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Review Article

The Role of EPAC in the Pathogenesis of Cardiovascular Complications: A Review

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ABSTRACT

Cardiovascular disease is a primary cause of mortality and disability and it has long been a focus of clinical and scientific investigation. There is still much to learn about the intricate pathophysiology of cardiovascular disease. The energy needed for circulatory function is provided by mitochondria. Cyclic adenosine monophosphate (cAMP) signalling is directly connected to the mitochondrial action mechanism. cAMP is a ubiquitous second messenger that regulates gene expression, cell shape and function. The identification of the exchange protein directly activated by cAMP (EPAC) eighteen years ago was a significant step towards a better understanding of cAMP signalling. Several studies in the literature have shown that since the introduction of EPAC pharmacological modulators, EPAC plays a critical role in the regulation of many cAMP-determined cardiac functions. The multidomain form of EPAC proteins allows them to be connected to several effectors in different subcellular compartments. Several cardiovascular disorders such as cardiac arrhythmia, atherosclerosis, heart failure, cardiac apoptosis, cardiac hypertrophy and many more, may be treated with these novel cAMP sensors, which are also in connection to several physiological processes. This article provides a discussion of EPAC's mechanism of action in CVDs, which may serve as a platform for targeted pharmacological research and expansion in innovation in the healing of disease processes.

Keywords: Apoptosis, cAMP, Cardiovascular disease, EPAC.

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INTRODUCTION

Cardiovascular Disease (CVD) is one of the well-known causes of death and disability worldwide.[1] CVD has been another leading cause of death in the US since 1975, accounting for 633,842 deaths, or one in every four fatalities. The Global Burden of Disease produced a research report indicating that India has a greater incidence of fatalities from CVD than any other country in the world (272 per 1,00,00 and 235 per 1,00,00 population, respectively). Approximately one-fourth of all deaths have also been found to be undoubtedly attributable to CVD.[2] The leading cause of mortality in 2015 was cardiovascular illness, which was followed by 595,930 fatalities from cancer.[3] According to estimates from the World Health Organisation (WHO), 17.7 million individuals worldwide lost their lives to CVD in 2015. As a result, it is the primary cause of mortality globally. Moreover, in Europe, CVDs cause 45% of deaths,[4] rendering them crucial to the general public's health. According to estimates, CVD costs $237 billion a year and by 2035, those costs are expected to climb to $368 billion, making it the costliest sickness overall-it even outspends diabetes and Alzheimer's disease in terms of indirect costs.[5] Long-term patients with CVD also have detrimental impacts on their mental health. In middle-class or low-income countries, basic medical treatment is not readily available due to the high expenses of treating CVD and the lack of complete therapy. As a result, these countries have higher-than-average mortality rates. Given their wide range of symptoms, CVDs are quite common and may be caused by a mix of environmental and inherited factors.[6]

The pathophysiology of CVD is multifaceted and remains poorly understood despite an immense amount of research conducted from numerous perspectives. Cell migration, proliferation, apoptosis, hypertrophy, regeneration, endothelial cell dysfunction, cellular oxidative stress damage, inflammation reaction, fibrosis of myocardium, autophagy and development of new blood vessels are among the many cells pathological factors that are involved.[7-9] The organelles called mitochondria supply power to cardiac tissues and are crucial for preserving cellular balance. They have the ability to supply an abundance of adenosine triphosphate (ATP) via oxidative phosphorylation. In addition, also processes additional signalling molecules linked to calcium homeostasis

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and apoptosis, as well as neurotransmitters and reactive oxygen species (ROS). The capacity of the mitochondria to function is essential for the physiological activities that occur in the heart. However, abnormal mitochondrial function is a major factor in the formation of CVDs.[10,11] The process of mitochondrial-dependent apoptosis, for example, is linked to the cAMP pathway,[12] and also essential for pathway transduction inside the cells.[13] Exchange protein that cAMP precisely triggers is at a recent time found guanine nucleotide exchange factor (EPAC). Over time, studies on EPAC have gradually supplanted studies on protein kinase A (PKA).[14,15] It has been shown in earlier studies that EPAC controls many functions, essentially cardiovascular electrical remodelling, cardiovascular hypertrophy, fibrosis in the myocardium and the death of the cardiomyocytes. Additionally, it is a major regulator of angiogenesis. From these results, it seems that EPAC might be a new therapeutic target for CVD.[16,17] Research suggests that EPAC may be involved in cardiac hypertrophy, cardiac apoptosis, arrhythmia, atherosclerosis and many more cardiac-related diseases. The latest research findings on EPAC and heart disorders are covered in this review, along with the notion that addressing EPAC's signalling pathways might be a therapeutic target for heart therapy. Additionally, this study serves as a foundation for future drug development and research.

EPAC: Structure

cAMP is an intracellular second messenger that regulates substance energy metabolism including biological activities. By influencing the intracellular actions of several hormones and neurotransmitters, cAMP may serve as a signal transducer.[16] The majority of cAMP's signal transduction activities are accomplished via PKA activation. Besides PKA, cyclic nucleotide-gated ion channels and a classical effector called EPAC.[17] Through the cAMP signalling pathway, EPAC may be implicated in the pathogenesis of extensive diseases. Further, the structure of EPAC is given in Figure 1.

EPAC is a Guanine Exchange Factor (GEF) that interacts with Ras-related protein (Rap) which is a part of Ras subfamily of protein GTPases. Thus, Rap is induced by EPAC to change starting with GDP-bound inactive arrangement to its GTP-bound active arrangement. For EPAC1 as well as EPAC2, the RAPGEF3 and RAPGEF4 DNAs are found on chromosomes 12q13.11 along 2q31.1, respectively, encode single polypeptides, each of which has several isoforms. EPAC1 expression is widespread, however, EPAC2 expression is relatively limited. EPAC2A is mostly denoted in the central nervous system, pituitary gland and pancreas whereas EPAC2B is found in the testis and adrenal glands steroid cells. Moreover, EPAC2C is virtually entirely denoted in the liver.[18]

EPAC proteins are structurally composed of catalytic and regulatory domains.[19,20] The catalytically active C-terminus is regulated by the N-terminus.[21] The regulatory subunit is composed of the cAMP-binding regulatory cyclic nucleotide-binding region and the Dishevelled/Egl-10/pleckstrin domain.[22,23] However, the catalytic subunit is made up of a CDC25 homology domain (CDC25-HD), a Ras exchange motif (REM) and a Ras-association region.[24] Specifically, REM stabilises the association with the substrate without directly interfering with the activity, while CDC25-HD is primarily in charge of the catalytic GDP-to-GTP interchange.[25] In contrast to this conventional EPAC structure, only EPAC2A is known to possess the extra cAMP binding region known as CNBD-A in addition to the CNBD-B that is often seen in other variants.[26] EPAC2B has the same binding domain as EPAC1 and EPAC2C possesses less cAMP binding domain known as DEP shown in Figure 1.

EPAC: Localization and Downstream Signaling

EPAC differentiation is facilitated and controlled by specific EPAC protein categories, as well as a number of interacting effectors. EPAC1 and EPAC2 might ultimately localise to the cytosol, mitochondria, nuclear membrane, or cell membrane under the direction of their molecular connections.[27-30] For example, EPAC-1's translocation to the plasma membrane is mediated by its DEP domain.[31] A conformational shift in the DEP domain is triggered when cAMP binds to EPAC, boosting its relationship with the membrane's phosphatidic acid.[32,33] Significantly, this translocation is inhibited by pharmacological treatments that decrease phosphatidic acids.[22] Ezrin, Radixin and Moesin (ERM) proteins are another significant modulator of cell membrane localization.[34] Specifically, EPAC1 docks to the phospholipid bilayer partly due to its association with ERM proteins via its 49 N-terminal amino acids.[34,35] On the other hand, EPAC1's ability to target the nuclear membrane depends on how well the region of RA interacts with minor G protein Ran. The interaction between bound GTP and Ran-binding protein 2 (RanBP2), which is found at nuclear pores, allows Ran to promote nuclear transport.[36] Furthermore, there is evidence that EPAC1 is localised to the mitochondria. However, future study is required to regulate the precise domains and effectors involved.[30] According to this, the initial 73 N-terminal amino acids of the EPAC1 protein include the mitochondrial targeting motif.[30] Remarkably, this section and mitochondrial targeting pre-sequences have one thing in common, they are both positively charged.[37,38] However, EPAC2A exhibits distinct localization processes. Indeed, in pancreatic cells, CNBD-A helps this isoform localise to the plasma membrane.[39] Furthermore, while interacting with GTP-bound Ras, the RA domain of EPAC2 facilitates its translocation to cell membranes, in contrast to that of EPAC1.[40] Both the selectivity of EPAC signalling and the creation of signalosomes are facilitated by the evoked different positioning of EPAC variants to certain cellular divisions.

Numerous downstream effector associations regulate the vast range of EPAC activities. These include the minor G-proteins belonging to the Ras superfamily, known as Rap proteins.

Moreover, EPAC serves as a GEF for the R-Ras protein, which belongs to the same protein GTPase subfamily as Rap.[41] The direct connection between EPAC-R-Ras and phospholipase D is eventually seen in HEK-293 cells. Since EPAC2 regulates the production of insulin from pancreatic β-cells, its downstream targets have been well understood.[42] Piccolo, Rim2 and Sulfonylurea receptor 1 are the three intracellular effectors that EPAC2 seems to directly interact with throughout this process.[43] To induce cell depolarization, EPAC2 indicates to have a direct relationship with sulfonylurea receptor 1, a subunit of ATP-dependent Potassium (K^+) channels. Importantly, insulin release depends on cell depolarization, which is brought on by the closing of ATP-dependent K^+ channels.[43-45] Moreover, EPAC2 directly engages in interactions with secretory granule-associated proteins that are implicated in the exocytosis of insulin.[46] Among these are the Rab-interacting protein Rim2 along with the Rim2-associated protein Piccolo.[47,48] Additionally, it seems that EPAC activates the small protein GTPase Rit, which is important for neuronal development. But because this activation is neither Rap-mediated nor direct, it is possible that another downstream effector serves as the gap between Rit and EPAC.[49] Likewise, EPAC has been seen to induce c-Jun N-terminal kinase in an independent manner from Rap.[50,51] The REM domain of EPAC is pretty important to this process. It is possible to suggest that a REM-interacting protein mediates or directly connects this two.[51] Without a doubt, using proteomic analysis and *in silico* research on EPAC may assist in completing the gaps in signalling pathways and identifying new downstream effectors.[52]

DISCUSSION

Role of EPAC in Cardiac Hypertrophy

Cardiac hypertrophy is a changing response to hemodynamic pressure, which is considered a compensating function in enhancing the heart's function and decreasing ventricular wall tension and consumption of oxygen.[53] Exercise or pregnancy may cause cardiac muscle to enlarge physiologically, this condition is considered minor or reversible.[54,55] On the other hand, a kind of pathological hypertrophy known as enormous hypertrophy of the ventricular walls that is distinguished by a significant rise in the measurement of ventricles together with malfunctioning myocardium and fibrosis, occurs existence of persistent mental stress circumstances such as high blood pressure as well as valvular disorder.[56] These are warning signals of developing heart failure and abnormal remodelling.[57] Clarifying the molecular processes behind the cardiac muscle's hypertrophic development process has been the focus of many investigations.[58,59] One mechanism that has drawn interest is facilitated by calcineurin (PP2B), a calcium/calmodulin-activated protein phosphatase. Continuous increase in intracellular calcium stimulate the release of calcineurin and make it easier for it to bind to the main downstream response, the NFAT or nuclear factor of activated T cells. NFAT transcription factors-which are typically hyperphosphorylated or confined in the cytoplasm-quickly relocate to the nucleus.[60] Transgenic mice may develop a strong hypertrophic response only via cardiovascular-related stimulation of NFAT which is a downstream effector and stimulation of calcineurin.[61] The pathway that is responsible for the activation of calcineurin is Calmodulin (CaM) detects and communicates with calcineurin the persistent increase of Calcium ions (Ca^{2+}) downstream of GPCR (αq/α11 isoform).[62]

According to preliminary research in primary cardiac cells, EPAC hypertrophic signalling was intricate and connected a number of effector proteins, including the Ca^{2+}-sensitive proteins calcineurin and CaMKII, the small GTPases Rap, PLC, Rac and H-Ras, as well as their downstream pro-hypertrophic transcription factors, including myocyte enhancer factor 2 along with nuclear factor of activated T cells.[63-65] The cAMP signalling pathway in cardiomyocytes is linked to catecholamine-induced β-Adrenergic Receptor (β-AR) activation as well as cAMP-induced EPAC activation. When β1-AR is stimulated, EPAC1 promotes cardiac hypertrophy by activating Ras, calcineurin and CaMKII instead of its traditional effector Rap.[63] According to reports, the indirect action of EPAC on H-Ras activation entailed Rap2B-dependent PLC (presumably PLCε) stimulation, which resulted in the formation of inositol 1,3,5 triphosphate or a rise in nuclear calcium ion.[65] The only way to prevent EPAC-induced hypertrophy was to pharmacologically inhibit either calcineurin or CaMKII.[64] The role of EPAC in cardiac hypertrophy is given in Figure 2.

Role of EPAC in Cardiac Fibrosis

Myocardial calcification, another name for cardiac fibrosis, has been classified into two types: repair fibrosis and reactive fibrosis. ECM or extracellular matrix accumulation in fluid-filled space of certain blood vessels and interstitially is abundant in the former, which is caused by blood flow stressors for example pressure overload, on the other hand, the latter is a flexible reaction to fix increasing wall pressure in order to sustain heart output.[66] A variety of cells, including fibroblasts, endothelial cells, immune cells and cardiomyocytes, make up the multicellular organ that is the heart. Communication between myocytes and non-cardiomyocytes is crucial for the formation of fibrosis.[67] When it comes to quantity, cardiac fibroblasts are the greatest prevalent cell type in the myocardial.[68] Fibroblasts become myofibroblasts when they activate, multiply and differentiate in response to fibrotic stimuli. At the molecular level, ET-1 or endothelin-1 may stimulate cardiac fibroblast increase and encourage collagen production, TGF-β or transforming growth factor β is a primary controller of fibrotic activities, as well as Ang II or angiotensin II is a crucial fibrosis formation fixer. TGF-β, Ang II and ET-1 are linked to fibrosis formation.

Signalling of cAMP is an important regulator of fibrosis formation. Specifically, cardiac fibroblasts may produce α-Smooth Muscle Actin (α-SMA) and synthesize collagen as a result of

Ang II induction and over-activation of endothelin receptors. Increased amounts of endogenous and exogenous adenosine may both prevent Ang II-induced effects. Following stimulation of the adenosine A subtype 2B Receptor (A2BR) and activation of Adenylyl Cyclase (AC), cAMP, as well as EPAC extent were elevated, PI3K or phosphoinositide 3-kinase along with protein kinase B (Akt) were activated, also induction of Ang II fibrosis was inhibited.[69] Upregulation of TGF-β1 and EPAC1 levels were suppressed in animal heart failure models. Following myocardial infarction, EPAC1 activation may alleviate cardiac dysfunction, inhibit ventricular remodelling and treat left atrial fibrosis.[70] Myocardial fibrosis induced by osteopontin is inhibited by cAMP/EPAC1 by modulating the activation of β2AR. Remarkably, EPAC has been shown to work via a distinct mode of action throughout the myocardial fibrosis process to reduce cardiac dysfunction. Moreover, the function of EPAC in cardiac fibrosis is depicted in Figure 3.

Role of EPAC in Cardiac Apoptosis

Apoptosis is a highly controlled biological process that balances pro-death and pro-survival cell impulses, with the conclusion determining cell destiny. The group of proteins known as Bcl-2 has come to be recognised as an important controller of the process of cellular death. The developing Bcl-2 family consists of death agonists (Bax, Bak) and antagonists (Bcl-2, Bcl-xL), which are mainly involved in controlling the release of (pro) apoptotic intermembrane proteins and protecting or rupturing the integrity of the mitochondrial membrane. A wide range of conditions may induce pathological cardiomyocyte apoptosis, including an increase in ischemia, hypoxia medication, infectious diseases, inflammatory mediators and reactive oxygen species.[71] The stimulation of cAMP and subsequent EPAC activation, which decreases apoptosis, are mediated by a variety of receptors.

Studies in the past have shown that cAMP levels rise when the heart's glucagon-like peptide 1 receptor (GLP-1R) is activated. Exendin-4 stimulates GLP-1Rs, which increase cAMP levels, activates PKA and EPAC, has antioxidant benefits via EPAC signalling, inhibits the activity of caspase-3, increases Bcl-2 expression and has antiapoptotic properties.[72] Additionally, GLP-1R activation may enhance the gene expression linked to mitochondrial dynamics and function as well as the potential of the mitochondrial membrane.[73] In rat cardiomyocytes, the GLP-1 analogue liraglutide may increase EPAC1 expression and encourage Akt phosphorylation.[74] By interacting with EPAC, GLP-1R stimulators and analogues may shield cardiac apoptosis brought on by elevated hyperglycemia. It has been discovered that C1q/Tumour necrosis factor-related protein 3 (CTRP3) inhibits high glucose-induced oxidative stress, inflammation and apoptosis by increasing Akt and AMPKα or AMP-activated protein kinase α phosphorylation, upregulating Bcl-2 level, also decreasing Bax level. Additionally, CTRP3-mediated AMPKα activation may be attenuated in EPAC knockout.[75] Remarkably, future research is anticipated to shed light on this matter because of the variations in the way that EPAC inhibits cardiomyocyte apoptosis and the precise function that EPAC performs in this process.

Role of EPAC in Atherosclerosis

Atherosclerosis is a complicated pathogenic process that causes a variety of illnesses, including arrhythmias, angina and myocardial infarctions. The development of foam cells, dysfunction of endothelium and increase in proliferation and migration of arterial smooth muscle cells (SMCs) are hallmarks of atherosclerosis. One of the main factors responsible for the progress of atherosclerosis is inappropriate vascular SMC activation.[76,77] Since EPAC1 is highly present in cardiac cells, a number of researches have shown that it may be possible to treat atherosclerosis by targeting it.[78-80] According to previous research, elevated EPAC1 levels stimulate platelet-derived growth factor-BB-induced SMC migration, which accelerates

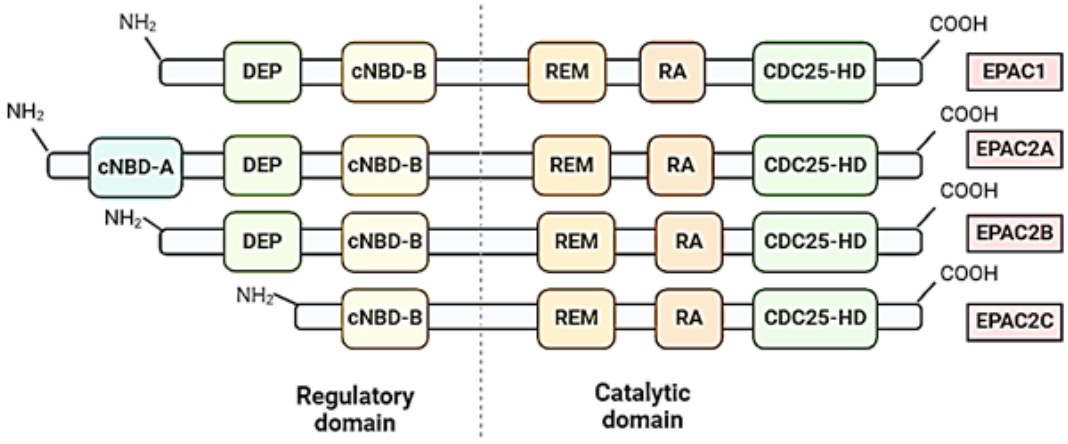

Figure 1: Structure of EPAC.

atherosclerosis occurrence. Additionally, in EPAC1$^{-/-}$ mice, the PI3K/Akt pathway as well as SMC proliferation were inhibited. Furthermore, ESI-09, an EPAC inhibitor, may lessen the *in vivo* production of neointima. These results support the use of EPAC inhibition as a therapeutic intervention for vascular proliferative disorders.[79] According to recent research, EPAC1 may enhance the production of foam cells and the progression of atherosclerosis by increasing LOX1 or oxidised low-density lipoprotein receptor 1 by activating protein kinase C (PKC), a critical stage in the development of atherosclerosis. In regions where atherosclerosis is present, EPAC1 downregulation may lower foam cells and macrophages.[80] These results imply that blocking EPAC1 could be a useful tactic in the management of atherosclerosis.

Role of EPAC in Arrhythmia

A cardiac arrhythmia is simply described as a deviation from the normal heart rate and/or rhythm.[81] Arrhythmias may arise independently from several biological cardiac disorders, including myocardial infarction and Heart Failure (HF). Arrhythmias have a complicated mechanism, which makes a permanent treatment impossible. Thus, there is an urgent need for new treatment approaches. Atrial fibrillation is significantly influenced by fibrotic remodelling.[82] According to previous research, inhibition of EPAC1 techniques decreased the amount of collagen secreted by left atrial fibroblasts.[70] Further, Rajesh Prajapati *et al.*, showed that EPAC1$^{-/-}$ mice in cardiac cells have decreased sarcoplasmic reticulum Ca^{2+} leak generated by sympathetic stimulation and that animals may be spared atrial and ventricular arrhythmias by using CE3F4, a specific EPAC1 inhibitor. According to Zhang MX and colleagues, HF was induced by isoproterenol in a mouse model because of which there is an increase in stroke as well as mortality and also causes frequent cardiac arrhythmia, change in LTCC or L-type calcium channels because of EPAC1 may enhance susceptibility to atrial fibrillation. AP or action potential may be prolonged to produce atrial fibrillation by EPAC1-induced LTCC opening, suggesting that EPAC1 activation can enhance atrial fibrillation.[83] Thus, blocking the EPAC1 signal might be a practical and safe way to treat arrhythmia. Through oxidative stress, late sodium currents are stimulated and impaired EPAC2/Rap1 signalling may result in potentially fatal arrhythmias.[14] EPAC proteins trigger electrophysiological remodelling and arrhythmogenic activity in human atrial cardiomyocytes. Both the EPAC1 and EPAC2 isoforms play a role in this process. The PLC/PKC and nitric oxide synthase (NO)/PKG pathways regulate K^+ repolarising current, although calmodulin-dependent protein kinase II (CaMKII), a well-known EPAC downstream effector, does not. This might have a pathogenic impact because EPAC is raised in diseases such as cardiac hypertrophy. Thus, EPAC inhibition might be a new method to avoid arrhythmias in pathological conditions.[84,85] Moreover, a map of the pathway of cAMP-signalings' genetic alterations in patient atria revealed, AF is associated with elevated EPAC2 expression.[86] Thus, in addition to EPAC1, EPAC2 may possibly have an impact on heart function in atrial fibrillation. In conclusion, there are several functions that the EPAC family performs in arrhythmia treatment. More studies are essential to determine the precise background of EPAC2 in

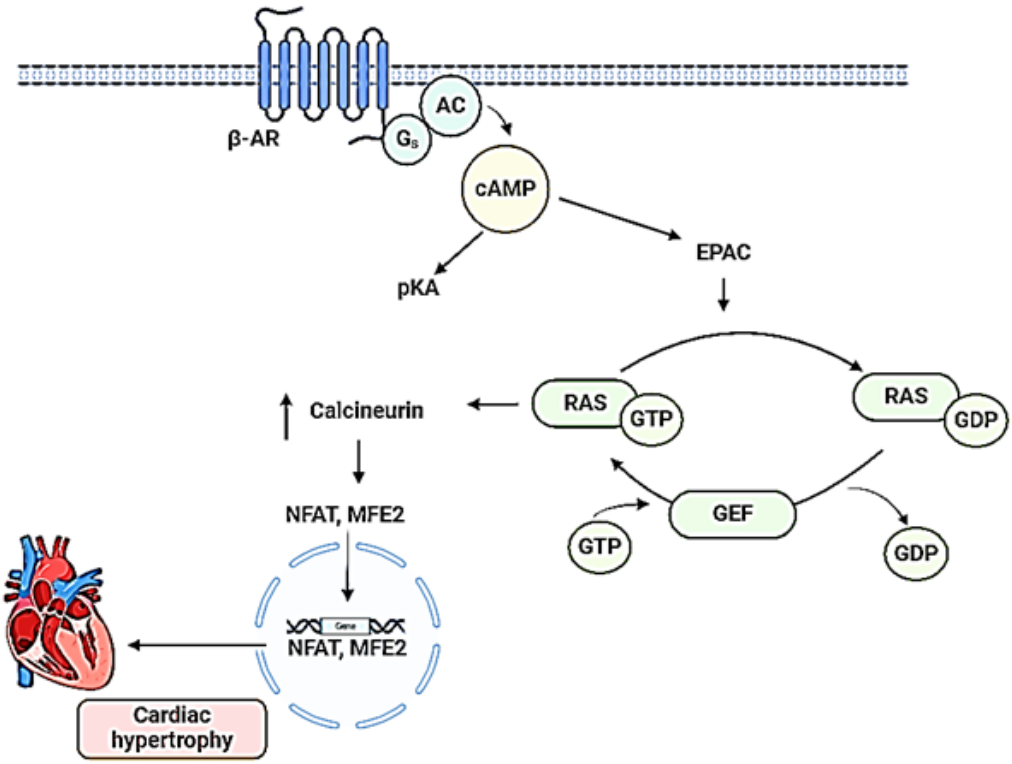

Figure 2: Role of EPAC in cardiac hypertrophy.

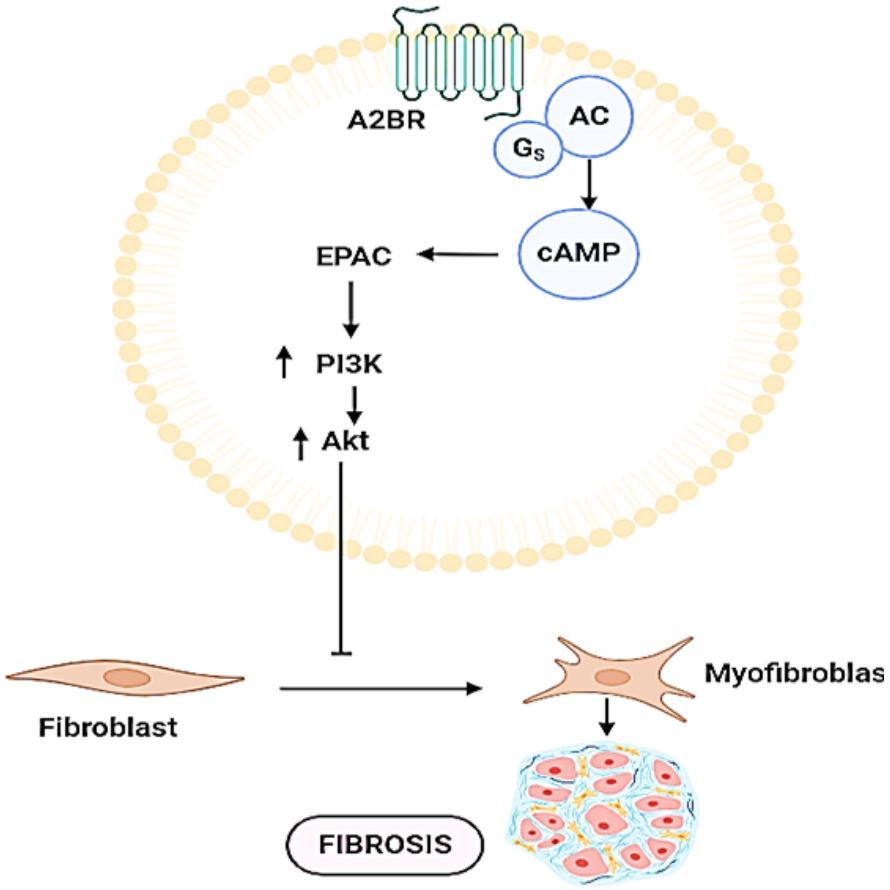

Figure 3: Role of EPAC in cardiac fibrosis.

atrial fibrillation, although blocking EPAC1 may be a potent therapeutic treatment for arrhythmia.

Role of EPAC in Heart Failure

Heart failure is a complicated medical illness defined by the heart's incapacity to pump blood at a rate sufficient to fulfil the body's needs. Almost all cardiovascular illnesses may ultimately lead to the formation of HF, the last stage of heart disease progression. The hallmarks of HF include remodelling and fibrosis. It is essential for HF treatment that Ca^{2+} levels be regulated. According to the work of Anne-Coline Laurent *et al.*, β-AR causes intracellular Ca^{2+} release via activating Rap2B and PLC through the stimulation of EPAC1 via cAMP. Subsequently, the release of Ca^{2+} stimulates CaMMKβ, which in turn causes AMPK phosphorylation. Finally, to counteract EPAC1-induced pathological cardiac remodelling, adaptive autophagy is triggered and mTOR1 is suppressed.[87] Furthermore, by preventing serine-16 and phospholamban (PLN) phosphorylation, EPAC1 inhibition may shield the heart from long-term catecholamine stress and pressure excessive load.[88] Thus, EPAC1 inhibition may be a helpful treatment for heart failure. Furthermore, a decrease in abnormal cardiac remodelling was seen by the specific EPAC1 inhibitor AM001, which was triggered via the activation of β-AR. EPAC1 inhibitor decreased GRK5 nuclear translocation, leading to HDAC5 nuclear aggregation.[15]

Role of EPAC in Ischemia-Reperfusion Injury

Ischemic heart disease has been recognised as a remarkable beginning of disease along with death.[89] Ischemia-reperfusion injury, often known as I/R injury, is the result of an ischemic heart's sudden reperfusion causing damage to the myocardium.[90] Ischemic occurrences may be treated by revascularization, which preserves the myocardium. Reperfusion, however, has the potential to exacerbate I/R or ischemia-reperfusion damage, which is considered as most common origin for mortality and increases rates of disability as well as death. The majority of earlier research has been on the possible therapeutic benefits of EPAC1 suppression. According to Fazal *et al.*, EPAC1 controls the generation of ROS, the uptake of Ca^{2+} and the opening of the mitochondrial permeability transition pore. Pharmacological suppression of EPAC1 or genetic ablation may stop I/R-induced cardiomyocyte death.[91] An investigation conducted recently showed that by blocking the EPAC1/Rap1/NOX4 signalling pathway, EPAC1 inhibition may considerably reduce myocardial I/R damage (MIRI).[92] On the other hand, Khaliulin *et al.*, found contradictory evidence suggesting that concurrent activation of PKA and EPAC might provide a notable cardioprotective effect

Table 1: Mechanisms of EPAC in cardiac diseases.

Sl. No.	Name of Compound/ Formulations (dose used)	Site of administration with the agent used for disease induction	Animal used/Cell culture/Patients	Major Outcomes	References
1.	CV1808 (Adenosine 2R agonist)	Cells were given 200 nM Ang II for 6 hr.	Neonatal Sprague-Dawley rats.	Enhanced α-SMA production, activated EPAC and cAMP signals.	69
2.	EPAC agonist (8-pCPT-2′-O-Me-cAMP)	Chronic isoproterenol was administered via an osmotic mini-pump at a dose of 5 mg/kg/day for 7 days.	AC5 Transgenic (AC5TG)- EPAC1 KO mice.	Increased phosphorylation of RyR2, PLN through the phospholipase C (PLC) ε/ protein kinase C (PKC) ε/ calmodulin-dependent protein Kinase II (CaMKII) pathway.	94
3.	NA	*In vivo* Doxorubicin was given 4 mg/kg, i.v. *In vitro* Doxorubicin was given 2 mg/mL.	*In vivo* C57BL6 wild type and EPAC1 KO mice. *In vitro* MCF-7 and HeLa cell lines.	EPAC1 inhibition attenuated sarcoplasmic reticulum (SR) Ca^{2+} load. EPAC inhibition decreased mptp opening.	96
4.	AM-001 (EPAC antagonist) (10 mg/kg/d, i.p.)	Chronic isoproterenol was induced by osmotic mini-pumps at 60 mg/kg.	C57BL/6 mice.	Decreased GRK5, HDAC5 and downregulated MEF2 transcriptional activity.	15
5.	Liraglutide (0.3 mg/kg, subcutaneously)	Streptozotocin was induced at 30 mg/kg through the caudal vein.	Male Wistar rats.	Enhanced the expression of EPAC1 and increased Akt phosphorylation.	74
6.	Exendin-4 (20 nM)	100 μM H_2O_2	Rat cardiomyocytes.	Increased levels of Protein kinase A, EPAC, raised the expression of antiapoptotic protein B-cell lymphoma 2 and decreased caspase-3 activity.	72
7.	Roflumilast (30 μM)	NO-induced apoptosis	H9c2 embryonal rat heart-derived cell line	Enhanced Akt phosphorylation, increased EPAC1/GTP-Rap1 and PI3K/ Akt was upregulated	97,98

against I/R damage. Through EPAC, PKC is crucial in providing cardioprotection.[93] Thus, further studies are necessary for the confirmation of the precise role of EPAC1 in I/R treatment and it is important to determine the involvement of EPAC2 in I/R damage.

Clinical Trials

A clinical study evaluated how dysfunctional EAT (epicardial adipose tissue) promotes maladaptive cardiac remodelling in CVDs via ST2 synthesis linked with EPAC proteins. The results indicated that both EPAC2 and ST2 expression were closely connected to maladaptive cardiac remodelling indices, implying that EAT measures might be relevant in the early detection of CVD problems.[94] Additionally, a study investigated the association between EPAC1 expression and several clinicopathologic characteristics along with the survival of patients with gastric cancer. The results indicated that EPAC1 upregulation can be utilised as an indicator for estimating the fate of GC patients and it represents a possible therapeutic method for GC treatment.[95]

CONCLUSION

The article addressed the relationship between EPAC and CVDs and covered the structural features of EPAC. Moreover, the research discussed in this article shows that the localisation of cAMP signalling and a particular cellular function in several subcellular compartments are affected by EPAC molecular complexes or signalosomes. Even if the mechanistic results of some of the experiments were contradictory, this helped to highlight how intricate EPAC's mechanism of action is. These differing

perspectives are the most intriguing aspect of scientific study. A crucial pathway in the pathogenesis of CVDs is EPAC. Table 1 summarizes the different mechanisms of EPAC in various cardiac disorders. Moreover, to propose new treatment possibilities for arrhythmia, heart failure and vascular remodelling, future research should investigate its complicated mechanism of action.

The participation of EPAC in the development of cardiovascular disease is now carried out by several recent researches, which raises the possibility that EPAC may be an appealing therapeutic target for the management of a variety of cardiovascular conditions.

Pharmacological suppression of EPAC, which slows cardiac remodelling, may be beneficial for treating arrhythmia and HF, perhaps working in combination with β-blockers. *In vitro*, biochemical tests and cell culture experiments have been effective in testing the majority of EPAC pharmacological antagonists so far. Even with all of the knowledge, there are still a few unanswered questions. Future research should try to determine underlying molecular processes intricated in EPAC expression control, EPAC epigenetic modification and their possible relation to cardiovascular disease.

LIMITATIONS AND STRENGTHS

The number of clinical investigations on EPAC as a therapeutic target in CVDs is limited and the sample size of the studies is not large enough. This review combines the available research on cardiovascular illnesses and highlights the role of EPAC in CVDs. We believe that EPAC can identify the disease progression and prognosis of the CVD. Further, the research of targeted medications is dependent on additional investigation and validation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

A2BR: A subtype 2B receptor; **AC:** Adenylyl cyclase; **Akt:** Protein kinase B; **AMPKα:** AMP-activated protein kinase α; **Ang II:** Angiotensin II; **ATP:** Adenosine triphosphate; **Cam:** Calmodulin; **cAMP:** Cyclic adenosine monophosphate; **CDC25-HD:** CDC25 homology domain; **CTRP3:** C1q/tumour necrosis factor-related protein 3; **CVD:** Cardiovascular disease; **EPAC:** Exchange protein directly activated by cAMP; **ERM:** Ezrin, radixin and moesin; **ET-1:** Endothelin-1; **GEF:** Guanine exchange factor; **GLP-1R:** Glucagon-like peptide 1 receptor; **HF:** Heart failure; **LOX1:** Low-density lipoprotein receptor 1; **LTCC:** L-type calcium channels PI3K Phosphoinositide 3-kinase; **PKA:** Protein kinase A; **PKC:** Protein kinase C; **PLN:** Phospholamban; **RanBP2:** Ran-binding protein 2; **Rap:** Ras-related protein; **REM:** Ras exchange motif; **Rim2:** Rab-interacting protein; **ROS:** Reactive oxygen species; **SMCs:** Smooth muscle cells; **TGF-β:** Transforming growth factor β; **α-SMA:** α-Smooth muscle actin.

SUMMARY

Cardiovascular Disease (CVD) is a leading cause of death worldwide. Its pathophysiology is complex, involving cell migration, oxidative stress and inflammation, with mitochondrial dysfunction playing a crucial role. Emerging research identifies the Exchange Protein directly activated by cAMP (EPAC) as a potential therapeutic target. EPAC plays a crucial role in various cardiac conditions, including cardiac hypertrophy, fibrosis, apoptosis, atherosclerosis, arrhythmia, heart failure and Ischemia-Reperfusion (I/R) injury. It regulates fibroblast activity and collagen production, affecting both repair and reactive fibrosis. EPAC activation reduces cardiomyocyte apoptosis by modulating Bcl-2 family proteins and enhancing mitochondrial function. EPAC1 promotes smooth muscle cell migration and foam cell formation, suggesting its inhibition as a therapeutic strategy. EPAC influences calcium handling, contributes to arrhythmias and modulates calcium signalling and cardiac remodelling, indicating potential benefits in heart failure management. EPAC1 has a dual role in I/R injury, with both protective and harmful effects depending on the context. This review emphasizes the diverse roles of EPAC in cardiovascular health and disease, proposing it as a promising therapeutic target for various cardiac conditions. Additional research is necessary to elucidate its mechanisms and refine treatment strategies that involve EPAC modulation.

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