Cell Calcium 56 (2014) 428–435

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Review

Functional and structural impact of pirfenidone on the alterations of cardiac disease and diabetes mellitus

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ARTICLE INFO

Article history:
Available online 23 July 2014

Keywords:
TGF-β1
Calcium channel
Intracellular calcium
Ion channel
Action potential
Cardiac myocyte

ABSTRACT

A synthetic compound, termed pirfenidone (PFD), is considered promising for the treatment of cardiac disease. It leads to beneficial effects in animal models of diabetes mellitus (DM); as well as in heart attack, atrial fibrillation, muscular dystrophy, and diabetic cardiomyopathy (DC). The latter is a result of alterations linked to metabolic syndrome as they promote cardiac hypertrophy, fibrosis and contractile dysfunction. Although reduced level of fibrosis and stiffness represent an essential step in the mechanism of PFD action, a wide range of functional effects might also contribute to the therapeutic benefits. For example, PFD stimulates L-type voltage-gated Ca^{2+} channels (LTCCs), which are pivotal for a process known as excitation–contraction coupling (ECC). Recent evidence suggests that these two types of actions – namely structural and functional – aid in treating both cardiac disease and DM. This view is supported by the fact that in DC, for example, systolic dysfunction arises from both cardiac stiffness linked to fibrosis and down-regulation of ECC. Thus, not surprisingly, clinical trials have been conducted with PFD in the settings of DM, for treating not only cardiac but also renal disease. This review presents all these concepts, along with the possible mechanisms and pathophysiological consequences.

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1. Introduction

Diabetic cardiomyopathy (DC) is a condition in which diabetes mellitus (DM) results in heart dysfunction, in the absence of coronary disease or high blood pressure. DM also results in a higher risk for many other pathological conditions, such as cerebrovascular accidents and nephropathy (termed diabetic nephropathy, DN). It is well known that a close relationship exists between all these conditions and metabolic syndrome (MetS); which is characterized by the presence of dyslipidaemia, hypertension, insulin resistance and obesity [1,2].

Pirfenidone (PFD), on the other hand, is a synthetic compound of low molecular weight (185 g/mol), which initial therapeutic properties were reported many years ago by Gadekar; when it was described as a novel analgesic, anti-pyretic, and anti-inflammatory compound [3]. In the clinic, it is used to treat idiopathic pulmonary fibrosis, based on the fact that not only inhibits the development of interstitial fibrosis, but also reverts this process [4–6]. To date, PFD has been used in a number of clinical trials for both heart and renal disease linked to DM [7–9]. Unfortunately, however, apart from inhibiting fibrosis; little is known about the primary mechanism of action of this drug [6].

It is well known that pathological remodeling of the heart involves changes of both morphological and functional nature (also known as structural and electrophysiological remodeling, respectively), and there is evidence that PFD has the potential to modulate both of them. Structural changes involve hypertrophy, stiffness and fibrosis, while the functional ones consist of alterations in the expression and function of ion channels and transporters, which in turn modify the form of action potentials and intracellular Ca^{2+} levels [10].

DC involves a progressive loss of ventricular function. It represents a major risk of hospitalization and mortality after acute myocardial infarction [11]. Both the systolic and diastolic functions of ventricles are impaired [1,2]. Accordingly, a number of studies have focused on studying the underlying mechanisms of DC in isolated ventricular myocytes. In contrast, both structural and functional alterations have been described in atria almost exclusively at the clinical level [12].

The next sections discuss alterations associated to DC, with regard to ion channels, Ca^{2+} handling and the corresponding

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http://dx.doi.org/10.1016/j.ceca.2014.07.008
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molecular mechanisms. The actions of PFD, including the modulation of ion channels and its corresponding implications, are discussed at the end of the review. For simplicity, the term "myocytes" is used to refer to ventricular cardiomyocytes, unless otherwise specified. Likewise, as much work has been performed in streptozotocin-induced diabetic rats, this model has been abbreviated as S-IDRs.

2. Voltage-gated ion channels and action potentials (APs)

Ion channels and in particular those regulated by voltage (i.e. voltage-gated ion channels, VGCC) are responsible for shaping the action potential (AP) waveform. The cardiac AP consists of five phases, which not only reflect but also modulate the activity of ion channels as a feedback mechanism. Phase 0 is known as the depolarization phase, in which the Na^+ channels (Na_V) are activated, causing a fast depolarization of the membrane potential (V_m). This depolarization activates both K^+ (K_V) and Ca^{2+} (Ca_v) channels, so that the efflux of K^+ leads to a transient and small repolarization (phase 1), but the influx of Ca^{2+} opposes to the outward K^+ current generating the plateau of the AP (phase 2). Then, as Ca^{2+} channels start to inactivate and more K^+ ions are moving out of the cell, the V_m begins to repolarize more rapidly (phase 3); until it reaches an almost steady-state level (phase 4), and it is kept there by the efflux of K^+ until another phase 0 begins. It is well recognized that the shape of the AP varies according to different factors, such as animal species, heart frequency, location in the heart, developmental stage, and exposure to hormones or drugs [13,14].

2.1. Na^+ channels

Na^+ channels (Na_V) consist of a principal α subunit that can be linked with other auxiliary subunits. The α subunit contains four homologue domains (I–IV), each one with six transmembrane regions (S1–S6). A prominent feature of these channels is that they exhibit voltage-dependent inactivation, which leads to a process known as the refractory period. The inactivation requires an inactivating particle, which is present in the intracellular loop that links domains III and IV. Although there are many isoforms of the α subunit, the isoform $Na_V1.5$ is the prevailing one expressed in mammal hearts [15].

Under normal conditions ischemia results in elevated intracellular Na^+ levels, but this insult in the diabetic heart is considered to increase Na^+ less efficiently. In theory, this limited rise in Na^+ may protect against Ca^{2+} overload, by preserving high capacity to extrude Ca^{2+} via sarcolemmal Na^+-Ca^{2+} exchange [16,17]. Although this point remains controversial, it is interesting that the amplitude of a slowly inactivating component of I_{Na} was decreased in myocytes from S-IDRs, and this was proposed to explain why less intracellular Na^+ accumulates following ischemia [18]. However, in another study performed in the same model changes in the diastolic level of Na^+ were not observed [19]. Instead, this study reported a slightly reduced density of peak I_{Na} that leads to attenuation of the AP (lower amplitude and upstroke) [19]. Conceivable, the latter effect may contribute to explaining the corresponding systolic dysfunction in DC; due to a possible less efficient activation of $Ca_V1.2$ (see Section 3 and Fig. 1).

2.2. K^+ channels

In the case of K^+ channels (K_V), the main (α) subunit consists of six transmembrane segments and a functional channel is thought to arise from the union of four of these α subunits. The functional properties of these channels are strongly influenced by the N- and C-terminal domains of each α-subunit. Moreover, a higher degree

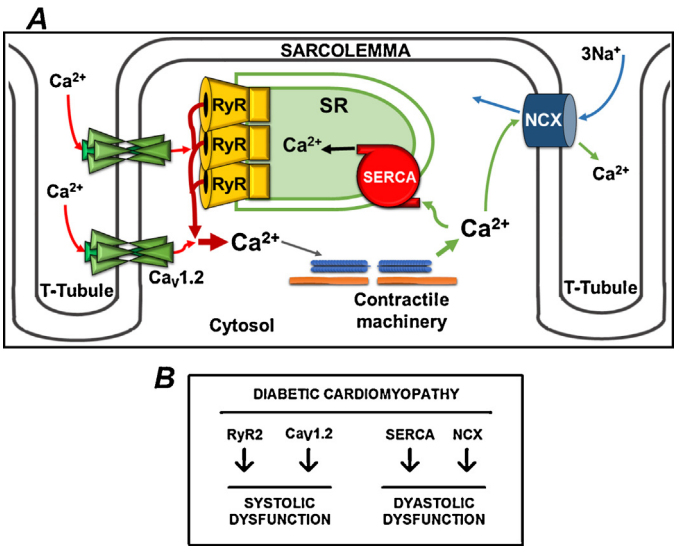

Fig. 1. Molecular mechanisms that underlie excitation–contraction coupling (ECC). (A) ECC begins with a sudden depolarization of plasma membrane, which activates VDCCs ($Ca_V1.2$), allowing the influx of Ca^{2+} (I_{CaL}). These ions bind to, and activate, ryanodine receptors (RyRs), which results in release of Ca^{2+} from the sarcoplasmic reticulum (SR). As a consequence, the $[Ca^{2+}]_i$ is increased and this activates the contractile machinery. The increase in $[Ca^{2+}]_i$ is transitory, because high levels of Ca^{2+} inhibits the flux of this ion via both $Ca_V1.2$ and RyR2. Moreover, high levels of Ca^{2+} also activate both the reuptake of SR Ca^{2+} by SERCA and the extrusion of Ca^{2+} via NCX. The figure is based on [30]. (B) In DC, changes in the expression and/or function of $Ca_V1.2$ and RyR2 are implicated in systolic dysfunction, while those corresponding to SERCA and NCX contribute to diastolic dysfunction (see the text for further details).

of complexity arises from the fact that different α subunits can associate to form heterotetramers. As with other voltage-dependent channels, K_V can associate with auxiliary subunits, and all these options explain why K^+ currents are extremely diverse from both the molecular and functional point of view. For simplicity they can be classified in two big families: transient outward K^+ currents (I_{to}), and delayed rectifier K^+ currents (I_{sus}) [13].

An enlargement of the cardiac AP duration (APD) has been commonly reported in DM and this alteration has been explained by a lower density of outward K^+ currents (both I_{to} and I_{sus}) [20–26].

2.3. Ca^{2+} channels

In the heart, there are mainly two types of Ca^{2+} channels (Ca_V), L-and T-type (LTCCs and TTCCs, respectively). Although the T-type calcium current (I_{CaT}) has been detected in atrial cells of some animal species, it is not present in humans, and it is absent in adult ventricular cells. However, it appears that TTCCs may play an important role in some pathologies, as they have been found to be expressed in ventricular cells but in the diseased heart [27]. The structure of the principal subunit of Ca^{2+} channels (α) is very similar to that of Na_V. It has four homologous domains (I–IV), each consisting of six transmembrane segments (S1–S6). The selectivity filter is thought to be formed by segments 5 and 6 (S5 and S6), while the voltage sensor is located in segments 4 (S4). The LTCC is a protein complex, which includes the principal (α_{1C} or $Ca_V1.2$) and two auxiliary subunits (α_2-δ and β). These are capable of modulating both the intracellular traffic and functional properties of the former [28].

To this date, only one study has investigated the properties of cardiac TTCCs in the settings of diabetes. Briefly, it was found that neonatal rat myocytes exposed chronically (48 h) to high-glucose (25 mM) show higher levels of both $Ca_V3.1$ and $Ca_V3.2$ (i.e. the principal subunits of TTCCs, corresponding to α_{1G} and α_{1H}, respectively)

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