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Review article

Epac in cardiac calcium signaling

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ABSTRACT

Epac, exchange protein directly activated by cAMP, is emerging as a new regulator of cardiac physiopathology. Although its effects are much less known than the classical cAMP effector, PKA, several studies have investigated the cardiac role of Epac, providing evidences that Epac modulates intracellular Ca^{2+}. In one of the first analyses, it was shown that Epac can increase the frequency of spontaneous Ca^{2+} oscillations in cultured rat cardiomyocytes. Later on, in adult cardiomyocytes, it was shown that Epac can induce sarcoplasmic reticulum (SR) Ca^{2+} release in a PKA independent manner. The pathway identified involved phospholipase C (PLC) and Ca^{2+}/calmodulin kinase II (CaMKII). The latter phosphorylates the ryanodine receptor (RyR), increasing the Ca^{2+} spark probability. The RyR, Ca^{2+} release channel located in the SR membrane, is a key element in the excitation–contraction coupling. Thus Epac participates in the excitation–contraction coupling. Moreover, by inducing RyR phosphorylation, Epac is arrhythmogenic. A detailed analysis of Ca^{2+} mobilization in different microdomains showed that Epac preferently elevated Ca^{2+} in the nucleoplasm ($[Ca^{2+}]_n$). This effect, besides PLC and CaMKII, required inositol 1,4,5 trisphosphate receptor (IP_3R) activation. IP_3R is other Ca^{2+} release channel located mainly in the perinuclear area in the adult ventricular myocytes, where it has been shown to participate in the excitation–transcription coupling (the process by which Ca^{2+} activates transcription). If Epac activation is maintained for some time, the histone deacetylase (HDAC) is translocated out of the nucleus de-repressing the transcription factor myocyte enhancer factor (MEF2). These evidences also pointed to Epac role in activating the excitation–transcription coupling. In fact, it has been shown that Epac induces cardiomyocyte hypertrophy. Epac activation for several hours, even before the cell hypertrophies, induces a profound modulation of the excitation–contraction coupling: increasing the $[Ca^{2+}]_i$ transient amplitude and cellular contraction. Thus Epac actions are rapid but time and microdomain dependent in the cardiac myocyte. Taken together the results collected indicate that Epac may have an important role in the cardiac response to stress. This article is part of a Special Issue entitled "Calcium Signaling in Heart".

Contents

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1. Introduction

Epac, an abbreviation for exchange protein directly activated by cAMP, belongs to a family of guanine nucleotide exchange factors and has only recently emerged as an important cyclic adenosine 3′,5′-monophosphate (cAMP) effector [1]. cAMP is one of the most important second messengers in the heart, regulating many physiological processes, such as cardiac contractility, relaxation, and automaticity. Although protein kinase A (PKA) is generally recognized as the primary effector of cAMP signaling [2], other effectors are known to transduce cyclic nucleotide-encoded information. They encompass a class of cyclic nucleotide gated (CNG) cation channels and phosphodiesterases (PDEs) [3,4]. With the development of specific Epac agonists such as 8-pCPT-2′-O-Me-cAMP (8pCPT) [5,6], many data in the literature point out now the critical role of Epac proteins in multiple cellular events mediated by the second messenger cAMP [7]. The multidomain structure of Epac indicates that it may have multiple binding partners. Compelling evidence is now accumulating about the formation of molecular complexes in distinct cellular compartments that influence Epac signaling and cellular function. A relevant question in cardiac signaling is how cAMP can differentially relay environmental signals associated with a large number of surface neurotransmitter or hormone receptors to effectively regulate cardiac function and to understand how these signals are deregulated in pathological conditions such as cardiac hypertrophy.

Initial investigations in the heart uncovered Epac as a positive regulator of myocyte hypertrophy [8,9]. Concomitantly, Epac has been shown to regulate cardiac Ca^{2+} homeostasis [8,10–13]. Ca^{2+} is an essential second messenger in the cardiac physiology because its rhythmic variations activate contraction in each heartbeat through the mechanism of excitation–contraction (EC) coupling. Recent data indicate that Epac actions upon hypertrophy development and Ca^{2+} homeostasis may be inter-regulated. In fact, Ca^{2+} is involved in other processes through Ca^{2+} activated signaling proteins with known hypertrophic transducing activity, notably the so-called excitation–transcription (ET) coupling. It has been recently shown that Epac regulation of intracellular Ca^{2+} activates Ca^{2+}-dependent transcription factors, activators of the hypertrophic program, and thus participating to the ET coupling [14,15]. For those reasons it is the purpose of this review to discuss the involvement of the cAMP-binding protein Epac in EC and ET coupling. We start by describing Epac proteins and finish by citing the known pathological implication of Epac in the heart. We apologize for those authors whose valuable work is not cited.

2. Epac proteins

Two isoforms of Epac exist, Epac1 and Epac2 which are coded by two distinct genes RAPGEF3 and RAPGEF4, respectively [16,17]. Epac isoforms respond to physiologically relevant cAMP concentrations and can be activated by Gs protein–coupled receptor (GsPCRs) such as β-adrenergic receptors (β-ARs) in cardiac myocytes [7,18]. The cAMP analog and Epac agonist, 8-pCPT does not discriminate between Epac1 and Epac2 [6]. Epac isoforms are multi-domain proteins that include an N-terminal regulatory region and a C-terminal catalytic guanine nucleotide exchange factor (GEF) region. The C-terminal catalytic region consists of a CDC25 homology domain responsible for GEF activity, a Ras exchange motif (REM), which stabilizes the CDC25 homology domain, and a Ras association (RA) domain [1]. Epac1 and Epac2 promote the exchange of GDP for GTP in the Ras-like GTPases Rap1 and Rap2 upon binding to cAMP [7]. The N-terminal regulatory region of Epac proteins contains two domains: a disheveled, Egl-10, pleckstrin (DEP) domain which is responsible for membrane association and a high-affinity cAMP conserved binding domain. Epac2 isoform has an additional cyclic nucleotide binding domain which has 20 fold lower affinity for cAMP than the conserved binding domain and is dispensable for cAMP-induced Rap activation [19]. In the absence of cAMP, the regulatory region containing the cAMP-binding domain directly interacts with the catalytic region and inhibits GEF activity. Binding of cAMP to Epac induces large conformational changes within the protein and releases the auto-inhibitory effect of the N-terminal region, leading to Rap activation [1]. Although expressed in almost all tissues, Epac proteins have different patterns of expression and are developmentally regulated [20]. Epac1 mRNA is widely expressed but particularly abundant in kidney and heart while Epac2 is predominant in the brain and adrenal gland [17].

3. Epac modulator of intracellular calcium

After the first evidences of Epac effects in intracellular Ca^{2+} observed in pancreatic cells [21,22], several studies have demonstrated that the activation of endogenous Epac is also able to regulate Ca^{2+} handling in cardiomyocytes [8,10–13,15,23,24]. Although there may be time, microdomain, and species differences in the published data, it is clear today that Epac modulates cardiac Ca^{2+} handling. In order to simplify, we have arbitrarily divided below the known actions of Epac on different compartments of the cell, including the effects on the cytosolic Ca^{2+} ($[Ca^{2+}]_i$) under the EC coupling subheading and the effects on intranuclear Ca^{2+} ($[Ca^{2+}]_n$) under the ET coupling subheading, although cytosolic Ca^{2+} also participates in ET coupling through calcineurin/NFAT pathway.

3.1. Epac action on cytosolic Ca^{2+} handling: EC coupling

Ca^{2+} is a key element in the process denominated EC coupling. In each heartbeat, the membrane depolarization during an action potential induces the activation of L-type Ca^{2+} channels located at the sarcolemma and the subsequent Ca^{2+} entry into the cytoplasm. The subsequent local elevation of Ca^{2+} in the dyadic cleft induces activation of neighboring ryanodine receptors (RyRs), producing Ca^{2+} release to the cytosol from the sarcoplasmic reticulum (SR). This coordinated process is named Ca^{2+}-induced Ca^{2+} release (CICR) and supply the Ca^{2+} necessary to activate the contraction of the myofibrils [25–27]. CICR is regulated by cAMP through PKA phosphorylation of key proteins as follows: activation of GsPCR such as β-ARs activates adenylyl cyclase producing cAMP from adenosine triphosphate (ATP) and activating PKA [27]. PKA phosphorylates: L-type calcium channels, increasing Ca^{2+} entry (the trigger); the RyRs (the amplifier), increasing their open probability; and phospholamban (PLB), releasing its inhibition on sarcoplasmic reticulum Ca^{2+} ATPase (SERCA), increasing the Ca^{2+} load [27]. The PKA phosphorylation of these 3 proteins participates to the positive inotropic effect of β-AR stimulation. The effect of PKA on myofilament protein phosphorylation also modulates contractility by decreasing their Ca^{2+} sensitivity and thus favoring relaxation. Together with fastened Ca^{2+} reuptake through SERCA, this mechanism participates to the lusitropic action of β-AR activation. This is the main mechanism by