues to the action of insulin that results in increased insulin needs to maintain normal glycemia, and an alteration in insulin secretion that does not allow β cells to fulfill the increased needs. Resistance to insulin action in T2D is also favored by genetic susceptibility but also sociological and environmental factors such as life style with an excess of poor quality diet and lack of sufficient physical activity resulting in obesity often associated with hypertension. Such obesity realizes currently a serious epidemic worldwide with a current prevalence of approximately 400 million (8.3% of world population) and an anticipated prevalence of approximately 600 million (8.9%) in 2035 [2].

Untreated or poorly controlled diabetes is a serious threat for most tissues and organs of the body. Together with other risk factors, it contributes to the development of atherosclerosis of large arteries. More specific of diabetes is the damage caused to microvessels such as those of the retina or kidneys. There have been controversies regarding the existence of a specific diabetic cardiomyopathy (DCM), independent from coronary artery disease, as this concept has emerged mainly from experimental studies [3].

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Nevertheless, a specific type of cardiomyopathy was first described 40 years ago based on the pathologic observations of hypertrophied and fibrotic hearts in patients with heart failure (HF) in the absence of coronary artery disease or any other pathophysiological process susceptible to explain HF [4]. This initial study has been confirmed and extended by others and DCM is now defined as the existence of LV dysfunction in diabetic patients lacking other potential etiological condition. The mechanisms underlying DCM seem to involve a cardiac remodeling associating LV hypertrophy with increased myocardial collagen and lipid content metabolic changes and alteration in Ca^{2+} signaling in cardiac myocytes [5–8]. However, the multifactorial etiology of the disease contributes to its complexity and cellular and molecular dysfunctions occurring at the level of cardiac myocytes are not yet fully understood. In this review we will focus on Ca^{2+} signaling alterations and how they compromise contraction and relaxation of the diabetic heart.

2. Ca^{2+} signaling in cardiomyocytes

2.1. Ca^{2+}-induced Ca^{2+}-release (CICR)

Ca^{2+} plays a fundamental role in heart function by activating contraction and regulating gene transcription, metabolism and cell death [9]. Cardiac contractility is triggered by Ca^{2+}-induced Ca^{2+}-release (CICR) mechanism during the excitation-contraction (EC) coupling [10]. The EC coupling is described as follow: For each cardiac cycle, membrane depolarization, generated during the action potential, induced an initial Ca^{2+} signal. This initial signal is produced by the entry of Ca^{2+} through the sarcolemmal L type Ca^{2+} channels (LTCC). The resultant elevation in cytosolic $[Ca^{2+}]_i$ is not enough to activate contraction. However, this Ca^{2+} influx is sufficient to activate the Ca^{2+} release channels (ryanodine receptors, RyR) located at the sarcoplasmic reticulum (SR), to amplify the initial signal and provide enough Ca^{2+} to activate contractile myofibrils. The close proximity between LTCC, at the transverse tubules of the sarcolemma, and the RyRs at the junctional SR confers a local control of the CICR mechanism where only the RyRs that are close to the LTCC get activated. This characteristic allows the signal to be graded, so contraction can be modulated depending on how many channels are activated, among other factors. Different expression or spatial distribution (such as TT remodeling) of one or both of these channels may underlie defects in contraction [11]. The activity of LTCC is measured by patch-clamp as a Ca^{2+} current (I_{Ca}) and variations on I_{Ca} density have been found in some models of diabetic cardiomyopathy (see below). The $[Ca^{2+}]_i$ variations may be analyzed, among other methods, by fluorescence techniques loading the cardiac myocytes with Ca^{2+} fluorescence dyes. Confocal imaging has provided a useful tool to analyze $[Ca^{2+}]_i$ at the global ($[Ca^{2+}]_i$ transients) and local (Ca^{2+} sparks) level. Ca^{2+} sparks were first identified by Cheng et al. as local, rapid, and brief elevations in $[Ca^{2+}]_i$ [12] whereas $[Ca^{2+}]_i$ transients correspond to simultaneous Ca^{2+} release through the RyRs in response to membrane depolarization. Since then, Ca^{2+} sparks have been used to measure the activity of RyRs, in normal cardiomyocytes and also some pathologic states including diabetic cardiomyopathy [13,14].

2.2. Relaxation phase

The relaxation phase is the result of the decrease in the cytosolic $[Ca^{2+}]_i$ and is regulated by two main components: the SR Ca^{2+} pump (SERCA) and the Na^+/Ca^{2+} exchanger (NCX). The SERCA reduces cytosolic $[Ca^{2+}]_i$ level by pumping back the Ca^{2+} to the SR, expending energy in the form of ATP. Its activity is tightly regulated by phospholamban (PLB), which slows down SERCA activity when unphosphorylated. In addition, the Na^+/Ca^{2+} exchanger (NCX) extrudes the Ca^{2+} out of the cardiomyocytes by exchanging one Ca^{2+} ion with 3 Na^+. The relative contribution of both systems depends on the analyzed species and may be altered in pathological states. However, other slow systems contributes to $[Ca^{2+}]_i$ transient relaxation as well, but at a much limited rate: Namely the plasmalemal Ca^{2+} ATPase (PMCA) and the mitochondrial transport. The NCX is reversible and depends on $[Na^+]_i$ and $[Ca^{2+}]_i$ at both sides of the membrane, and on voltage. Thus it may also contribute to triggering Ca^{2+} release. Because it is electrogenic, the NCX may be involved in arrhythmia by inducing delayed after depolarization (DAD) and triggered activity in conditions of aberrant Ca^{2+} release during diastole.

3. Ca^{2+} signaling in type 1 diabetes

Type 1 diabetes (T1D) experimental models, such as the streptozotocin (STZ)-induced diabetic (mouse or rat) [15] and the insulin-deficient diabetic mice heterozygous C57BL/6 for the $Ins2^{Akita}$ mutation (Akita mice) [16] are similar to human T1D. They display cardiomyopathy with significant systolic and diastolic dysfunction leading to heart failure (HF). T1D contractile dysfunction is characterized by a decrease in fractional shortening [17,18], ejection fraction [19], and heart rate [20]. However, unlike other heart failure models, they do not always develop cardiac hypertrophy [20,21], heart weight change [18,22] or cardiac atrophy [23]. This particularity is possibly due to apoptosis [24] and/or depression of cardiomyocyte volume [25]. Moreover, T1D show alterations of the left ventricular rate of systolic pressure ($+dP/dt$), the rate of decline ($-dP/dt$) with abnormal time to relaxation [20,22,23] suggesting that contractile dysfunction of T1D is mainly due to intrinsic factors within the diabetic heart. Though, an increase in the amplitude of shortening but with prolonged time to peak has been also described by other authors [26]. These discrepancies could result from STZ dose used which highly influence the severity of T1D, its stage of development and also the age of onset of diabetes. In either case, it is commonly admitted that, changes in contractile function in T1D are the reflection of a deep alteration of Ca^{2+} signaling at different levels: (i) Ca^{2+} entry/influx; (ii) intracellular Ca^{2+} cycling; (iii) Ca^{2+} extrusion/efflux.

3.1. Ca^{2+} entry/influx

Several studies showed normal I_{Ca} density but prolonged action potential duration due to down regulation of potassium currents. However, different studies and models have provided conflicting data: Increased PH200-110, a dihydropyridine derivative, binding sites in diabetic cardiac SL membrane [27], or decreased nitrendipine binding sites with increased affinity were observed in diabetic cardiac membranes [28]. Net influx of Ca^{2+} was reported to be significantly reduced in chronic 4–8 weeks diabetic rat myocardium [29]. Although some studies have shown normal function of LTCC [18,20,30], others have established a reduction in LTCC protein expression with the consequent decrease in I_{Ca} density in T1D myocytes compared with control myocytes [17,28,31,32]. Besides LTCC expression, the biophysical properties of the LTCCs are altered. I_{Ca} shows altered voltage dependence with the steady-state activation and inactivation curve shifted toward more positive potentials in diabetic compared with nondiabetic myocytes [17]. These changes in the biophysical properties, together with a reduced membrane expression of LTCCs [28], may suggest that only a smaller proportion of the LTCCs are available to open during each action potential, thus reducing the net influx of Ca^{2+} though LTCCs in T1D myocytes [17].

However, some studies have suggested that the reduced Ca^{2+} entry together with the inability of cardiomyocyte to utilize