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ABOUT COVER

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REVIEW

Diabetes-induced changes in cardiac voltage-gated ion channels

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Abstract

Diabetes mellitus affects the heart through various mechanisms such as microvascular defects, metabolic abnormalities, autonomic dysfunction and incompatible immune response. Furthermore, it can also cause functional and structural changes in the myocardium by a disease known as diabetic cardiomyopathy (DCM) in the absence of coronary artery disease. As DCM progresses it causes electrical remodeling of the heart, left ventricular dysfunction and heart failure. Electrophysiological changes in the diabetic heart contribute significantly to the incidence of arrhythmias and sudden cardiac death in diabetes mellitus patients. In recent studies, significant changes in repolarizing K^+ currents, Na^+ currents and L-type Ca^{2+} currents along with impaired Ca^{2+} homeostasis and defective contractile function have been identified in the diabetic heart. In addition, insulin levels and other trophic factors change significantly to maintain the ionic channel expression in diabetic patients. There are many diagnostic tools and management options for DCM, but it is difficult to detect its development and to effectively prevent its progress. In this review, diabetes-associated alterations in voltage-sensitive cardiac ion channels are comprehensively assessed to understand their potential role in the pathophysiology and pathogenesis of DCM.

Key Words: Diabetes; Action potential; Cardiac ion channels; L-type Ca^{2+} channels; Potassium channels; Sodium channels

Core Tip: Diabetes mellitus is a multisystemic disease that affects many organs. It causes diabetic cardiomyopathy (DCM) in the heart which is a distinctive pathology that occurs independent of vascular complications. In DCM, altered action potential morphology and contractile dysfunction are mostly associated with defective cardiac ion channels such as voltage-gated K^+, Na^+ and Ca^{2+} channels. Therefore, with therapeutic agents specific to cardiac ion channels, both arrhythmogenic events and

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other functional problems can be mitigated in the diabetic heart.

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INTRODUCTION

Diabetes mellitus (DM) is a complex and heterogeneous chronic metabolic disease caused by high blood sugar levels. Diabetic heart disease is a growing and serious public health risk which affects more than 350 million people worldwide[1]. Considering the fact that these figures refer to the year 2011, it is unfortunate to note that the numbers will increase much more in the coming years. DM is divided into four different etiological categories: Type 1, type 2, gestational DM and other specific types. Type 1 DM results from T cell-mediated autoimmune destruction of pancreatic cells which leads to insulin deficiency[2] and it mostly occurs in young people, usually up to the age of 30. Type 2 DM is characterized by both insulin resistance and the failure of pancreatic cells. Other specific types of DM are caused either by other pathological diseases of the pancreas due probably to single genetic mutations or drugs. Gestational diabetes, on the other hand, develops during pregnancy.

The mortality rate associated with DM due to cardiovascular disease is 65%. It is, therefore, considered a risk equivalent to coronary heart disease and generally affects the heart in three ways: Cardiac autonomic neuropathy, coronary artery disease (CAD) and diabetic cardiomyopathy (DCM)[3]. DCM is characterized by abnormal myocardial structure and reduced contractile performance even in the absence of other risk factors such as CAD, hypertension and significant valvular heart disease in individuals with DM. It was first described in the postmortem pathological findings of 4 diabetic patients who showed heart failure (HF) symptoms without coronary artery or valvular heart disease in 1972, and it was later confirmed in diabetic women with a 5-fold higher incidence of HF in the Framingham Heart Study in 1974[4,5]. DCM was described in 2013 as a clinical condition of ventricular dysfunction in patients with DM in the absence of coronary atherosclerosis and hypertension, in collaboration with the American College of Cardiology Foundation, the American Heart Association, the European Society of Cardiology and the European Association for Diabetes Research[6,7].

In the early stages of DM, significant changes occur in myocardial function and structure due to DCM, and these changes include left ventricular hypertrophy, increased fibrous tissue and cell signal abnormalities. These pathological changes cause cardiac contractile and diastolic dysfunction associated with ventricular fibrosis and hypertrophy which are the earliest pathophysiological complications in DCM[8,9]. Mechanisms underlying these changes include hyperglycemia, systemic and cardiac insulin resistance, increased free fatty acid levels, systemic and tissue inflammation, oxidative stress, renin-angiotensin-aldosterone system and activation of the sympathetic nervous system[10]. On the other hand, systolic dysfunction develops in the later stages of the disease and may be caused by diastolic dysfunction and decreased cardiac compliance resulting from the progression of DCM[8-10]. Furthermore, when systolic dysfunction occurs, the cardiac output gradually decreases with the severity of the disease and thus leads to HF. Consistent with this, The Framingham Heart Study showed that the frequency of HF was five times higher in diabetic women and two times higher in diabetic men than in age-matched control subjects[11]. HF leads to a low quality of life in individuals and makes it quite difficult to treat DM by simply changing the pharmacokinetics of anti-diabetic drugs. Therefore, diagnosing these patients faster and treating them earlier is extremely important. This review focuses on the role of voltage-sensitive ion channels in the electrophysiological disturbance of the diabetic heart and thus provides refined evidence that enables the understanding of the molecular mechanisms underlying the pathogenesis of DCM which may help to develop diagnostic methods and treatment strategies.

ELECTROPHYSIOLOGICAL CHANGES IN THE DIABETIC HEART

In diabetic patients, the incidence of cardiac arrhythmia is higher, as well as ventricular fibrillation and sudden death, and significant changes mostly associated with the repolarization of ventricles are observed in the electrocardiogram (ECG). Diabetic patients have higher heart rates, lower ECG potential amplitudes and more T-wave inversions than normal individuals. In addition, DM leads to sudden cardiac deaths that may be associated with an increase in the QT interval[12,13]. In type 1 DM, prolonged QTc interval and increased QTc dispersion have been observed[14,15]. In follow-up using Holter ECG monitoring, the occurrence of ventricular late potentials in patients with type 1 DM is observed more frequently than in healthy people and is more common in patients with type 2 DM[4,5]. This increased QTc interval is thought to be associated with an increased risk of mortality, like non-diabetic subjects with QTc prolongation[16,17]. Studies performed in twins have shown that QTc is longer in type 1 diabetic than non-diabetic subjects which implies that QTc prolongation is caused by diabetes rather than genetic factors[18]. The changes in the ECG are mostly associated with the prolonged cardiac action potential (AP) which is mostly ascribed to diabetes-induced alterations in repolarizing potassium currents (Figure 1)[19-21]. On the other hand, experimental studies have shown that these changes in repolarizing currents of cardiac myocytes can be different depending on the species of animal used, the type and duration of diabetes (Table 1)[22-25].

DIABETES-INDUCED ALTERATIONS IN CARDIAC ACTION POTENTIAL

DCM is often associated with impaired contraction and ECG abnormalities. The changes in the ECG that have been attributed to prolonged cardiac AP duration arise due to a decrease in repolarizing potassium currents caused by diabetes (Figure 1)[19-21].

The set off and regular spread of cardiac electrical stimulation depends on the formation of a normal cardiac AP throughout the myocardium. Depolarization and repolarization of AP are mediated by multiple inward and outward currents passing through specific membrane ion channels. The initial depolarization phase is generated by the inward Na^+ current (I_{Na}), mainly through voltage-sensitive sodium channels (Nav1.5), in the form of a rapid upstroke. In the subsequent early repolarization and plateau phases, the transient outward K^+ current and the inward L-type Ca^{2+} current (I_{CaL}) are prevalent, respectively. During this process, the Ca^{2+} ions entering through L-type Ca^{2+} channels (LTCC) induce a large amount of Ca^{2+} release from the sarcoplasmic reticulum (SR), thereby activating the excitation-contraction coupling. The repolarization, which ultimately returns the membrane to its resting potential, is mainly driven by the outward current through the voltage-gated K^+ channels (Kv)[26]. K^+ channel activity is the main determinant of AP duration as it limits depolarization time and the refractory period as well as the time period of Ca^{2+} -mediated contraction. There are numerous and diverse types of K^+ channels, each with specific kinetic and voltage dependent properties. They have specific roles in different repolarization stages of cardiac AP such that they determine the repolarization time and repolarization reserve as well as maintaining the resting membrane potential. The repolarization reserve refers to the partially overlapping function of these currents, namely rapid delayed rectifier K^+ currents (I_{Kr}), slow delayed rectifier K^+ currents (I_{Ks}) and inward rectifier K^+ currents (I_{K1})[27]. Repolarization kinetics of these K^+ currents is highly variable depending on the region of the heart and the species studied. This reflects the difference in the expression and density of different K^+ channel subtypes. Experimental studies have shown that different repolarizing currents decrease depending on the type of animal used to induce type 1 DM[28-30]. In the human heart ventricle, the main repolarizing currents are fast transient-outward K^+ current ($I_{to,f}$), slow transient-outward K^+ current ($I_{to,s}$), I_{Kr}, I_{Ks} and steady-state K^+ current (I_{ss}), while they are $I_{to,f}$, ultra-rapid delayed rectifier K^+ current (I_{Kur}) and I_{Ks} current in the atrium. All these features suggest that the investigation of the K^+ channels is important for understanding the mechanisms underlying cardiac dysfunction and arrhythmias caused by DCM and this can be a useful pharmacological target for the development of therapeutic agents.

Table 1 Overview of diabetes mellitus-induced alterations in cardiac K⁺ currents

Diabetes Mellitus Type	Duration	Transient outward K⁺ currents		Delayed rectifier K⁺ currents		Inward rectifier K⁺ currents	Ref.
		I_{to}	I_{ss}	I_{Kr}	I_{Ks}	I_{K1}	
Type 1	≤ 4 wk	↓	↓	?	↓	↔	[20,45,49,50,54,72,73,143-145]
	4-8 wk	↓	↓	↓↔	↓	↔	[19,21,29,40-43]
	> 8 wk	↓	↔	↓↔	↓	↓↔	[51,52,69]
Type 2		↓	↓	?	↓	↔	[30,39,49]

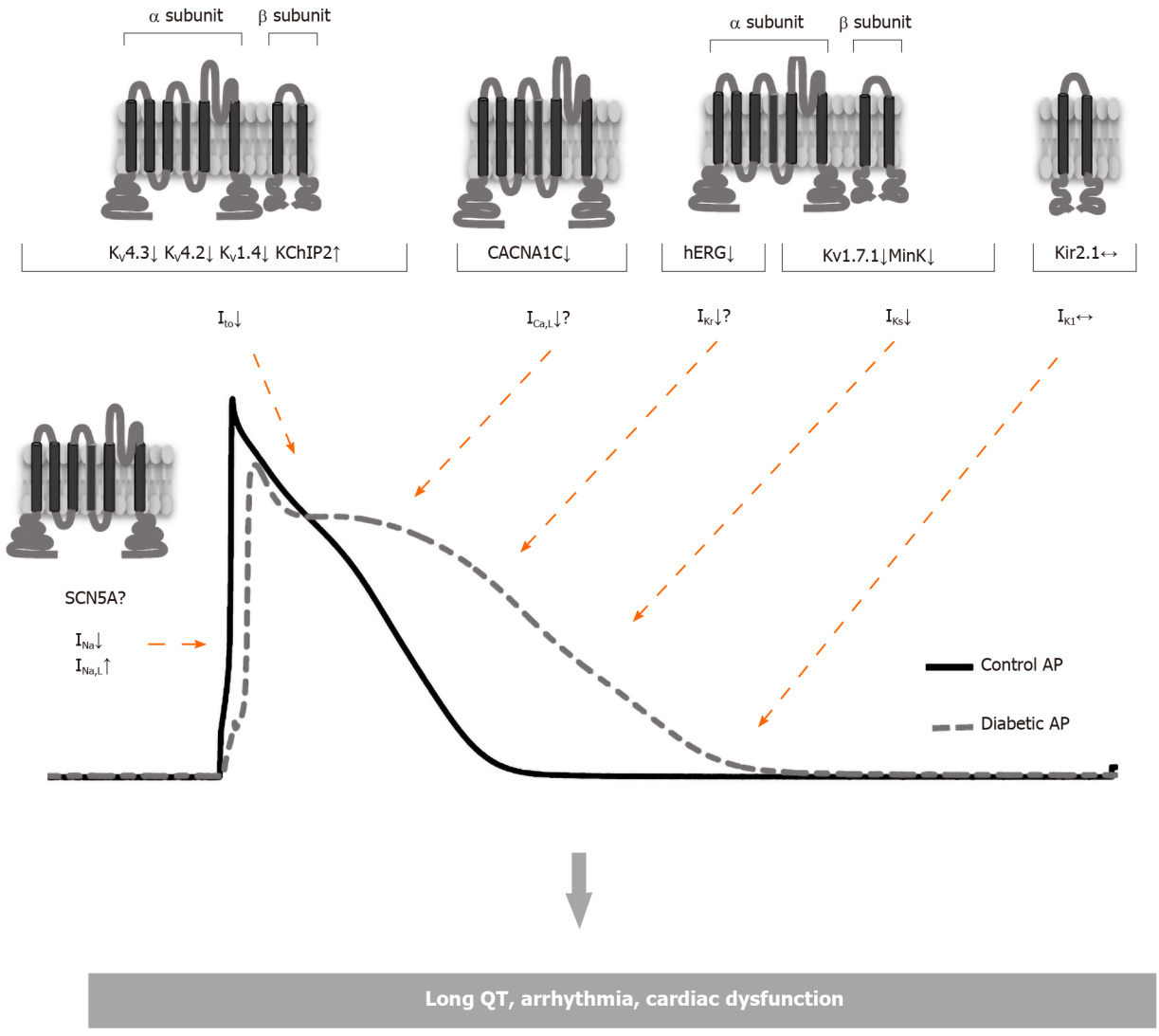

Figure 1 Pathological alterations in voltage-gated cardiac ion channels that contribute to the action potential of the ventricular myocytes due to diabetes mellitus.

POTASSIUM CURRENTS IN DIABETIC CARDIOMYOCYTES

K⁺ channels represent the most functional and diverse types of cardiac ion channels[31-34]. They tightly regulate the cardiac repolarization, thereby providing a stable and consistent AP signal. Different K⁺ channel types may have overlapping functions that provide some degree of functional redundancy and thereby contribute to the repolarization reserve[27,35]. All of the α-subunits of different K⁺ channel types have a pore-forming region that has a selective permeability to the K⁺ ion. This can be associated with a particular structural motif and allows K⁺ movement from the plasma

membrane under the effect of an electrochemical gradient. In addition, there are ligand binding sites that can change the channel conformation and gating mechanisms in response to membrane depolarization.

Transient outward potassium current (I_{to})

In diabetic patients, the incidence of cardiac arrhythmia, ventricular fibrillation and sudden cardiac death is higher, and most of them have significant changes in ECG recordings due most probably to abnormal AP repolarization. Accordingly, in myocytes isolated from diabetic hearts, I_{to} is the mainly affected repolarizing current.

I_{to} is basically responsible for the early repolarization phase of the AP. Two subtypes of I_{to} are defined; one is blocked by 4-aminopyridine (4-AP) and not dependent on Ca^{2+} (I_{to1}), while the other is not blocked by 4-AP but modulated by Ca^{2+} (I_{to2})[34]. Cardiac regions with shorter AP duration, such as the epicardium, right ventricle, and septum, have higher transient outward K^+ channel expression. Due to their discrete characteristics, I_{to1} currents are subdivided into $I_{to,f}$ and $I_{to,s}$ components. $I_{to,f}$ and $I_{to,s}$ currents are both present in the ventricles, however, $I_{to,f}$ is the dominant current expressed in the atrium[36]. Although the $I_{to,s}$ currents have not so long inactivation time, their classification as "slow" is only relative to $I_{to,f}$. Nevertheless, both $I_{to,f}$ and $I_{to,s}$ channels are activated and inactivated rapidly compared to other K^+ channels.

Many studies have been conducted in rats to elucidate the cellular mechanisms of diabetes-induced repolarization abnormalities[19,37-43]. In these studies, it has been shown that the I_{to} amplitude reduction which is responsible for the prolongation of AP repolarization in diabetic rats is associated with downregulation of the expression of Kv4.3 and Kv4.2 channel proteins[39-42,44]. However, an increase in the protein expression of Kv1.4, which is responsible for the regulation of $I_{to,s}$ currents has been reported[29,44,45]. In the case of a depressed I_{to} channel, protein expression may change in the opposite direction and thus the upregulation of Kv1.4 and KChIP2 may be associated with a decrease in Kv4.3 expression (Figure 1). Consistently, in the Kv4.3 gating model supported by Patel *et al*[46], KChIP2 isoforms have suggested an acceleration in the recovery from inactivation and promotion of the open-state inactivation with slower closed-state inactivation. As a result, the upregulated KChIP2 causes slower inactivation in depolarized potentials and enhances the re-opening of the I_{to} channels during membrane repolarization. This eventually increases the repolarizing force in the plateau phase which may contribute to late repolarization[46]. However, in rat myocardium, ventricular repolarization includes different mechanisms to dogs, humans, and other mammals as it lacks a pronounced plateau phase and has a short AP duration. Therefore, these results obtained in rats have relatively limited value in understanding the repolarization abnormalities observed in diabetic myocardium. Expression of ion channel proteins has also been widely investigated to elicit the molecular mechanisms underlying electrophysiological changes by generating an experimental type 1 DM model in animal species with a pattern of cardiac repolarization and ionic currents that are more similar to those in the human heart. In dog cardiomyocytes, both I_{to} reduction and downregulation of Kv4.3 protein (the dominant subunit forming the pore in dog and human ventricular myocytes) are consistent with the data obtained in rats[29]. As a result, I_{to} currents and expression of those proteins involved in channel regulation are consistent in rats and dogs. Contrary to these findings obtained in other studies, no significant change in I_{to} current was observed in rabbits. The reason for this discrepancy can be explained by the fact that the rabbit I_{to} current has a different molecular basis. In rabbits, I_{to} is mediated mostly by Kv1.4 channels, but not Kv4.3 channels as in rats, dogs and humans[47]. Nevertheless, different results have also been obtained in animal models in which the experimental type 2 DM model was induced by different methods. In myocytes isolated from db/db mice, a leptin receptor mutant showing type 2 DM symptoms, K^+ currents have been shown to decrease and AP duration is prolonged[48]. On the other hand, there was no change in K^+ currents and AP duration measured in the type 2 DM rat model induced by feeding on a diet enriched with fructose for 6-10 wk[49]. Thus, it can be concluded that ionic currents and the expression of protein channel domains that precipitate the prolongation of AP duration observed in diabetes vary according to the animal species studied, the diabetes model created and duration of the diabetic condition.

Although studies have demonstrated that DM causes a significant decrease in $I_{to,f}$ and $I_{to,s}$ current amplitudes, neither the voltage dependence of the inactivation nor the time dependency of the reactivation has changed[20,30,50,51]. However, contrary to the results generally obtained, in long-term diabetes (24-30 wk) significant changes in inactivation and reactivation kinetics of I_{to} have also been reported in rat cardiac myocytes[52]. Therefore, it seems likely that different results in channel kinetics will be

seen depending on the duration of the diabetic state.

Two hypotheses have been proposed regarding the effects of type 1 DM on potassium currents in the heart muscle. The first hypothesis involves insulin deficiency as it affects the gene expression of a large number of proteins, including potassium channel proteins[53]. Incubation of diabetic cardiac myocytes with insulin for 6 h restored the $I_{to,f}$ to control values and this effect was prevented by protein synthase inhibitors[54]. In a study using a cardiomyocyte-restricted insulin receptor knockout (CIRKO, cardiac-specific insulin receptor knockout) mouse model, impaired insulin signaling resulted in a decrease in mRNA and protein expression of K^+ channels prominent in ventricular repolarization. Specifically, in isolated left ventricular CIRKO myocytes, Kv4.2 and KChiP2 expression decreased, consistent with a decrease in $I_{to,f}$ amplitude. The alleviated $I_{to,f}$ in turn resulted in a prolonged ventricular AP and prolonged QT interval in surface ECG[30]. These results support the idea that the lack of insulin signal in the heart is sufficient to cause repolarization abnormalities described in other diabetic animal models. The second hypothesis assumes that the cause of decreased cardiac $I_{to,f}$ in DM is defective glucose metabolism. This hypothesis was supported by the reversal of potassium currents in diabetic cardiomyocytes to normal levels after 6 h of incubation with metabolic enhancers such as L-carnitine, glutathione, or pyruvate[38,51,55].

Activation of the renin-angiotensin system has also been demonstrated in insulin-dependent diabetic rats, and I_{to} has been reduced with increased angiotensin II (Ang II) levels[56]. Inhibition of the production or action of Ang II has been found to reverse the decreased I_{to} in both type 1 and type 2 DM. In ventricular myocytes of streptozotocin (STZ)-induced type 1 DM rats, decreased I_{to} and I_{ss} currents have been shown to be significantly increased after incubation with the Ang II receptor blockers saralasin or valsartan[48]. Incubation of ventricular myocytes isolated from the mutant db/db mice with valsartan (> 6 h) has been shown to reverse the reduced I_{to} and I_{ss} currents[48]. These results confirm that cardiac myocytes contain a local renin-angiotensin system that is activated in diabetes. These effects of Ang II can be explained by the fact that it has a large number of various cellular effects mediated by protein kinase A, protein kinase C and tyrosine kinases that may lead to inhibition of some ionic channels. It is suggested that the changes caused by the chronic release of Ang II on ionic currents and AP can be eliminated by blocking the formation or effect of Ang II. Consistently this implies that Ang II receptor blockage or angiotensin-converting enzyme inhibition can protect against cardiac arrhythmias that may occur in DCM. However, more studies are needed to explain these elaborate findings unequivocally.

Delayed rectifier potassium current

Delayed rectifiers, along with other ion channels, mainly determine the waveform as well as the AP duration and thus play critical roles in heart physiology and pathophysiology (Figure 1). Disruption of the normal functions of the delayed rectifier channels makes the heart more sensitive to abnormal electrical activity and prone to arrhythmia. This class of K^+ channels includes I_{Ks}, I_{Kr} and atrial specific I_{Kur} channels.

Like I_{to}, I_{Kur} is also effective in the early repolarization phase of the AP. This current quickly activates in less than 10 milliseconds at plateau voltage ranges and slowly disappears through the AP repolarization period[57-59]. I_{Kur} current is the dominant delayed rectifier current for atria, and therefore shorter AP duration is seen in the atrial myocytes compared to ventricles[36,57,59,60]. In regions where I_{Kur} currents are observed, ion channels are not evenly distributed on the myocyte membrane and are mostly localized in the intercalated discs[32]. This specific localization of I_{Kur} in the atrium makes it an interesting target for atrial selective treatment, so that inhibition of I_{Kur} prolongs the AP duration of atrial myocytes, this prolongation is not observed in the ventricles[32].

On the other hand, I_{Kr} currents are critical for phase 3 repolarization of AP. It shows a relatively rapid activation with depolarization, however, the rate of inactivation is about 10 times higher than the rate of activation. This ensures that these channels are relatively non-conductive during the 1st and 2nd stages of cardiac AP[61-63]. So even though this current is called delayed rectifier, it also shows an inward rectification property at positive potentials[24,62,63]. However, as the membrane potential reaches 0 mV with the end of phases 1 and 2, I_{Kr} is activated once again, but deactivation is much slower during this phase. This causes a large outward flow of K^+ ions during phase 3 repolarization[27,64]. I_{Kr} is found in both the atrium and ventricles of humans but is expressed at higher levels in the left atrium and ventricular endocardium[36].

Cardiac repolarization is also affected by the I_{Ks} current which is slowly activated at potentials around -20 mV. Unlike I_{Kr}, I_{Ks} is almost completely inactive in phase 2 repolarization and significantly affects phase 3 repolarization of cardiac AP[27,65,66]. This

feature of I_{Ks} is especially important in relatively longer atrial and ventricular APs. It is also important for the reactive shortening of AP duration during a physiological increase in heart rate. Namely, a significant increase in the heart rate leads to a decrease in the inactivation time of I_{Ks} current which results in higher I_{Ks} and a steeper decrease in the repolarization phase of AP[67,68]. Blocking I_{Ks} current causes a prolongation in AP duration at particularly increased heart rates[68]. Inhibition of I_{Ks} current can also increase the reactivation of voltage-sensitive Ca^{2+} channels, thereby increasing the risk of arrhythmic events[27]. All cardiac cell types have I_{Ks}, but their expression is significantly reduced in the middle of the myocardial wall; this explains the longer AP duration in this region[36].

Studies performed using various animal models have reported a decreased I_{Ks} current in diabetic dog and rabbit hearts[28,29]. However, there are controversial findings regarding the effects of diabetes on I_{Kr} current because it has been reported to decrease in diabetic rabbits[21] or not to change in diabetic rabbits, dogs, and mice[28,29,51]. A significant reduction in I_{Kr} current and hERG expression along with a prolonged QTc interval have been demonstrated in alloxan-induced diabetic rabbits[21,69,70]. In these reports, the DM-induced changes are apparent after an 11-wk period, whereas QTc prolongation is less pronounced in rabbits at the end of the 3-wk diabetes period, and no changes were observed in the I_{Kr} current[28]. These results show that DM-induced changes in different ionic currents of cardiac myocytes may develop at different time points of the disease. However, neither activation nor deactivation kinetics of I_{Kr} current have been changed in diabetic cardiac myocytes[28]. In addition, it has been shown that the suppression of I_{Ks} current along with a moderate extension of the QTc interval occurs at an early stage, such as the third week of DM. However, after the eighth week of alloxan-induced diabetes, no change in I_{Kr} current has been observed, whereas I_{Ks} current was suppressed in dog myocytes[29]. In addition to the fact that the regional differences in AP duration and left ventricular ionic currents are important in the reduction of the repolarization reserve in diabetes, the severity of diabetes is also prominent in the extent of these changes[37,71-73]. Therefore, more experimental and clinical data are needed to clarify this issue.

It is surprising that the decrease in the density of the I_{Ks} and the expression of the regulatory β-subunit channel protein, MinK, is associated with increased expression of the pore-forming α-subunit Kv1.7.1[74]. On the other hand, there may be more direct interactions between Kv1.7.1 and hERG, which are α subunits of I_{Ks} and I_{Kr} currents, respectively, and Kv1.7.1 can modulate not only the distribution but also the biophysical properties of hERG. Indeed, Kv1.7.1 overexpression has been shown to elicit a dramatic increase in hERG current density[74]. Therefore, it can be considered that the downregulation of MinK is the primary result of diabetes, and the concomitant upregulation of Kv1.7.1 may be a secondary compensatory process that can partially oppose the downregulation of MinK arising due to diabetes. Besides, it has been demonstrated that hERG is negatively modulated by hyperglycemia, tumor necrosis factor, ceramide and reactive oxygen species which are cellular metabolites accumulated in diabetic tissues[75,76]. It has also been reported that insulin metabolism affects the hERG expression as well as I_{Kr}/hERG function and it is quite possible for insulin to modulate different ion channels through separate mechanisms[21]. These results in total suggest that I_{Kr}/hERG is a potential target for the treatment of cardiac arrhythmias in diabetic patients.

Deschênes *et al*[77] reported that when Kv4.3 was co-expressed with MinK, the current density was five times higher than that of Kv4.3 expressed alone and that the inactivation and reactivation kinetics of Kv4.3 slowed down through MinK. Therefore, modifying MinK by diabetes can at least partially explain the diminution of I_{to} density in the dog myocytes. It is also worth noting that insulin administration can completely prevent the diabetes-induced reduction of I_{Ks} current (and associated changes in the expression of channel proteins), but only a limited protective effect on I_{to}. The reason for this discrepancy remains uncertain, but it should be noted that patients with type 1 DM may have an increased proarrhythmic risk even when they are treated regularly with insulin.

Inward rectifier K^+ current (I_{K1})

Inward rectifier K^+ current is active in a narrow membrane potential range. The rectifying property results in a marked decrease in I_{K1} conductivity in positive depolarized membrane potentials and an increase in I_{K1} current in negative membrane potentials. As a result, this has the effect of stabilizing the resting membrane potential close to the K^+ equilibrium potential[64]. The channel mediating the I_{K1} current does not show voltage-dependent activation and does not have a voltage sensor. However, the I_{K1} current modulation associated with the movement of Mg^{2+} and polyamines

provides indirect sensitivity of the channel to voltage[78-81]. Since the channel is inhibited by Mg^{2+} and polyamines at membrane potentials more positive than 20 mV, I_{K1} channel has no conductivity between phase 0 and phase 2 of the AP. When the potential returns to more negative values (typically around -40 mV), the blockade mediated by Mg^{2+} and polyamines on I_{K1} channel conductivity is relieved, and this contributes to the phase 3 repolarization of cardiac AP[80]. I_{K1} current is present in both atria and ventricles and therefore plays an important role in determining resting membrane potentials. Channels that transmit I_{K1} current are more expressed in the ventricles, making the ventricles less sensitive to the pacemaker effect[36].

As mentioned, I_{K1} current has been one of the most widely studied K^+ currents in DCM due to its importance in stabilizing the membrane potential and its contribution to AP duration (Figure 1). In these studies where different animal species (mouse, rat, rabbit, and dog) were used and different diabetes periods were applied (3 wk, 4 wk, 8 wk, 10 wk) changes in I_{K1} were extensively examined. However, neither the I_{K1} current amplitude[19,20,38,49,50] nor the expression of Kir2.1, the main component of the I_{K1} channel, changed in the diabetic heart[69,82]. Therefore, these findings confirming the absence of a shift in resting membrane potential of diabetic cardiomyocytes imply that I_{K1} current is less likely to contribute to DM-induced AP prolongation as well.

VOLTAGE-GATED Ca^{2+} CHANNELS IN DIABETIC CARDIOMYOCYTES

Intracellular Ca^{2+} dysregulation is a well-defined complication in DCM and it has been demonstrated in both type 1 and type 2 DM (Figure 1 and Table 2)[83-86]. Although the cellular mechanisms underlying this impaired Ca^{2+} handling have not been fully explained, a significant decrease in SR Ca^{2+} content associated with reduced SERCA2 expression/activity, decreased phospholamban phosphorylation and increased ryanodine receptor (RyR) Ca^{2+}-leak have been widely reported in type 1 and type 2 diabetic heart myocytes, and as a result the diastolic Ca^{2+} concentration increased and the amplitude and decay rate of the Ca^{2+} transients significantly decreased[40,84,87-91]. Also, there was a decrease in Na^+-Ca^{2+} exchanger (NCX) expression in type 1 diabetic myocardium[92]. In addition to these findings, the role of LTCC in the impaired Ca^{+2} handling in DCM has not been fully clarified.

Basically, bulk Ca^{2+} release from SR into the cytosol is mediated by activation of RyR which is triggered by inward Ca^{2+} current through LTCC. This mechanism is described as Ca^{2+}-induced Ca^{2+} release and it is a critical event for excitation-contraction coupling in cardiac myocytes[93,94]. LTCC which acts as a trigger for excitation-contraction coupling is an ion channel family with four different members. Of these, $Ca_V1.2$ is the main Ca^{2+} channel expressed in cardiomyocytes which has four homologous domains and expressed by CACNA1C or α1C[95]. Each of these domains is characterized by six transmembrane α-helix structures. This channel has a current-voltage relationship that activates at the potential value of -40 mV, gives the maximum amplitude at potentials between 0-10 mV, and reverses at +60 to +70 mV[96,97].

Many studies have examined LTCC in DCM. However, contradictory findings have been reported about the activity of LTCC in these studies (Table 2). Some of them have demonstrated an unchanged current-voltage relationship of LTCC in DCM[29,50,98-102]. In these studies, diabetes duration is generally less than 10 wk (4-8 wk)[50,99,101,102]. The lack of significant change in L-type Ca^{2+} current (I_{CaL}) despite the reduced Ca^{2+} transient amplitude and slowed rate of removal indicates that the coupling between the LTCC and RyR is impaired in DCM[99,101]. Accordingly, Lacombe *et al*[101] showed a reduced gain in the Ca^{2+}-induced Ca^{2+} release mechanism of diabetic myocytes due most probably to altered LTCC-RyR coupling. Dysregulation of intracellular Ca^{2+} handling in the diabetic heart might also be mediated by alterations in NCX, SERCA2, PLB and RyR expression or phosphorylation[98].

However, some other studies have reported significant changes in the amplitude of I_{CaL} current[52,89,103-108]. This discrepancy regarding the activation of I_{CaL} current might have arisen due to two main factors: the diabetes model used in the study and the duration of the diabetic state. For type 2 DM, transgenic animal models have been mostly used and, in these studies generally, I_{CaL} current has been found to decrease in ventricular myocytes[89,105-107]. However, in the type 1 DM models induced by chemical agents, the experimental period varies between 4 and 12 wk and this may at least partially explain the difference observed in I_{CaL} current densities[109]. Nevertheless, some studies using a similar duration of diabetes have also demonstrated different I_{CaL} current amplitudes in ventricular myocytes. In general, it is most likely that there is a decrease in the amplitude of I_{CaL} current of the ventricular myocytes in the STZ-

Table 2 Changes in L-type Ca^{2+} and Na^{+} currents in diabetic heart myocytes

Diabetes Mellitus Type	Duration	Ca^{2+} currents	Ref.	Na^{+} currents		Ref.
		I_{CaL}		I_{Na}	$I_{Na,L}$	
Type 1	≤ 4 wk	↔	[50]	↔	?	[130]
	4-8 wk	↓↔	[29,99,101-103,108]	↓	?	[130,132]
	> 8 wk	↓↔	[52,98]	↔↓	?	[69]
Type 1 transgenic		↓	[104]	?	↑	[135]
Type 2		↓	[89,105-108]	?	↑	[135]

induced DM model after ten or more weeks of diabetes duration[52,103]. Similar to that of the type 2 DM model, the density of I_{CaL} current decreased in cardiac myocytes of transgenic animals with type 1 DM[104].

In the studies where I_{CaL} current amplitude was found to be decreased in diabetic heart myocytes compared to that of control, it was approximately 15%-30% lower in the negative membrane potentials range, and this difference maintains up to +20 mV[89,104,106,108]. This reduction in I_{CaL} current may be due to the activation/inactivation kinetics of the channels, the expression of the channel proteins, or the change in the single-channel conductance. Pereira *et al*[89] measured the single-channel current in diabetic myocytes to test whether it is the likely explanation for the reduced I_{CaL} current and they did not find a significant difference compared to control myocytes. Thus, it was concluded that the activity of the single-channel current is not responsible for the decreased macroscopic I_{CaL} currents in the diabetic heart. Instead, it can be ascribed to the altered channel kinetics or reduced expression of channel proteins due to diabetes.

Considering that I_{CaL} current reaches its maximum value between 0-10 mV membrane potentials, the DCM-related decrease in current amplitude may have occurred due to the altered channel kinetics. As a matter of fact, the potential value required for half of the channels to be open (V_h) has shifted to more positive values in diabetic myocytes. This may explain why fewer LTCC channels are opened at lower potentials and why the measured current is lower. There was no significant difference observed in the half-inactivation potential ($V_{1/2}$) where half of the channels are closed and recovered from inactivation in diabetic myocytes[89,104,106,110].

Another explanation for the reduced I_{CaL} current in DM is the change in channel protein expression. As mentioned earlier, $Ca_V1.2$ is the main Ca^{2+} channel type expressed in the heart, and studies have shown that expression of the a1C subunit of $Ca_V1.2$ decreases in type 1 and type 2 diabetic hearts[89,104]. Therefore, it is likely that the decrease in I_{CaL} is due to both the change in LTCC activation and the change in channel expression[111].

The physiological mechanisms underlying this decrease in I_{CaL} current in diabetic cardiac myocytes could be the phosphatidylinositol 3-kinase (PI3K)/Akt pathway[112-114]. Consistently, activation of the PI3K/Akt pathway, which is a potent modulator of I_{CaL} currents, is downregulated due to diabetes and this decrease triggered the reduction of I_{CaL} in diabetic myocytes[115]. It is known that insulin or insulin growth factor (IGF-1) mediated activation of PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to form phosphatidylinositol 3,4,5-trisphosphate (PIP3), and thus PIP3 synthesis stimulates Akt (protein kinase B)[112]. Recent studies have shown that the PI3K/PIP3/Akt pathway performs its mediator effect by providing phosphorylation of the $Ca_V\beta2$ subunit of LTCC[116,117]. However, PI3Ks are a large molecular family in which PI3Kα is in the class I group and it is one of the prominent mediators in the activation of LTCC in cardiac myocytes. Consistently, I_{CaL} current density has been shown to decrease in PI3Kα-null cells due to the downregulation of LTCC[118]. It has also been demonstrated that the activation of Akt with PIP3 infusion can reverse the decrease in I_{CaL} current and that $Ca_V\beta2$ phosphorylation protects the $Ca_V1.2$ pore-forming subunit from proteolytic degradation[116].

Another important point is that PI3Kα and PI3Kβ both take part in the T-tubule network. Since LTCC is primarily located in the T-tubule, I_{CaL} current density decreases due to T-tubule disorganization in PI3Kα and PI3Kβ deficiency[119]. As mentioned earlier, the subunits of PI3Ks is an important point that needs to be considered during intervention since I_{CaL} density may decrease in treatments that are not specific to

PI3Kα[112,120-122]. PI3Ks can also reduce the response to β-AR stimulation through associated kinases. Particularly, PI3-δ, which is in the class I B PI3K group, shows its effect through the G proteins. Accordingly, in a study of transgenic PI3K$^{-/-}$ animals, isoproterenol application to ventricular myocytes increased I_{CaL} and intracellular Ca^{2+} transients more than control myocytes, and this was claimed to lead to HF[121,123].

In conclusion, conflicting findings in I_{CaL} current densities and $Ca_V1.2$ expression in DCM may be related to the type of diabetes model and its duration. In studies using transgenic animals for both type 1 and type 2 DM models, have been shown to cause a marked reduction in I_{CaL} current density and $Ca_V1.2$ expression. The difference observed in the diabetes model induced with STZ injection may be related to the duration of diabetes and the amount of STZ administered. As previously emphasized, I_{CaL} current has been shown to decrease significantly in diabetes periods of more than 10 wk, while findings varied in studies with shorter diabetes duration. This may be due to multiple physiological mechanisms acting on I_{CaL} current, whose activity is changed by the duration of the diabetic condition. Currently, the most likely mechanism suggested to be responsible for the reduced I_{CaL} current in DCM is the altered PI3K/PIP3/Akt pathway due to insulin or IGF-1 decrease. However, current findings need to be supported using comparable models for both types of diabetes, and it is also important to clearly determine whether cellular signaling mechanisms underlying the pathogenesis of these types of disease are similar and how changes in these molecular pathways affect I_{CaL} current depending on the duration of the disease.

VOLTAGE-GATED Na^+ CHANNELS IN DIABETIC CARDIOMYOCYTES

Na^+ ion plays a vital role in many cellular mechanisms such as the upstroke phase of AP (voltage-dependent Na channels, Na_V), Ca^{2+} cycling (NCX), metabolic processes (Na^+-glucose cotransporter) and regulation of the intracellular pH (Na^+-HCO_3^- cotransporter, Na^+/H^+ exchanger) in cardiomyocytes[93,124,125]. However, the main scope of this review is the Na_V channels that ensure the fast depolarization phase of cardiac AP. So far, nine different Na_V types have been identified ($Na_V1.1$ to $Na_V1.9$, respectively)[126], and the major Na_V type expressed in cardiomyocytes is $Na_V1.5$ encoded by the SCN5A gene[127]. This channel has four homologous domains (D1-D4) and each domain consists of six transmembrane segments (S1-S6)[128,129].

Although the intracellular Na^+ concentration has been shown to increase dramatically in diabetic cardiomyocytes, few studies have examined the changes in the structure and activation of Na_V channels[125]. Earlier studies have suggested that there is no significant change in Na_V channels associated with DCM, while recent studies have shown altered I_{Na} current in diabetic cardiac myocytes (Table 2)[69,130-132]. These conflicting results regarding the amplitude of I_{Na} current may be related to the duration of diabetes, as in Ca^{2+} channels. As a matter of fact, Bilginoglu *et al*[130] reported that there was no change in I_{Na} current of ventricular myocytes at the end of the 4-wk diabetes period, whereas there was a significant decrease at 7-8 wk. In addition, a leftward shift has been observed in both activation and inactivation curves of Na_V channels in diabetic myocytes[130]. The observation of similar findings in metabolic syndrome, in which insulin resistance is increased, suggests that these effects may be mediated directly or indirectly by insulin signaling[133,134]. Stabler *et al*[131] have also observed a significant decrease in the amplitude of I_{Na} current in diabetic rabbit ventricles, while the channel kinetics did not change.

There is also a significant change in late Na^+ currents ($I_{Na,L}$), which have recently been reported to be responsible for many cardiologic pathologies including DCM[135-137]. Although the amplitudes of these currents are up to only 1% of conventional voltage-dependent fast Na^+ currents, it is thought that the long-term activation of Na^+ channels can trigger pathological changes in AP[136,138].

$I_{Na,L}$ current has been shown to increase significantly in DCM and is therefore suggested to increase the likelihood of arrhythmia by causing prolongation of AP[135]. Although many different treatments and interventions (ranolazine, mexiletine, PIP3, *etc*) to inhibit $I_{Na,L}$ current have been shown to reverse the prolonged AP duration, it is difficult to attribute the prolongation of AP solely to $I_{Na,L}$ current due to the prominent role of K^+ and Ca^{2+} currents in AP morphology[113,132,135,139]. Most importantly the role of K^+ currents in AP prolongation has been extensively investigated in diabetic hearts for a long time even though the number of studies showing the effect of $I_{Na,L}$ current on AP duration is relatively limited. Therefore, this finding should be carefully examined and confirmed by new studies in both type 1 and type 2 DM models.

CONCLUSION

DM is one of the most common chronic diseases worldwide and is mostly associated with serious cardiovascular complications that significantly increase the risk of mortality in diabetic patients. The abnormalities observed in the ECG and cardiac function of diabetic patients are mostly related to alterations in the voltage-gated ion channels that are critical determinants of the duration and morphology of cardiac AP. At the cellular level, prolongation of AP and defective contractile function typically arise due to a combination of reduced K^+ currents, irregularities in Na^+ currents and changes in Ca^{2+} currents along with impaired intracellular Ca^{2+} handling in diabetic cardiomyocytes. DM can affect not only the amplitude but also kinetics of the cardiac ion channels by modifying the biophysical behavior and/or the expression levels of the channel-forming proteins. Disruption of protein expression or alteration of biophysical properties of ion channels or both can contribute to the reduced currents caused by DM in diabetic cardiomyocytes. However, observing that there is often no change in the inactivation or reactivation kinetics of the cardiac ion channels in diabetic cardiomyocytes suggests that an abnormality in protein expression is more likely.

As a result, under pathological conditions such as DM, depressed K^+ currents may cause abnormal prolongation in AP duration due to insufficient repolarization and therefore lead to the development of early and late afterdepolarizations[140-142]. Therefore, it is likely that decreased K^+ currents in diabetic myocardium will reduce the repolarization reserve and increase the risk of arrhythmias. Nevertheless, as stated earlier, cardiac Na^+ and Ca^{2+} channels also have important effects that cannot be neglected in diabetic cardiac pathologies and should be taken into account in order to understand the pathogenesis of DCM.

Future perspectives

The effect of DM on the electrical conduction of the myocardium and the development of cardiac arrhythmias is becoming more evident. Due to its complex and multifactorial nature, the relationship between diabetes and cardiac arrhythmias is not yet fully understood. Hence, understanding the precise ionic mechanisms of APD/QT prolongation in DM is of great importance to develop more distinctive approaches for the prevention and treatment of electrical disturbance in diabetic patients.

Remodeling of the expression of K^+, Na^+ and Ca^{2+} channels in various physiological and pathological conditions is a complex phenomenon that can alter both the morphology of cardiac AP and contractile function of the heart. In diabetic patients, voltage-gated ion channels play a vital role in cardiac AP repolarization, and expectedly they are potential targets for the development of specific treatments to prevent cardiac arrhythmia and DCM-associated ventricular dysfunction. Using drugs particularly effective on ion channels and optimizing the effectiveness of their therapeutic action on the arrhythmogenic trend will minimize the potential cardiac and extracardiac toxicity problems. However, due to their complex mechanisms, more experimental and clinical research is needed to fully elucidate the relationship between diabetes and arrhythmias and to develop new therapeutic strategies.

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