Nusier et al. Scr Med 2023 Jun;54(2):181-95. DOI:10.5937/scriptamed54-42460

REVIEW ARTICLE

Regulatory Role of Some Protein Kinases in Signal Transduction Pathways in Heart Health and Disease

Mohamad Nusier,[1] Vijayan Elimban,[2] Jaykishan Prasad,[2] Anureet K Shah,[3] Naranjan S Dhalla[2]

1. Department of Biochemistry and Molecular Biology, Jordan University of Science and Technology, Irbid, Jordan.
2. Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre and Department of Physiology and Pathophysiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada.
3. School of Kinesiology, Nutrition and Food Sciences, California State University, Los Angeles, CA, USA.

Abstract

Various protein kinases including protein kinase A (PKA), Ca^{2+}-calmodulin kinase (CaMK), phosphoinositide 3-kinase (PI3K), protein kinase C (PKC) and mitogen-activated protein kinase (MAPK: ERK1/2, p38-MAPK and JNK) are integral part of different signal transduction pathways, which are known to regulate cardiac structure, function and metabolism. In addition, these signal transducing proteins are involved in the regulation of cation transport, cellular growth, gene expression, apoptosis and fibrosis by modifying the function of different target sites of subcellular organelles in the myocardium. However, the information regarding these signal transducing molecules is scattered and mechanisms of their involvement in diverse regulatory processes are poorly understood. While PKA, CaMK, PI3K and PKC are activated by different hormones and mechanical stimuli, MAPKs are activated by growth factors and some cellular stresses such as oxidative stress, inflammation and Ca^{2+}-overload. Each type of these protein kinases is expressed in the form of two or more isozymes showing different biochemical characteristics and distinct biological functions. It has been demonstrated that all specific isoforms of these kinases produce both beneficial and detrimental effects on the heart, which are dependent upon the intensity and duration of stimulus for their activation. While PKA, PKC and CaMK are mainly involved in augmenting cardiac function as well as inducing cardiac hypertrophy and arrhythmias, PI3K is mainly involved in maintaining β-adrenoceptor function and inducing inflammation as well as arrhythmias. On the other hand, ERK1/2 mainly participate in the genesis of cardiac hypertrophy and cytoprotection whereas p38-MAPK and JNK are primarily involved in cardiac dysfunction, apoptosis and fibrosis. Since the activities of most protein kinases are increased under prolonged pathological conditions, a wide variety of their inhibitors have been shown to produce beneficial effects. However, extensive research needs to be carried out to understand the pathophysiology of different isoforms of each protein kinase as well as for the development of their isoform-specific inhibitors.

Key words: Protein kinase A; Protein kinase C; Ca^{2+}-calmodulin kinase; Phosphoinositide 3-kinase; MAP kinase; Extracellular regulated protein kinase; p38-MAP kinase; Cardiac hypertrophy; Arrhythmias; Cardiac function.

Correspondence:
NARANJAN S DHALLA
T: (204)235-3417
E: nsdhalla@sbrc.ca

ARTICLE INFO

Received: 26 January 2023
Revision received: 31 March 2023
Accepted: 1 April 2023

Introduction

It is now well known that a wide variety of signal transduction pathways are activated by different extracellular (chemical and mechanical) stimuli as well as cellular stresses to modify the structure and function of cardiomyocytes in health and disease.[1-11] One of the common components

Copyright © 2023 Nusier et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

This article should be cited as follows: Nusier M, Elimban V, Prasad J, Shah AK, Dhalla NS. Regulatory role of some protein kinases in signal transduction pathways in heart health and disease. Scr Med 2023 Jun;54(2):181-95.

of these signal transducing systems is a group of several protein kinases, which not only transmit the signals to their target sites but also regulate the functions of different subcellular organelles such as sarcolemma, sarcoplasmic reticulum, mitochondria, myofibrils, nucleus and extracellular matrix in the heart.[12-14] Several types of protein kinases are present in the myocardium and each of these enzymes have two or more isoforms with some overlapping structural characteristics but distinct biological functions. Some of these signal transducing proteins include protein kinase A (PKA), protein kinase C (PKC), Ca^{2+}-calmodulin dependent kinase (CaMK), phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK). These protein kinases have been demonstrated to regulate cation transport, cellular growth, gene expression, cellular apoptosis and fibrosis as well as myocardial metabolism[15-17] and are thus considered to play a major role in the regulation of cardiac function.

It is pointed out that all protein kinases, upon activation by diverse agents or interventions, evoke immediate biological actions for the regulation of several subcellular protein activities. A schematic representation of different protein kinases and their activators is shown in Figure 1 whereas that for major sites and targets of the activated transducing proteins is given in Figure 2. The process of activation involves the transfer of γ-phosphate group from ATP to hydroxyl group of serine/threonine protein kinases or tyrosine residue of tyrosine protein kinases. It should be noted that most of these protein kinases exert both beneficial and detrimental effects depending upon the intensity and duration of the stimulus as well as isoform of the enzyme involved in the process of signal transduction. A few beneficial effects of some inhibitors of the activated protein kinases are shown in Figure 3. In the present article, the existing information regarding some protein kinases for their activation, actions as well as participation in various signal transduction pathways in normal and diseased hearts is updated. In view of the complex mode of involvement of various protein kinases in diverse signal transduction pathways, it is intended to briefly discuss

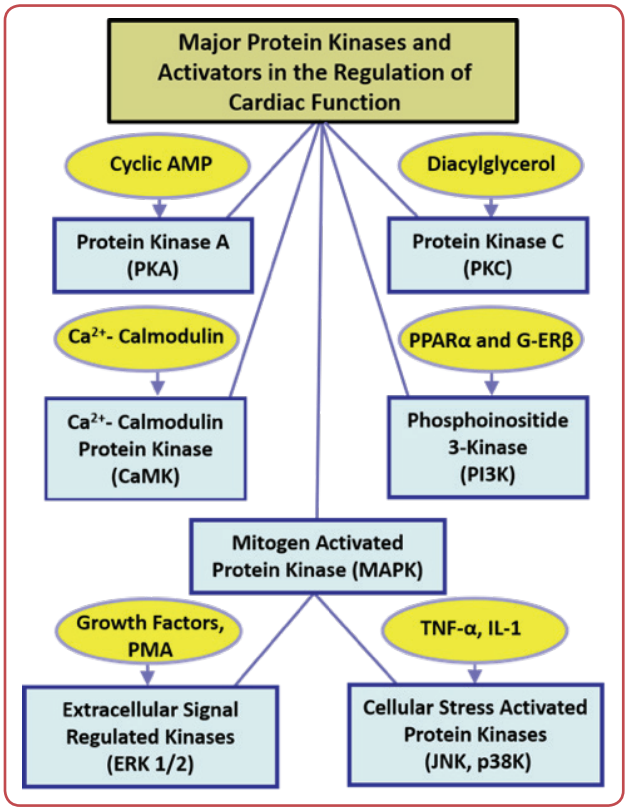

Figure 1: Activation of different protein kinases in the heart by some intracellularly produced complex factors and metabolites as well as extracellular growth factors and agents

PPAR α, peroxisome proliferator-activated receptor α; G-ERB, G-protein coupled estrogen receptor B; PMA, phorbol myristate acetate; TNF-α, tumor necrosis factor -α; IL-1, interleukin-1; JNK, c-jun N-terminal protein kinase;

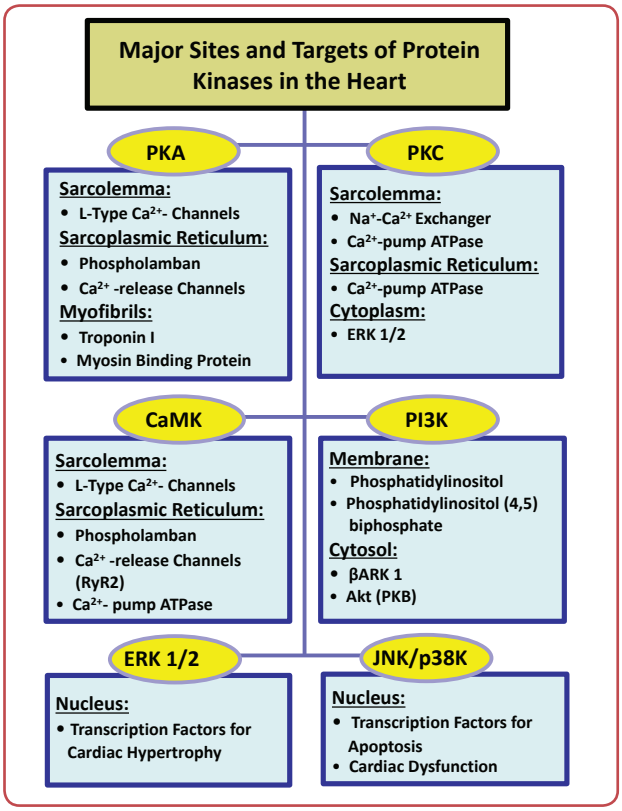

Figure 2: Major sites and targets of some activated protein kinases in the heart

PKA, protein kinase A; PKC, protein kinase C; CaMK, Ca^{2+}- calmodulin protein kinase; RyR2, ryanodine receptors; PI3K, phosphoinositide 3-kinase; ERK1/2, extracellular regulated protein kinase 1 and 2; JNK/p38K, cellular stress activated MAP kinases; βARK1, β-adrenergic receptor kinase 1; Akt, protein kinase B;

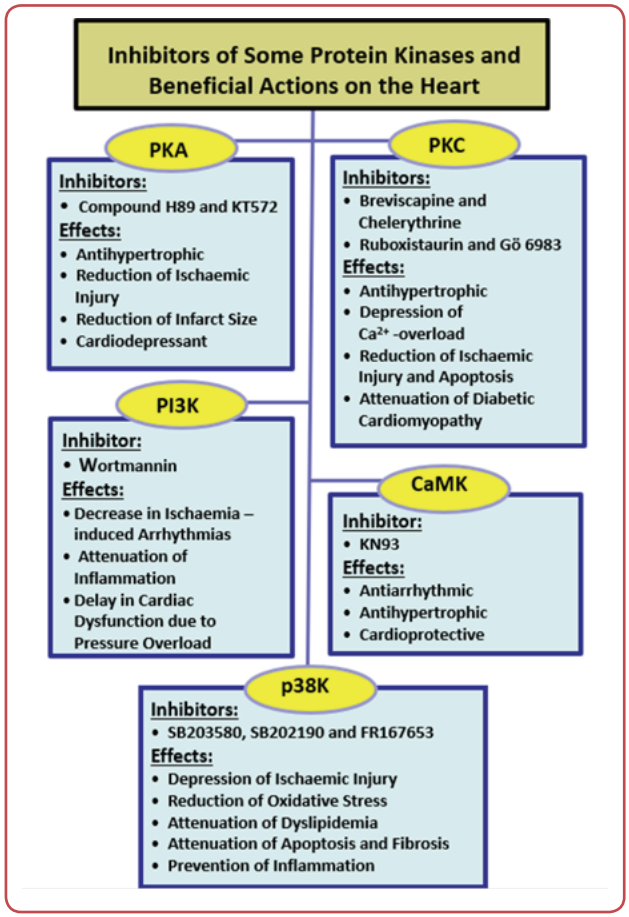

Figure 3: Beneficial effects of different inhibitors of some protein kinases in heart disease

PKA, protein kinase A; PKC, protein kinase C; CaMK, Ca^{2+}- calmodulin protein kinase; PI3K, phosphoinositide 3-kinase; p38-Kinase, cellular stress activated MAP kinase;

the role of these signalling proteins in modifying different biological processes. Since all protein kinase are activated during the development of heart disease, an attempt has also made to identify appropriate protein kinases as targets for drug development for improving cardiac performance.

Role of Protein Kinase A

PKA is a tetramer holoenzyme, which consists of two regulatory subunits and two catalytic subunits. The catalytic subunits harbour the active site, a sequence of canonical amino acid residues that bind and hydrolyse ATP and a domain that binds the regulatory subunit. The regulatory subunits have three domains – one that binds cyclic AMP, another domain which interacts with catalytic subunit and an autoinhibitory domain.[18] Upon binding of cyclic AMP to regulatory subunits, dissociation and release of active regulatory monomers occur for the transduction of signal.[19] There are four types of PKA – RIα, PKA-IIα, PKA-Iβ and PKA-IIβ, which are expressed in cardiomyocytes.[20] It is noteworthy that PKA is responsible for phosphorylation of numerous proteins involved in the regulation of myocardial contraction and relaxation. The activation of PKA has been reported to phosphorylate sarcolemma (SL) Ca^{2+} channels to increase the influx of Ca^{2+} into cardiomyocytes for the occurrence of an increase in cardiac contractibility. Several studies addressing the interaction of PKA with sarcoplasmic reticulum (SR), at phospholamban (PLB) and ryanodine receptor 2 (RyR_2, Ca^{2+}- release channel proteins), have appeared in the literature to promote Ca^{2+}-uptake and Ca^{2+}-release activities for the regulation of myofibrils for affecting the overall cardiac performance.[21-23] Furthermore, it has been reported that PLB, a SERCA regulatory protein, is phosphorylated by PKA in cardiomyocytes in response to stimulation by β-adrenoceptor (β-AR) agonists, catecholamines, which relieve the inhibitory effect of PLB on SERCA2 and thus increase the SR Ca^{2+}-pump activity.[24-28] PKA was also shown to phosphorylate and stimulate the activity of RyR2 to release Ca^{2+} from the SR Ca^{2+}-stores.[29] PKA-dependent SR phosphorylation following β-AR stimulation has also been observed to produce an increase in the leakage of SR Ca^{2+}.[30] In addition, to increasing the intracellular concentration of Ca^{2+}, phosphorylation of myofibrillar proteins by PKA has been reported to cause stimulation of cardiac filament change in orientation and affect contractility of the heart.[31] Moreover, stimulation of cardiomyocytes by β-AR is associated with phosphorylation of both myosin C protein and troponin I (cTn1) by PKA in thick myofilaments and thin myofilaments, respectively.[32] It has also been reported that cTn1 phosphorylation by PKA increases cardiac rate of relaxation and crossbridge cycle kinetics and is associated with frequency and after-load dependent enhancement of heart function.[33-35]

It should be pointed out that phosphorylated PKA in the cytoplasm also enters the nucleus to activate appropriate transcription factors to induce cardiac hypotrophy and improve cardiac function.[1, 2, 17] Since PKA induced phosphorylation of various subcellular proteins increases cardiac function, inhibition of the PKA can be seen to depress heart performance. Such an effect of PKA inhibitors was demonstrated to reduce infarct size and prevent complications following myocardial infarction.[28, 36] Because proteasome assembly is

facilitated by PKA phosphorylation, this assembly of proteasome is also blocked upon PKA inhibition.[37] It is noteworthy that PKA inhibition has been reported to play a role in decreasing apoptosis in cardiomyocytes.[38, 39] Furthermore, PKA inhibition was shown to exert cardioprotective effect during ischaemic injury and promote growth hormone induced cardioprotection during ischaemia reperfusion as well.[28, 40] On the other hand, prolonged activation of PKA invariably results in cardiac dysfunction for the development of heart failure. These observations are consistent with the view that the activation of PKA not only induces cardiac hypertrophy and improves cardiac performance upon β-AR stimulation, but also plays a role in cardioprotection under different pathological situations such as ischaemia-reperfusion injury.

Role of Ca^{2+}-Calmodulin Dependent Protein Kinase

CaMK is a ubiquitous mediator of Ca^{2+}-linked signalling, which phosphorylates various substrates to regulate Ca^{2+}-mediated modifications in cardiac function.[41] CaMK exits in four isoforms which are encoded by highly related genes α, β, γ and δ.[42] Although, the activation of CaMK by Ca^{2+}-calmodulin is brief in nature, the oligomerisation of CaMK subunits is associated with a prolonged activation process.[43, 44] It may be noted CaMKII is one of the main effector enzymes involved in Ca^{2+} signalling in eukaryotic cells but the position of the catalytic domain, Ca^{2+} sensitivity and autophosphorylation are altered by hetero-oligomerisation processes for α, β and δ subunits of the variable domain spacers of CaMK II.[42] The involvement of CaMKII in the modification of excitation-contraction coupling by phosphorylating RyR, PLB and SERCA2, makes it a major player in modulating cardiac function and performance.[6, 45, 46] While the activation of CaMK for a short period is known to improve cardiac performance, a damaging effect on heart function has been reported to be due to excessive or prolonged activation of CaMKII in the myocardium, which is associated with the development of hypertrophic and apoptotic cardiomyopathy.[47-49] It has been demonstrated that reactive oxygen species (ROS) increase the sensitivity of CaMKII to Ca^{2+} and this ROS-dependent CaMKII activation has been shown to initiate angiotensin II induced apoptotic cascade.[50] Therefore, the positive and negative effects of CaMKII activation are dependent on the intensity and duration of stimulation. Different CaMKII inhibitors have also reported to exert both negative and positive effects on the heart. Activation of CaMKII was observed to augment oxidative stress and cause lethal ventricular arrhythmias.[51-53] CaMKII inhibition was also shown to prevent maladaptive remodelling due to excessive β-AR stimulation, Ca^{2+} handling abnormalities, as well as arrhythmias under *in vivo* conditions.[52, 54-56] An increase in RyR2-dependent Ca^{2+} leakage due to increased phosphorylation of the RyR2 has been suggested to explain the enhancement of CaMKII activity in subjects susceptible to atrial fibrillation[57] and this effect of CaMKII was also demonstrated to play a role in arrhythmias in a mouse model of heart failure.[58] Furthermore, it has been shown that induction of CaMKII by pressure overload may enhance protein synthesis and cause hypertrophy, a process that is considered to be adaptive initially but when prolonged it becomes pathological.[59]

It has been reported, that δ isoform of CaMKII plays a major role in the pathophysiological remodelling of the heart due to pressure overload.[60, 61] In fact, various CaMKII isoforms has been demonstrated to affect the heart function differently. It was shown that the levels of δ and γ isoforms of CaMKII were increased, following cardiac hypertrophy induced by aortic constriction[62, 63] and a substantial reduction in cardiac hypertrophy was observed when δ isoform was inhibited with a minimal disruption of CaMKII function. Functionally, cardiac CaMKII-δB and δC are also different as these isoforms are inversely regulated in response to IR injury and oxidative stress. While, δB inhibits myocyte apoptosis, δC triggers the opposite effect.[64, 65] Additionally, it has been reported that CaMKII δB overexpression is cardioprotective against hypoxia, oxidative stress and angiotensin-II induced apoptosis, probably as a consequence of CaMKII δC inhibition.[66, 67] It has been shown that acute overexpression of CaMKII δC alters RyR function, leading to enhanced SR Ca^{2+} leakage, which may cause ventricular arrhythmia in mice.[57, 58] This damaging effect was prevented when CaMKII inhibitors such as KN93 and autocamtide2-related inhibitory peptides were used.[69, 70] Collectively, these reports support the concept that both positive and negative effects of CaMKII signal transduction pathway depend on the involvement of specific isoform of the enzyme.

While cardiomyocyte hypertrophy has been shown to be induced by CaMKII δ3 via the activation of apoptosis signal-regulating kinase 1 (ASK-1), phosphorylation of Ca^{2+}-induced ASK-1 was reported to be inhibited by KN93.[71, 72] Since numerous studies have revealed that CaMKII is a key player in addition to CaMKI and CaMKIV for the induction of hypertrophy in cardiomyocytes *in vivo*,[73-75] it has been suggested that CaMKII inhibition may reduce the development of hypertrophy in the heart. Although, it was shown that the left ventricular end-diastolic diameter is increased and the fractional shortening is decreased upon overexpression of CaMKIV in mice,[73, 74] the advantage of CaMK inhibition in other pathological settings is speculative. Nonetheless, it has been reported that the recovery of cardiac function after I/R is facilitated by ischaemic preconditioning and is inhibited by KN93; these findings provide evidence for the activation of CaMKII in the preconditioning process.[76, 77] The impairment in the SR function in the myocardium has also been shown to be due to modification in SR CaMK-facilitated phosphorylation, as well as due to reduction in the level of SR proteins and activity of SR CaMKII.[78, 79] Regardless of the involvement of CaMKII δC in the process of hypertrophy, it has been reported to phosphorylate calcineurin and cause inhibition of its activity. It was also shown that cardiac hypertrophy, dysfunction and arrhythmias are caused by calcineurin[80, 81] indicating that inhibition by calcineurin of active CaMKII δ is probably more efficient than inhibition of the inactive form of CaMKII δ. These observations support the view regarding the differential significance of CaMK isoforms in affecting the cardiac function.

Role of Protein Kinase C

PKC plays an important role in relaying information for a variety of extracellular signals across the membrane to regulate several Ca^{2+}-linked activities. The PKC family has many isoforms that share a conserved kinase domain with an ATP-binding site at the carboxyl terminal.[3, 82] Major PKC isoforms expressed in hearts are α and β with α being more human specific.[83] Depending upon the mode of activation, PKC is divided into 3 classes namely conventional (cPKC), novel (nPKC) and atypical (aPKC). Conventional ones respond to Ca^{2+} and diacylglycerol (DAG) to express their activities and have α, βI, βII and γ isoforms. The novel ones are activated by DAG, independent of Ca^{2+} and exhibit δ, ε, η and θ isoforms. Atypical ones respond to phosphoinositide-dependent kinase-1, independent of Ca^{2+} and show ζ and λ isoforms.[4, 84, 85] It has been reported that phorbol esters increase the activity of PKC associated with membranes to produce cardiac dysfunction.[86] It was shown that PKC isoforms α, β, ε, ζ and Ca^{2+}-independent activity are increased in cytosolic and homogenate fractions of diabetic hearts; this increase demonstrates a link between subcellular modifications and cardiac activity in these hearts.[87] Additionally, hormone induced hypertrophy in hearts was linked to PKC activation as it was found that both membrane and nuclear cytoskeletal fractions of hypertrophied heart due to pressure overload were associated with increase in levels and activities of specific PKC isoforms, PKC-β1,2 and PKC-ε.[88] Braun and coworkers[89] have also reported an increase in PKC δ, unlike PKC α or ε isoforms, in the left ventricular hypertrophy induced by volume overload whereas an increase in the activity and protein expression of both α and δ isoforms of PKC was observed in the right ventricular hypertrophy. It was shown that the left ventricular dilatation due to angiotensin II was associated with the activation of phospholipase C, causing phosphatidylinositol (PI) hydrolysis and PKCε activation. Similarly, an increase in the autophosphorylation of PKC-δ was seen to occur prior to the development of left ventricular hypertrophy as well as during the transition to heart failure. Although the expression of PKC-α was unchanged during the induction of cardiac hypertrophy, it was augmented prior to the development of left ventricular hypertrophy.[91, 92] Therefore, it was concluded that activation of specific PKC isoforms plays an important role in either the positive or the negative effect of the PKC signal transduction pathway. Nonetheless, inhibition of PKC was reported to prevent the occurrence of abnormal myocyte mechanics in diabetes and improve contractility of the heart.[83, 93] It is pointed out that an increased expression of PKC-α and PKC-β isoforms was linked to the loss of cardiac contractile function in diabetes, which eventually caused heart failure because of the regulatory effect on Ca^{2+}-cycling proteins.[83, 94-97]

It has been reported that ruboxistaurin, an inhibitor of PKC-β, attenuates diastolic dysfunction, myocyte hypertrophy, as well as collagen deposition for preserving cardiac contractility in diabetic cardiomyopathy.[98, 99] Additionally, Boyle

and coworkers[100] reported that inhibition of PKC with ruboxistaurin attenuated the pathological fibrosis and impairment of cardiac function in experimentally induced myocardial infarction. Deterioration in cardiac contractility and depression of metabolic activities in the ischaemic heart conditions were shown as an effect of aldosterone induced vasoconstriction through PKC-dependent pathways.[101, 102] Furthermore, Wang et al[91] reported a close association between the upregulation of PKC-α, PKC-β and PKC-ε expressions and the activity of PKC in cardiac dysfunction following MI. It was observed that inhibition of PKC by ruboxistaurin decreased ventricular dilation, improved ventricular performance and reduced fibrosis in mice following 10 weeks of pressure-overload.[98] It was also shown that PKC-α -/- mice were less vulnerable to heart failure, while PKC-β/γ -/- mice showed severe heart failure by a longstanding pressure overload.[98] Upon subjecting transgenic mice to inhibition with ruboxistaurin, an increase in cardiac contractility was noticed in the PKC-β/γ -/- model but not in the PKC-α -/- model.[98] These results provide further evidence concerning the significance of PKC isoform inhibitor specificity. It was also observed that Ro-318110, a PKC-α selective inhibitor, caused an increase in cardiac contractile function of the heart and improved the pump function in heart failure in a mouse model.[83] These studies also indicated the effectiveness of the specific inhibition of PKC-α by Ro-320432 in improving heart contractile function.

It was claimed that the compound Gö 6983 provides better cardioprotection than other PKC inhibitors when administered at the start of reperfusion, because it averts intracellular Ca^{2+} overload following ischaemic reperfusion injury and in addition to PKCξ inhibition, it also depressed other PKC isoforms.[103, 104] Inhibition of PKC-βII was shown to improve contractility following cardiac dysfunction due to the ischaemia reperfusion induced by polymorphonuclear leukocytes (PMN). This action was due to inhibition of the release of PMN superoxide and the increase in the nitric oxide release from the endothelium.[105-107] Although the extent of inhibition of PKC was found crucial, the expression level of δ-specific PKC as well as inhibition of its translocation were also shown to impact heart function.[107] In fact, an improvement in heart dysfunction without significant changes in heart structure, function or gene expression has been reported in the presence of low levels of this inhibitor.[107] On the other hand, severe consequences were observed upon overexpression of PKC-δ V1, which were lethal with depressed cardiac contractile activity, increased expression of foetal cardiac genes and formation of myocyte protein aggregates.[108]

Inhibition of PKC attenuated the effects of ischaemic preconditioning on cardiac function and lipid peroxidation indicating that cardioprotection involving the activation of PKC may be a consequence of the depression in the reactive oxygen species (ROS) induced damage.[109, 110] In fact, the activation of PKC has been reported to play an important role in exercise-induced cardioprotection against ischaemia-reperfusion injury.[111, 112] Furthermore, the activation of PKC by angiotensin II, preceding ischaemia, was observed to limit myocardial infarct size.[113] Since the overexpression of the active cardiac-specific PKCε mutant in transgenic mice has been shown to cause concentric hypertrophy with normal *in vivo* cardiac function[114, 115] the association of cardioprotection and the activation of PKC, especially the isoform ε, has been established during ischaemia-reperfusion injury.[116, 117] While cardioprotection by improving vascular endothelial nitric oxide release was achieved when PKC-ε was activated upon the administration of a peptide activator prior to ischaemia, but not during preconditioning, a PKC-ε inhibitor was observed to eliminate the cardioprotective effects of PKC-ε activator.[118] PKC-ε translocation from the cytosol to the membrane has also been shown to modify the cardioprotective effects of opioid receptor stimulation, causing decrease in cellular injury due to lethal ischaemia.[119, 120] Since cardioprotection due to ischaemic preconditioning occurs in two phases, the mechanisms for the involvement of PKC in early and late phases of cardioprotection have been shown to be of a complex nature.[121-125] While cardioprotection in early phase involves posttranslational modification of redox sensitive proteins whereas the late phase is mediated by cardioprotection of gene expression.[121] Furthermore, neither the activation and translocation of any specific PKC isoforms nor the role of associated signal transduction pathways involving mitochondrial KATP channels, formation of oxyradicals species and generation of nitric oxide in both phases of cardioprotection by ischaemic preconditioning is fully understood.[122-125] On the other hand, translocation of PKC-ε has been demonstrated to be involved in exercise preconditioning induced by both early and late phases of cardioprotection.

Different cardiac PKC isoforms were found to modulate apoptosis induced by hyperglycaemia and cardiac PKCε activation was observed to protect ventricular myocytes in rats from death signals induced by hyperglycaemia.[127, 128] In addition, cardiac specific expression of the PKC-ε translocation activator ψε-RACK (a PKC ε-agonist) has been reported to protect cardiomyocytes from apoptosis signals induced by hyperglycaemia.[127, 129] Since PKC is an essential signalling component for the fibroblast growth factor 2 (FGF2)-induced cardioprotection, various interconnections between the MAPK and PKC pathways during ischaemia-reperfusion injury are considered to play a key role in cardioprotection produced by FGF2.[130, 131] Furthermore, Das and coworkers[132] have reported that selective translocation of PKC isoforms α, δ and θ from cytosol to membrane fractions and have thus suggested their probable role in cardioprotection induced by sildenafil. Accordingly, it is evident that not only there is a great deal of specificity of PKC isoforms but the selective transduction as well as translocation of some PKC isoforms are also a special feature of cardioprotection under various conditions.

Role of Phosphoinositide 3-Kinase

PI3K is a heterodimeric molecule which consists of 2 subunits; a regulatory p85 subunit and catalytic p110, subunit harbouring two SH2 domains.[133, 134] These subunits form adaptor motifs connecting tyrosine kinases and their substrates;[135] both catalytic p110 and regulatory p85 form *in vivo* obligate heterodimers.[136] The catalytic protein forms a bilobal structure with an ATP-binding pocket between N-terminal and C-terminal sections and the catalytic amino acid residues in the phosphate-binding subsite.[137, 138] Various isoforms of PI3K are involved in the regulation of different types of biological functions in the heart. For instance, PI3Kα isoform mediates changes in the size of cells whereas PI3Kγ isoform inhibits the production of cAMP and thus reduces cardiac contractile activity.[139, 140] PI3K inhibition has also been reported to decrease cardiac arrhythmias due to ischaemia as well as inflammation following MI.[141, 142] It was shown in an animal model with chronic pressure overload overexpressing PI3K that active endogenous PI3K was replaced by inactive PI3K and this shift resulted in delay in the development of cardiac dysfunction[143] indicating the role of PI3K in heart failure. Perrino and coworkers[144] have reported that targeting of PI3K at the site of activated βAR plays a central role in the downregulation of βAR. In this regard, competitive removal of PI3K from βARK1 was found to conserve βAR signalling in heart failure, defer cardiac dysfunction progression and prolong lifespan of the genetic heart failure animal model. These investigators have also reported that adenovirus gene transfer of PI3K domain resulted in a decrease in the activity of the receptor-localised PI3K and caused normalisation of contractility in failing pigs hearts.[145] Nienaber et al[146] have shown that PI3K participates in the regulation of the level as well as sensitivity of βAR function in hearts and observed a significant role of this kinase in βAR dysfunction in pressure overload-induced heart failure. Therefore, it was suggested that inhibition of PI3K may preserve βAR signalling to avert heart failure.

A decline in cardiac function due to free radicals has been linked to PI3Kγ activation by tumour necrosis factor-α (TNF-α) for causing remodelling of the myocardium.[147] Perrino et al[148] have also reported that pathological pressure overload enhances gene expression of PI3Kγ, suggesting that its inhibition may attenuate cardiac hypertrophy. Gene knockout animal models of PI3K regulatory subunit p85 has also revealed a decrease in heart size and preservation of cardiac contractility and structure.[149, 150] It was observed that G protein-coupled oestrogen receptor was upregulated in isolated rat hearts following ischaemia-reperfusion and thus may improve cardiac function recovery and reduce the infarct size; such positive effects were eliminated when PI3K was subjected to inhibition by wortmannin.[151, 152] It should be noted that PI3K inhibitor, wortmannin, eliminated the improvement in cardiac function recovery in epoxyeicosatrienoic acid treated hearts but did not inhibit the recovery of rBNP-treated hearts.[153] Furthermore, wortmannin has been observed to attenuate adrenomedullin-induced positive effects, such as infarct size reduction, haemodynamic improvements and apoptosis inhibition and therefore it was suggested that adrenomedullin induces cardioprotective effects through the PI3K/Akt pathway.[154, 155] In a genetic mouse model of atrial fibrillation associated with heart failure, it was shown that a reduction in PI3K (p110α) activity increases the susceptibility to atrial fibrillation, whereas an increase in the activity decreases atrial fibrosis and improve

cardiac conduction.[156] Additionally, contractile defects have been reported in cardiac myocytes lacking PI3K subunit p110α.[157] On the other hand, it was observed that an increase in the activity of PI3K p110α has positive effects on cardiac function in animal models of heart failure.[158] Absolute deficiency of PI3K-β subunit was found to result in dramatic reduction in myocardial contractile performance, while absolute deficiency of PI3K-γ resulted in myocardial infarction in mice.[159] Thus, PI3K can be seen to play an important regulatory role in inducing both beneficial and detrimental effects in heart function depending upon the involvement of its isoforms and subunits, which are activated by either by growth factors or by proinflammatory interventions.

Role of P38 Mitogen-Activated Kinases

MAPKs are intracellular signalling molecules which are activated by either growth factors or by proinflammatory cytokines[10, 11, 160] and are known to exert both beneficial and detrimental effects on the heart. Cardiac dysfunction and apoptosis have been linked to the activation of p38-MAPK when changes in Ca^{2+} status (Ca^{2+} depletion and Ca^{2+} repletion) occur.[161] While apoptosis has been shown to occur upon the activation of α-isoform of p38-MAPK, cardiac hypertrophy has been observed when p38-MAPK β-isoform was overexpressed.[162] Nonetheless, inhibition of p38-MAPK has been reported to be cardioprotective against ischaemic damage.[163-166] Otsu and coworkers[167] have demonstrated that a p38-MAPK knockout model was resistant to ischaemia/reperfusion injury. ROS has been reported to increase p38-MAPK activation and subsequently results in myocardial damage.[168] It was reported that rats treated with selective p38- MAPK inhibitors showed a decrease in angiotensin II-induced ROS production, hypertension and cardiac hypertrophy.[169] Since cardiac dysfunction due to inflammatory response has been associated with p38-MAPK activation as well as expression of inflammatory cytokines, the inhibition of p38-MAPK with specific inhibitors has been reported to avert the negative inflammatory effects on the heart function.[170-172] Li et al[173] have shown that p38-MAPK-α inhibition in a rat model of acute myocardial injury has a cardioprotective effect and substantially improved cardiac function. On the other hand, P38-MAPK-knock-out hamster model has been reported to develop early heart failure and cardiac dysfunction in comparison with the control group.[172] Although most of the regulatory actions of JNK are similar to those of p38-MAPK[10, 11] the effects of JNK and p38 inhibitors on cardiac dysfunction in hamsters are opposite to each other.[172] These observations are consistent with the view that p38-MAPK and JNK may exert both good and bad regulatory actions in the heart.

It needs to be emphasised that in addition to p38-MAPK and JNK, both ERKI and ERK2 belong to MAPK family of serine-threonine specific protein kinases.[10, 11, 16, 17] These proteins and their different isoforms and subunits share 60 to 70 % similarity and thus a great of caution be used while interpreting the effects of their inhibitors.[160, 162] Furthermore, it is pointed out that while p38-MAPK and JNK are mainly concerned with the regulation of transduction pathways for ischaemia-reperfusion injury, apoptosis and cardiac dysfunction, both ERK1 and ERK2 are known to play a major regulatory role in the processes concerned with the development of cardioprotection and cardiac hypertrophy.[10, 16, 173] Upon activation by PKC in the cytosol, both ERK1/2 enter the nucleus to phosphorylate different transcription factors for the regulation of hypertrophic response in the heart.[15, 174] Activation of ERK1/2 upon the induction of pressure overload has been reported to promote cardiomyocyte survival.[175] Multiple circulating hormones and growth factors such as angiotensin II, insulin, platelet derived growth factor and epidermal growth factor as well as tumour promoting phorbol esters have been shown to activate ERK1/2 and induce cardiac hypertrophy.[176-179] It should be also pointed out that prolonged activation of ERK1/2 has been demonstrated to result in the development of heart failure[180, 181] and thus antihypertrophic agents such as angiotensin II antagonists and angiotensin converting enzyme inhibitors can be seen to produce beneficial effects in heart failure as a consequence of reduction in the activity of ERK1/2.[12-14] It should be noted that both p38-MAPK and JNK are activated by the ischaemic insult[182, 183] whereas the effects of ischaemia-reperfusion on ERK1/2 activities are controversial.[184, 185] In fact, inhibition of ERK1/2 has been reported to enhance ischaemia-reperfusion injury as well as apoptosis.[186] Furthermore, ERK1/2 signal transduction pathway has been reported to

induce compensated cardiac hypertrophy.[187] Not only the effects of ERK1/2 activation on apoptosis are opposing to those p38K-JNK,[188] ERK1/2 signal transduction pathways have been reported to play an antiapoptotic role in the cell survival.[189] These observations support the view that ERK1/2 pathway is mainly cytoprotective.

Conclusion

From the foregoing discussion, it is evident that there are five major types of protein kinases, which participate in different signal transduction pathways for relaying information to target sites at the subcellular organelles in the heart. One group of these signal transducing proteins includes PKA, PKC, CaMK and PI3K (which are activated by various hormones and mechanical stimuli) whereas the other group (MAPK), includes two classes of proteins namely ERK1 and ERK2 (which are activated by growth factors) as well as p38-MAPK and JNK (which are activated by proinflammatory cytokines: TNF-α and IL-1). It is pointed out that in spite of the presence of numerous protein kinases, which may participate in diverse signal transduction pathways in the myocardium, some protein kinases such as PKA, PKC and CaMK are mainly involved in regulating cardiac function, cardiac hypertrophy and arrhythmias whereas PI3K is involved in inducing inflammation as well as modifying β-adrenoceptor-mediated pathway. Furthermore, ERK1/2 mainly participate in the development of cardiac hypertrophy and cytoprotection whereas p38-MAPK and JNK are involved in cardiac dysfunction as well as cellular injury. It also needs to be emphasised that all these protein kinases have been demonstrated to participate in inducing both beneficial and detrimental effects with respect to cation transport, cellular injury, apoptosis, fibrosis, cellular growth, gene expression, cardiac hypertrophy and cardiac dysfunction. However, these actions are of complex nature and are dependent upon the intensity and duration of stimulus. Accordingly, extensive work needs to be carried out in order to establish which effects is adaptive and which effect is harmful in nature. Nonetheless, it appears that these protein kinases are not only involved in the transmission of signals to subcellular organelles but are also involved in the regulation of their activities.

It is noteworthy that each type of protein kinase is expressed in the form of two to four isozymes which have been shown to produce distinctly different biological functions in the myocardium. In fact, the activation of some isoforms of a protein kinase have been reported to induce opposite actions in response to different interventions and thus both the beneficial and detrimental effects of various protein kinases upon their activation are difficult to interpret. Although a wide variety of inhibitors are available, their isoform specificity needs to be carefully determined during the development of various cardiovascular diseases. It is therefore suggested that time-course studies for different isoforms of each type of protein kinase be examined. Likewise, appropriate genetic animal models for each isoform of different protein kinases be developed to gain the information regarding their exact functional significance in different diseases. Since various protein kinases are activated during the development of heart failure, the status of each isoform of these signal transducing proteins be examined in order to understand their role in the pathophysiology of this major cardiac disorder as well as for the development of isoform specific inhibitors for the treatment of heart disease.

Acknowledgements

The infrastructure support for the preparation of this article was provided by the St. Boniface Hospital Albrechtsen Research Centre. Thanks are also due to Mrs Janice Fotheringham for typing this manuscript. Dr Mohamad Nusier was a Visiting Professor from the Jordan University of Science and Technology, Irbid, Jordan.

Conflict of interest

None.

References

1. Taylor SS, Buechler JA, Yonemoto W. cAMP-dependent protein kinase: Framework for a diverse family of regulatory enzymes. Annu Rev Biochem 1990;59:971-1005.
2. Dhalla NS, Wang J. Role of protein kinase C and protein kinase A in heart function in health and disease. Exp Clin Cardiol 1999;4:7-14.
3. Kikkawa U, Nishizuka Y. The role of protein kinase C in transmembrane signalling. Annu Rev Cell Biol 1986;2:149–78.
4. Mellor H, Parker PJ. The extended protein kinase C superfamily. Biochem J 1998;332:281-92.
5. Hook SS, Means AR. Ca2+/CaM-dependent kinases: From activation to function. Annu Rev Pharmacol Toxicol 2001;41:471-505.
6. Hudmon A, Schulman H. Neuronal Ca2+/calmodulin-dependent protein kinase II: the role of structure and autoregulation in cellular function. Annu Rev Biochem 2002;71:473–510.
7. Walker EH, Perisic O, Ried C, Stephens L, Williams RL. Structural insights into phosphoinositide 3-kinases catalysis and signaling. Nature 1999; 402:313-20.
8. Djordjevic S, Driscoll PC. Structural insight into substrate specificity and regulatory mechanisms of phosphoinositide 3-kinases. Trends Biochem Sci 2002;27:426–32.
9. Chan TO, Rittenhouse SE, Tsichlis PN. AKT/PKB and other D3 phosphoinositide-regulated kinases: Kinase activation by phosphoinositide-dependent phosphorylation. Annu Rev Biochem 1999;68:965-1014.
10. Zhang W, Elimban V, Nijjar MS, Gupta SK, Dhalla NS. Role of mitogen-activated protein kinase in cardiac hypertrophy and heart failure. Exp Clin Cardiol 2003;8:173-83.
11. Krishna M, Narang H. The complexity of mitogenactivated protein kinases (MAPKs) made simple. Cell Mol Life Sci 2008;65:3525–44.
12. Bhullar SK, Shah AK, Dhalla NS. Role of angiotensin II in the development of subcellular remodeling in heart failure. Explor Med 2021;2:352-71.
13. Bhullar SK, Dhalla, NS. Angiotensin II-induced signal transduction mechanisms for cardiac hypertrophy. Cells 2022;11: 3336. doi: 10.3390/cells11213336.
14. Bhullar SK, Shah AK, Dhalla, NS. Mechanisms for the development of heart failure and improvement of cardiac function by angiotensin-converting enzyme inhibitors. Scr Med 2022;53:51-76.
15. Bogoyevitch MA, Sugden PH. The role of protein kinases in adaptational growth of the heart. Int J Biochem Cell Biol 1996;28:1–12.
16. Sugden PH, Bogoyevitch, MA. Intracellular signaling through protein kinases in the heart. Cardiovasc Res 1995;30:478-92.
17. Dhalla NS, Muller AL. Protein kinase as drug development targets for heart disease therapy. Pharmaceuticals 2010;3:2111-45.
18. Turnham RE, Scott JD. Protein kinase A catalytic subunit isoform PRKACA; History, function and physiology. Gene 2016;577:101–8.
19. Heldin C-H. Dimerization of cell surface receptors in signal transduction. Cell 1995;80:213–23.
20. Di Benedetto G, Zoccarato A, Lissandron V, Terrin A, Li X, Houslay MD, et al. Protein kinase A type I as type II define distinct intercellur signaling compartments. Circ Res 2008;103:836-44.
21. Baryshnikova OK, Li MX, Sykes BD. Modulation of cardiac troponin C function by the cardiacspecific N-terminus of troponin I: influence of PKA phosphorylation and involvement in cardiomy-opathies. J Mol Biol 2008;375:735–51.
22. Shaffer JF, Kensler RW, Harris SP. The myosinbinding protein C motif binds to F-actin in a phosphorylation-sensitive manner. J Biol Chem 2009;284:12318–27.
23. Jones PP, Meng X, Xiao B, Cai S, Bolstad J, Wagenknecht T, et al. Localization of PKA phosphorylation site, Ser2030, in the three-dimensional structure of cardiac ryanodine receptor. Biochem J 2008;410:261–70.
24. Hakim K, Fischer M, Günnicker M, Poenicke K, Zerkowski HR, Brodde OE. Functional role of β2-adrenoceptors in the transplanted human heart. J Cardiovasc Pharmacol 1997;30:811–6.
25. Surdo NC, Berrera M, Koschinski A, Brescia M, Machado MR, Carr C, et al. FRET biosensor uncovers cAMP nanodomains at β-adrenergic targets that dictate precise tuning of cardiac contractility. Nat Commun 2017;8:1–14.
26. Böhm M, Reiger B, Schwinger RH, Erdmann E. cAMP concentrations, cAMP dependent protein kinase activity, and phospholamban in non-failing and failing myocardium. Cardiovasc Res 1994;28:1713–9.
27. Mattiazzi A, Hove-Madsen L, Bers DM. Protein kinase inhibitors reduce SR Ca transport in permeabilized cardiac myocytes. Am J Physiol Heart Circ Physiol 1994;267:H812–20.
28. Robinet A, Hoizey G, Millart H. PI 3-kinase, protein kinase C, and protein kinase A are involved in the trigger phase of β1-adrenergic preconditioning. Cardiovasc Res 2005;66:530–42.
29. Wehrens XH, Lehnart SE, Reiken S, Vest JA, Wronska A, Marks AR. Ryanodine receptor/calcium release channel PKA phosphorylation: a critical mediator of heart failure progression. Proc Natl Acad Sci 2006;103:511–8.
30. Ogrodnik J, Niggli E. Increased Ca2+ leak and spatiotemporal coherence of Ca2+ release in cardiomyocytes during β-adrenergic stimulation. J Physiol 2010;588:225–42.
31. Sadayappan S, Gulick J, Osinska H, Corbalán R, Foncea R, Ebensperger R, et al. A critical function for Ser-282 in cardiac Myosin binding protein-C phosphorylation and cardiac function. Circ Res 2011;109:141–50.
32. Piddo AM, Sánchez MI, Sapag-Hagar M, Corbalán R, Foncea R, Ebensperger R, et al. Cyclic AMP-dependent protein kinase and mechanical heart function in ventricular hypertrophy induced by pressure overload or secondary to myocardial infarction. J Mol Cell Cardiol 1996;28:1073–83.
33. Kentish JC, McCloskey DT, Layland J, Palmer S, Leiden JM, Martin AF, et al. Phosphorylation of troponin I by protein kinase A accelerates relaxation and crossbridge cycle kinetics in mouse ventricular muscle. Circ Res 2001;88:1059–65.
34. Zhang R, Zhao J, Mandveno A, Potter JD. Cardiac troponin I phosphorylation increases the rate of cardiac muscle relaxation. Circ Res 1995;76:1028–35.
35. Takimoto E, Soergel DG, Janssen PM, Stull LB, Kass DA, Murphy AM. Frequency-and afterload-dependent cardiac modulation in vivo by troponin I with constitutively active protein kinase A phosphorylation sites. Circ Res 2004;94:496–504.
36. Sanada S, Kitakaze M, Papst PJ, Asanuma H, Node K, Takashima S, et al. Cardioprotective effect afforded by transient exposure to phosphodiesterase III inhibitors: the role of protein kinase A and p38 mitogen-activated protein kinase. Circulation 2001;104:705–10.
37. Zhang F, Hu Y, Huang P, Toleman CA, Paterson AJ, Kudlow JE. Proteasome function is regulated by cyclic AMP-dependent protein kinase through phosphorylation of Rpt6. J Biol Chem 2007;282:22460–71.
38. Zhao ZQ, Velez DA, Wang NP, Hewan-Lowe KO, Nakamu-

ra M, Guyton RA, et al. Progressively developed myocardial apoptotic cell death during late phase of reperfusion. Apoptosis 2001;6:279–90.
39. Saraste A, Pulkki K, Kallajoki M, Heikkilä P, Laine P, Mattila S, et al. Cardiomyocyte apoptosis and progression of heart failure to transplantation. Eur J Clin Invest 1999;29:380-6.
40. Makaula S, Lochner A, Genade S, Sack MN, Awan MM, Opie LH. H-89, a non-specific inhibitor of protein kinase A, promotes post-ischemic cardiac contractile recovery and reduces infarct size. J Cardiovasc Pharmacol 2005;45:341–7.
41. Hudmon A, Schulman H. Structure–function of the multifunctional Ca2+/calmodulin-dependent protein kinase II. Biochem J 2002;364:593–611.
42. Tombes RM, Faison MO, Turbeville JM. Organization and evolution of multifunctional Ca2+/CaM-dependent protein kinase genes. Gene 2003;322:17–31.
43. De Koninck P, Schulman H. Sensitivity of CaM kinase II to the frequency of Ca2+ oscillations. Science 1998;279:227–30.
44. Meyer T, Hanson PI, Stryer L, Schulman H. Calmodulin trapping by calcium-calmodulin-dependent protein kinase. Science 1992;256:1199–202.
45. Soderling TR. The Ca2+–calmodulin-dependent protein kinase cascade. Trends Biochem Sci 1999;24:232–6.
46. Netticadam T, Temsah R, Osada M, Dhalla NS. Status of Ca2+/calmodulin protein kinase phosphorylation of cardiac SR proteins in ischemia-reperfusion. Am J Physiol Cell Physiol 1999;277:C384-91.
47. Koval OM, Guan X, Wu Y, Joiner ML, Gao Z, Chen B, et al. CaV1.2 β-subunit coordinates CaMKII-triggered cardiomyocyte death and afterdepolarizations. Proc Natl Acad Sci 2010;107:4996–5000.
48. Swaminathan PD, Purohit A, Soni S, Voigt N, Singh MV, Glukhov AV, et al. Oxidized CaMKII causes cardiac sinus node dysfunction in mice. J Clin Invest 2011;121:3277–88.
49. Kolodziej SJ, Hudmon A, Waxham MN, Stoops JK. Three-dimensional reconstructions of calcium/calmodulin-dependent (CaM) kinase IIα and truncated CaM kinase IIα reveal a unique organization for its structural core and functional domains. J Biol Chem 2000;275:14354–9.
50. Salas MA, Valverde CA, Sánchez G, Said M, Rodriguez JS, Portiansky EL, et al. The signalling pathway of CaMKII-mediated apoptosis and necrosis in the ischemia/reperfusion injury. J Mol Cell Cardiol 2010;48:1298–306.
51. Xie L-H, Chen F, Karagueuzian HS, Weiss JN. Oxidative stress–induced afterdepolarizations and calmodulin kinase II signaling. Circ Res 2009;104:79–86.
52. Maier LS, Bers DM. Role of Ca2+/calmodulin-dependent protein kinase (CaMK) in excitation–contraction coupling in the heart. Cardiovasc Res 2007;73:631–40.
53. Wagner S, Dybkova N, Rasenack EC, Jacobshagen C, Fabritz L, Kirchhof P, et al. Ca2+/calmodulin-dependent protein kinase II regulates cardiac Na+ channels. J Clin Invest 2006;116:3127–38.
54. Wu Y, Roden DM, Anderson ME. Calmodulin kinase inhibition prevents development of the arrhythmogenic transient inward current. Circ Res 1999;84:906–12.
55. Wu Y, Temple J, Zhang R, Dzhura I, Zhang W, Trimble R, et al. Calmodulin kinase II and arrhythmias in a mouse model of cardiac hypertrophy. Circulation 2002;106:1288–93.
56. Zhang R, Khoo MS, Wu Y, Yang Y, Grueter CE, Ni G, et al. Calmodulin kinase II inhibition protects against structural heart disease. Nat Med 2005;11:409–17.
57. Chelu MG, Sarma S, Sood S, Wang S, van Oort RJ, Skapura DG, et al. Calmodulin kinase II–mediated sarcoplasmic reticulum Ca 2+ leak promotes atrial fibrillation in mice. J Clin Invest 2009;119:1940–51.
58. van Oort RJ, McCauley MD, Dixit SS, Pereira L, Yang Y, Respress JL, et al. Ryanodine receptor phosphorylation by calcium/calmodulin-dependent protein kinase II promotes life-threatening ventricular arrhythmias in mice with heart failure. Circulation 2010;122:2669-79.
59. Zhu W, Zou Y, Shiojima I, Kudoh S, Aikawa R, Hayashi D, et al. Ca2+/calmodulin-dependent kinase II and calcineurin play critical roles in endothelin-1-induced cardiomyocyte hypertrophy. J Biol Chem 2000;275:15239–45.
60. Backs J, Backs T, Neef S, Kreusser MM, Lehmann LH, Patrick DM, et al. The δ isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. Proc Natl Acad Sci 2009;106:2342–7.
61. Ling H, Zhang T, Pereira L, Means CK, Cheng H, Gu Y, et al. Requirement for Ca 2+/calmodulin–dependent kinase II in the transition from pressure overload–induced cardiac hypertrophy to heart failure in mice. J Clin Invest 2009;119:1230–40.
62. Hagemann D, Bohlender J, Hoch B, Krause EG, Karczewski P. Expression of Ca2+/calmodulin-dependent protein kinase II δ-subunit isoforms in rats with hypertensive cardiac hypertrophy. Mol Cell Biochem 2009;220:69–76.
63. Colomer JM, Mao L, Rockman HA, Means AR. Pressure overload selectively upregulates Ca2+/calmodulin-dependent protein kinase II in vivo. Mol Endocrinol 2003;17:183–92.
64. Peng W, Zhang Y, Zheng M, Cheng H, Zhu W, Cao CM, et al. Cardioprotection by CaMKII-δB is mediated by phosphorylation of heat shock factor 1 and subsequent expression of inducible heat shock protein 70. Circ Res 2010;106:102–10.
65. Zhu W, Woo AY, Yang D, Cheng H, Crow MT, Xiao RP. Activation of CaMKIIδC is a common intermediate of diverse death stimuli-induced heart muscle cell apoptosis. J Biol Chem 2007;282:10833–9.
66. Erickson JR, He BJ, Grumbach IM, Anderson ME. CaMKII in the cardiovascular system: sensing redox states. Physiol Rev 2011: 91;889–915.
67. Mollova MY, Katus HA, Backs J. Regulation of CaMKII signaling in cardiovascular disease. Front Pharmacol 2015; 6:178. doi: 10.3389/fphar.2015.00178.
68. Maier LS, Zhang T, Chen L, DeSantiago J, Brown JH, Bers DM. Transgenic CaMKIIδC overexpression uniquely alters cardiac myocyte Ca2+ handling: reduced SR Ca2+ load and activated SR Ca2+ release. Circ Res 2003;92:904–11.
69. Kohlhaas M, Zhang T, Seidler T, Zibrova D, Dybkova N, Steen A, et al. Increased sarcoplasmic reticulum calcium leak but unaltered contractility by acute CaMKII overexpression in isolated rabbit cardiac myocytes. Circ Res 2006;98:235–44.
70. Sag CM, Wadsack DP, Khabbazzadeh S, Abesser M, Grefe C, Neumann K, et al. Calcium/calmodulin-dependent protein kinase II contributes to cardiac arrhythmogenesis in heart failure. Circ Heart Fail 2009;2:664–75.
71. Kashiwase K, Higuchi Y, Hirotani S, Yamaguchi O, Hikoso S, Takeda T, et al. CaMKII activates ASK1 and NF-κB to induce cardiomyocyte hypertrophy. Biochem Biophys Res Commun 2005:27:136–42.
72. Takeda K, Matsuzawa A, Nishitoh H, Tobiume K, Kishida S, Ninomiya-Tsuji J, et al. Involvement of ASK1 in Ca2+-induced p38 MAP kinase activation. EMBO Rep 2004;5:161–6.
73. Passier R, Zeng H, Frey N, Naya FJ, Nicol RL, McKinsey TA, et al. CaM kinase signaling induces cardiac hypertrophy and activates the MEF2 transcription factor in vivo. J Clin Invest 2000;105:1395–406.
74. Zhang T, Johnson EN, Gu Y, Morissette MR, Sah VP, Gigena MS, et al. The cardiac-specific nuclear δB isoform of Ca2+/calmodulin-dependent protein kinase II induces

hypertrophy and dilated cardiomyopathy associated with increased protein phosphatase 2A activity. J Biol Chem 2002;277:1261–7.
75. Woischwill C, Karczewski P, Bartsch H, Luther HP, Kott M, Haase H, et al. Regulation of the human atrial myosin light chain 1 promoter by Ca2+-calmodulin-dependent signaling pathways. FASEB J 2005;19:503–11.
76. Osada M, Netticadan T, Kawabata K, Tamura K, Dhalla NS. Ischemic preconditioning prevents I/R-induced alterations in SR calcium-calmodulin protein kinase II. Am J Physiol Heart Circ Physiol 2000;278:H1791–8.
77. Benter IF, Juggi JS, Khan I, Yousif MH, Canatan H, Akhtar S. Signal transduction mechanisms involved in cardiac preconditioning: role of Ras-GTPase, Ca2+/calmodulin-dependent protein kinase II and epidermal growth factor receptor. Mol Cell Biochem 2005;268:175–83.
78. Netticadan T, Temsah RM, Kawabata K, Dhalla NS. Sarcoplasmic reticulum Ca2+/calmodulin-dependent protein kinase is altered in heart failure. Circ Res 2007; 86:596–605.
79. Mishra S, Sabbah HN, Jain JC, Gupta RC. Reduced Ca2. calmodulin-dependent protein kinase activity and expression in LV myocardium of dogs with heart failure. Am J Physiol Heart Circ Physiol 2003;284:H876-83.
80. MacDonnell SM, Weisser-Thomas J, Kubo H, Hanscome M, Liu Q, et al. CaMKII negatively regulates calcineurin–NFAT signaling in cardiac myocytes. Circ Res 2009;105:316–25.
81. Kreusser MM, Lehmann LH, Keranov S, Hoting MO, Oehl U, Kohlhaas M, et al. Cardiac CaM Kinase II genes δ and γ contribute to adverse remodeling but redundantly inhibit calcineurin-induced myocardial hypertrophy. Circulation 2014;130:1262–73.
82. Newton AC. Protein kinase C: structure, function, and regulation. J Biol Chem 1995;270:28495–8.
83. Hambleton M, Hahn H, Pleger ST, Kuhn MC, Klevitsky R, Carr AN, et al. Pharmacological and gene theraphy-based inhibition of protein kinase C alpha/beta enhances contractility an attentuates heart failure. Circulation 2006;114:574-82.
84. Newton AC. Regulation of protein kinase C. Curr Opin Cell Biol 1997;9:161–7.
85. Nishizuka Y. Protein kinase C and lipid signaling for sustained cellular responses. FASEB J 1995;9:484–96.
86. Kraft AS, Anderson WB. Phorbol esters increase the amount of Ca2+, phospholipid-dependent protein kinase associated with plasma membrane. Nature 1983;301:621–3.
87. Toker A, Newton AC. Cellular signaling: pivoting around PDK-1. Cell 2000;103:185–8.
88. Gu X, Bishop SP. Increased protein kinase C and isozyme redistribution in pressure-overload cardiac hypertrophy in the rat. Circ Res 1994;75:926–31.
89. Braun MU, LaRosée P, Simonis G, Borst MM, Strasser RH. Regulation of protein kinase C isozymes in volume overload cardiac hypertrophy. Mol Cell Biochem 2004;262:135–43.
90. Paul K, Ball NA, Dorn GW, Walsh RA. Left ventricular stretch stimulates angiotensin II–mediated phosphatidylinositol hydrolysis and protein kinase C ε isoform translocation in adult guinea pig hearts. Circ Res 1997;81:643–50.
91. Wang J, Liu X, Sentex E, Takeda N, Dhalla NS. Increased expression of protein kinase C isoforms in heart failure due to myocardial infarction. Am J Physiol Heart Circ Physiol 2003;284:H2277–87.
92. Bayer AL, Heidkamp MC, Patel N, Porter M, Engman S, Samarel AM. Alterations in protein kinase C isoenzyme expression and autophosphorylation during the progression of pressure overload-induced left ventricular hypertrophy. Mol Cell Biochem 2003;242:145-52.
93. Landau D, Chayat C, Zucker N, Golomb E, Yagil C, Yagil Y, et al. Early blood pressure-independent cardiac changes in diabetic rats. J Endocrinol 2008;197:75–84.
94. Wang M, Zhang WB, Zhu JH, Fu GS, Zhou BQ. Breviscapine ameliorates cardiac dysfunction and regulates the myocardial Ca2+-cycling proteins in streptozotocin-induced diabetic rats. Acta Diabetol 2010;47:209–18.
95. Beckman JA, Goldfine AB, Gordon MB, Garrett LA, Creager MA. Inhibition of protein kinase Cβ prevents impaired endothelium-dependent vasodilation caused by hyperglycemia in humans. Circ Res 2002;90:107–11.
96. Bowling N, Walsh RA, Song G, Estridge T, Sandusky GE, Fouts RL, et al. Increased protein kinase C activity and expression of Ca2+-sensitive isoforms in the failing human heart. Circulation 1999;99:384–91.
97. Braz JC, Gregory K, Pathak A, Zhao W, Sahin B, Klevitsky R, et al. PKC-α regulates cardiac contractility and propensity toward heart failure. Nat Med 2004;10:248–54.
98. Liu Q, Chen X, Macdonnell SM, Kranias EG, Lorenz JN, Leitges M, et al. Protein kinase Cα, but not PKCβ or PKCγ, regulates contractility and heart failure susceptibility: implications for rubox-istaurin as a novel therapeutic approach. Circ Res 2009;105:194–200.
99. Connelly KA, Kelly DJ, Zhang Y, Prior DL, Advani A, Cox AJ, et al. Inhibition of protein kinase C–β by ruboxistaurin preserves cardiac function and reduces extracellular matrix production in diabetic cardiomyopathy. Circ Heart Fail 2009;2:129–37.
100. Boyle AJ, Kelly DJ, Zhang Y, Cox AJ, Gow RM, Way K, et al. Inhibition of protein kinase C reduces left ventricular fibrosis and dysfunction following myocardial infarction. J Mol Cell Cardiol 2005;39:213–21.
101. Schmidt K, Tissier R, Ghaleb B, Drogies T, Felix SB, Krieg T. Cardioprotective effects of mineralocorticoid receptor antagonists at reperfusion. Eur Heart J 2010;31:1655–62.
102. Chai W, Garrelds IM, de Vries R, Batenburg WW, van Kats JP, Danser AH. Nongenomic effects of aldosterone in the human heart: interaction with angiotensin II. Hypertension 2005;46:701–6.
103. Young LH, Balin BJ, Weis MT. Gö 6983: a fast acting protein kinase C inhibitor that attenuates myocardial ischemia/reperfusion injury. Cardiovasc Drug Rev 2005;23:255–72.
104. Peterman EE, Taormina P. Harvey M, Young LH. Gö 6983 exerts cardioprotective effects in myocardial ischemia/reperfusion. J Cardiovasc Pharmacol 2004;43:645–56.
105. Omiyi D, Brue RJ, Taormina P 2nd, Harvey M, Atkinson N, Young LH. Protein kinase C βII peptide inhibitor exerts cardioprotective effects in rat cardiac ischemia/reperfusion injury. J Pharmacol Exp Ther 2005;314:542–51.
106. Phillipson A, Peterman EE, Taormina P Jr, Harvey M, Brue RJ, Atkinson N, et al. Protein kinase C-ζ inhibition exerts cardioprotective effects in ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 2005;289:H898–907.
107. Hahn HS, Yussman MG, Toyokawa T, Marreez Y, Barrett TJ, Hilty KC, et al. Ischemic protection and myofibrillar cardiomyopathy: dosedependent effects of in vivo δPKC inhibition. Circ Res 2002;91:741–8.
108. Inagaki K, Hahn HS, Dorn GW, Mochly-Rosen D. Additive protection of the ischemic heart *ex vivo* by combined treatment with δ-protein kinase C inhibitor and ε-protein kinase C activator. Circulation 2003;108:869–75.
109. Fantinelli JC, Mosca SM.Comparative effects of ischemic pre and postconditioning on ischemia-reperfusion injury in spontaneously hypertensive rats (SHR). Mol Cell Biochem 2007;296:45–51.
110. Arbeláez LFG, Pardo AC, Fantinelli JC, Mosca SM. Cyclosporine-A mimicked the ischemic preand postconditioning-mediated cardioprotection in hypertensive rats: Role of PKCε. Exp Mol Pathol 2016;100:266–75.
111. Penna C, Alloatti G, Crisafulli A. Mechanisms involved in cardioprotection induced by physical exercise. Antioxid Redox Signal 2020; 32:1115-34.
112. Borges JP, da Silva Verdoorn K. Cardiac ischemia/reper-

fusion injury: the beneficial effects of exercise. In: Exercise for Cardiovascular Disease Prevention and Treatment. Berlin: Springer, 2017; pp 155–179.
113. Diaz RJ, Wilson GJ. Selective blockade of AT1angiotensin II receptors abolishes ischemic preconditioning in isolated rabbit hearts. J Mol Cell Cardiol 1997;29:129-39.
114. Takeishi Y, Ping P, Bolli R, Kirkpatrick DL, Hoit BD, Walsh RA. Transgenic overexpression of constitutively active protein kinase C ε causes concentric cardiac hypertrophy. Circ Res 2000;86:1218–23.
115. Newton AC, Antal CE, Steinberg SF. Protein kinase C mechanisms that contribute to cardiac remodelling. Clin Sci 2016;130:1499–510.
116. Ping P, Takano H, Zhang J, Tang XL, Qiu Y, Li RC, et al. Isoform-selective activation of protein kinase C by nitric oxide in the heart of conscious rabbits: a signaling mechanism for both nitric oxide–induced and ischemiainduced preconditioning. Circ Res 1999;84:587–604.
117. Qiu Y, Ping P, Tang XL, Manchikalapudi S, Rizvi A, Zhang J, et al. Direct evidence that protein kinase C plays an essential role in the development of late preconditioning against myocardial stunning in conscious rabbits and that epsilon is the isoform involved. J Clin Invest 1998;101:2182–98.
118. Teng JC, Kay H, Chen Q, Adams JS, Grilli C, Guglielmello G, et al. Mechanisms related to the cardioprotective effects of protein kinase C epsilon (PKC ε) peptide activator or inhibitor in rat ischemia/reperfusion injury. Naunyn Schmiedebergs Arch Pharmacol 2008;378:1–15.
119. Wang G-Y, Zhou JJ, Shan J, Wong T-M. Protein kinase C-ε is a trigger of delayed cardioprotection against myocardial ischemia of κ-opioid receptor stimulation in rat ventricular myocytes. J Pharmacol Exp Ther 2001;299:603–10.
120. Wu S, Li HY, Wong TM. Cardioprotection of preconditioning by metabolic inhibition in the rat ventricular myocyte: involvement of κ-opioid receptor. Circ Res 1999;84:1388–95.
121. Otani H. Reactive oxygen species as mediators of signal transduction in ischemic preconditioning. Antioxid Redox Signal 2004;6:449-69.
122. Uchiyama Y, Otani H, Wakeno M, Okada T, Uchiyama T, Sumida T, et al. Role of mitochondrial KATP channels and protein kinase C in ischaemic preconditioning. Clin Exp Pharmacol Physiol 2003;30:426-36.
123. Bolli R, Dawn B, Tang XL, Qiu Y, Ping P, Xuan YT, et al. The nitric oxide hypothesis of late pre-conditioning. Basic Res Cardiol 1998;93:325-38.
124. Nakano A, Liu GS, Heusch G, Downey JM, Cohen MV. Exogenous nitric oxide can trigger a pre-conditioned state through a free radical mechanism, but endogenous nitric oxide is not a trigger of classical ischemic preconditioning. J Mol Cell Cardiol 2000;32:1159-67.
125. Tappia PS, Shah AK, Ramjiawan B, Dhalla NS. Modification of ischemia/reperfusion-induced alterations in subcellular organelles by ischemic preconditioning. Int J Mol Sci 2022;23:3425. doi: 10.3390/ijms23073425.
126. Hao Z, Pan SS, Shen YJ, Ge J. Exercise preconditioninginduced early and late phase of cardioprotection is associated with protein kinase C epsilon translocation. Circ J 2014;78:1636-45.
127. Malhotra A, Kang BPS, Hashmi S, Meggs LG. PKCε inhibits the hyperglycemia-induced apoptosis signal in adult rat ventricular myocytes. Mol Cell Biochem 2005;268:169-73.
128. Shizukuda Y, Reyland ME, Buttrick PM. Protein kinase C-δ modulates apoptosis induced by hyperglycemia in adult ventricular myocytes. Am J Physiol Heart Circ Physiol 2002;282:H1625–34.
129. Malhotra A, Begley R, Kang BP, Rana I, Liu J, Yang G, et al. PKC-ε-dependent survival signals in diabetic hearts. Am J Physiol Heart Circ Physiol 2005;289:H1343–50.
130. House SL, Melhorn SJ, Newman G, Doetschman T, Schultz Jel J. The protein kinase C pathway mediates cardioprotection induced by cardiacspecific overexpression of fibroblast growth factor-2. Am J Physiol Heart Circ Physiol 2007;293:H354–65.
131. Liao S, Bodmer JR, Azhar M, Newman G, Coffin JD, Doetschman T, et al. The influence of FGF2 high molecular weight (HMW) isoforms in the development of cardiac ischemia–reperfusion injury. J Mol Cell Cardiol 2010;48:1245–54.
132. Das A, Ockaili R, Salloum F, Kukreja RC. Protein kinase C plays an essential role in sildenafil-induced cardioprotection in rabbits. Am J Physiol Heart Circ Physiol 2004;286:H1455–60.
133. Otsu M, Hiles I, Gout I, Fry MJ, Ruiz-Larrea F, Panayotou G, et al. Characterization of two 85 kd proteins that associate with receptor tyrosine kinases, middle-T/pp60c-src complexes, and PI3-kinase. Cell 1991;65:91–104.
134. Skolnik EY, Margolis B, Mohammadi M, Lowenstein E, Fischer R, Drepps A, et al. Cloning of PI3 kinase-associated p85 utilizing a novel method for expression/cloning of target proteins for receptor tyrosine kinases. Cell 1991;65:83–90.
135. Vanhaesebroeck B, Stephens L, Hawkins P. PI3K signalling: the path to discovery and understanding. Nat Rev Mol Cell Biol 2012;13:195–203.
136. Miled N, Yan Y, Hon WC, Perisic O, Zvelebil M, Inbar Y, et al. Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit. Science 2007;317:239–42.
137. Huang CH, Mandelker D, Schmidt-Kittler O, Samuels Y, Velculescu VE, Kinzler KW, et al. The structure of a human p110α/p85α complex elucidates the effects of oncogenic PI3Kα mutations. Science 2007;318:1744–8.
138. Walker EH, Pacold ME, Perisic O, Stephens L, Hawkins PT, Wymann MP, et al. Structural determinants of phosphoinositide 3-kinase inhibition by wortmannin, LY294002, quercetin, myricetin, and staurosporine. Mol Cell 2000;6:909–19.
139. Patrucco E, Notte A, Barberis L, Selvetella G, Maffei A, Brancaccio M, et al. PI3Kγ modulates the cardiac response to chronic pressure overload by distinct kinase-dependent andindependent effects. Cell 2004;118:375–87.
140. Hua R, Adamczyk A, Robbins C, Ray G, Rose RA. Distinct patterns of constitutive phosphodiesterase activity in mouse sinoatrial node and atrial myocardium. PLoS One 2012:7:e 47652. doi: 10.1371/journal.pone.0047652.
141. Kolár F, Jezková J, Balková P, Breh J, Neckár J, Novák F, et al. Role of oxidative stress in PKC-δ upregulation and cardioprotection induced by chronic intermittent hypoxia. Am J Physiol Heart Circ Physiol 2007;92:H224–30.
142. Collier PN, Martinez-Botella G, Cornebise M, Cottrell KM, Doran JD, Griffith JP, et al. Structural basis for isoform selectivity in a class of benzothiazole inhibitors of phosphoinositide 3-kinase γ. J Med Chem 20015;58:517–21.
143. Durrant TN, Hers I. PI3K inhibitors in thrombosis and cardiovascular disease. Clin Transl Med 2020;9:1–21.
144. Perrino C, Naga Prasad SV, Patel M, Wolf MJ, Rockman HA. Targeted inhibition of β-adrenergic receptor kinase-1–associated phosphoinositide-3 kinase activity preserves β-adrenergic receptor signaling and prolongs survival in heart failure induced by calsequestrin overexpression. J Am Coll Cardiol 2005;45:1862–70.
145. Perrino C, Naga Prasad SV, Schroder JN, Hata JA, Milano C, Rockman HA. Restoration of β-adrenergic receptor signaling and contractile function in heart failure by disruption of the βARK1/phosphoinositide 3-kinase complex. Circulation 2005;111:2579–87.
146. Nienaber JJ, Tachibana H, Naga Prasad SV, Esposito G,

Wu D, Mao L, et al. Inhibition of receptor-localized PI3K preserves cardiac β-adrenergic receptor function and ameliorates pressure overload heart failure. J Clin Invest 2003;112:1067–79.
147. Awad AE, Kandalam V, Chakrabarti S, Wang X, Penninger JM, Davidge ST, et al. Tumor necrosis factor induces matrix metalloproteinases in cardiomyocytes and cardiofibroblasts differentially via superoxide production in a PI3Kγ-dependent manner. Am J Physiol Cell Physiol 2010;298:C679–92.
148. Perrino C, Naga Prasad SV, Mao L, Noma T, Yan Z, Kim HS, et al. Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. J Clin Invest 2006;116:1547–60.
149. Luo J, McMullen JR, Sobkiw CL, Zhang L, Dorfman AL, Sherwood MC, et al. Class IA phosphoinositide 3-kinase regulates heart size and physiological cardiac hypertrophy. Mol Cell Biol 2005;25:9491–502.
150. Shioi T, Kang PM, Douglas PS, Hampe J, Yballe CM, Lawitts J, Cantley LC, et al. The conserved phosphoinositide 3-kinase pathway determines heart size in mice. EMBO J 2000;19:2537–48.
151. Deschamps AM, Murphy E. Activation of a novel estrogen receptor, GPER, is cardioprotective in male and female rats. Am J Physiol Heart Circ Physiol 2009;297:H1806–13.
152. Bopassa JC, Eghbali M, Toro L, Stefani E. A novel estrogen receptor GPER inhibits mitochondria permeability transition pore opening and protects the heart against ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 2010;298:H16–H23.
153. Chaudhary KR, Batchu SN, Das D, Suresh MR, Falck JR, et al. Role of B-type natriuretic peptide in epoxyeicosatrienoic acidmediated improved postischaemic recovery of heart contractile function. Cardiovasc Res 2009;83:362–70.
154. Okumura H, Nagaya N, Itoh T, Okano I, Hino J, Mori K, et al. Adrenomedullin infusion attenuates myocardial ischemia/reperfusion injury through the phosphatidylinositol 3-kinase/Aktdependent pathway. Circulation 2004;109:242–8.
155. Yin H, Chao L, Chao J. Adrenomedullin protects against myocardial apoptosis after ischemia/reperfusion through activation of Akt-GSK signaling. Hypertension 2004;43:109–16.
156. Pretorius L, Du XJ, Woodcock EA, Kiriazis H, Lin RC, Marasco S, et al. Reduced phosphoinositide 3-kinase (p110α) activation increases the susceptibility to atrial fibrillation. Am J Pathol 2009;175:998–1009.
157. Lu Z, Jiang YP, Wang W, Xu XH, Mathias RT, Entcheva E, et al. Loss of cardiac phosphoinositide 3-kinase p110α results in contractile dysfunction Circulation 2009;120:318-25.
158. McMullen JR, Amirahmadi F, Woodcock EA, Schinke-Braun M, Bouwman RD, Hewitt KA, et al. Protective effects of exercise and phosphoinositide 3-kinase (p110α) signaling in dilated and hypertrophic cardiomyopathy. Proc Natl Acad Sci 2007;104:612–7.
159. Curcio A, Noma T, Naga Prasad SV, Wolf MJ, Lemaire A, Perrino C, et al. Competitive displacement of phosphoinositide 3-kinase from β-adrenergic receptor kinase-1 improves postinfarction adverse myocardial remodeling. Am J Physiol Heart Circ Physiol 2006; 291:H1754-60.
160. Schindler JF, Monahan JB, Smith WG. p38 pathway kinases as antiinflammatory drug targets. J Dent Res 2007;86:800–11.
161. Xu YJ, Saini HK, Zhang M, Elimban V, Dhalla NS. MAPK activation and apoptotic alterations in hearts subjected to calcium paradox are attenuated by taurine. Cardiovasc Res 72:163–74.
162. Wang Y, Huang S, Sah VP, Ross J Jr, Brown JH, Han J, et al. Cardiac muscle cell hypertrophy and apoptosis induced by distinct members of the p38 mitogen-activated protein kinase family. J Biol Chem 1998;273:2161–8.
163. See F, Thomas W, Way K, Tzanidis A, Kompa A, Lewis D, et al. p38 mitogen-activated protein kinase inhibition improves cardiac function and attenuates left ventricular remodeling following myocardial infarction in the rat. J Am Coll Cardiol 2004;44:1679-89.
164. Barancik M, Htun P, Strohm C, Kilian S, Schaper W. Inhibition of the cardiac p38-MAPK pathway by SB203580 delays ischemic cell death. J Cardiovasc Pharmacol 2000;35:474–83.
165. Nagarkatti DS, Ramadan IS. Role of p38 MAP kinase in myocardial stress. J Mol Cell Cardiol 1998;30:1651–64.
166. Martin JL, Avkiran M, Quinlan RA, Cohen P, Marber MS. Antiischemic effects of SB203580 are mediated through the inhibition of p38α mitogen-activated protein kinase: evidence from ectopic expression of an inhibition-resistant kinase. Circ Res 2001;89:750-2.
167. Otsu K, Yamashita N, Nishida K, Hirotani S, Yamaguchi O, Watanabe T, et al. Disruption of a single copy of the p38α MAP kinase gene leads to cardioprotection against ischemia–reperfusion. Biochem Biophys Res Commun 2003;302:56–60.
168. Fan L, Sawbridge D, George V, Teng L, Bailey A, Kitchen I, et al. Chronic cocaine-induced cardiac oxidative stress and mitogen-activated protein kinase activation: the role of Nox2 ocidase. J Pharmacol Exp Ther 2009;328:99-106.
169. Bao W, Behm DJ, Nerurkar SS, Ao Z, Bentley R, Mirabile RC, et al. Effects of p38 MAPK Inhibitor on angiotensin II-dependent hypertension, organ damage, and superoxide anion production. J Cardiovasc Pharmacol 2007;49:362–8.
170. Sato H, Tanaka T, Kasai K, Kita T, Tanaka N. Role of p38 mitogen-activated protein kinase on cardiac dysfunction after hemorrhagic shock in rats. Shock 2007;28:291–9.
171. Westermann D, Rutschow S, Van Linthout S, Linderer A, Bücker-Gärtner C, Sobirey M, et al. Inhibition of p38 mitogen-activated protein kinase attenuates left ventricular dysfunction by mediating proinflammatory cardiac cytokine levels in a mouse model of diabetes mellitus. Diabetologia 2006;49:2507–13.
172. Kyoi S, Otani H, Matsuhisa S, Akita Y, Tatsumi K, Enoki C, et al. Opposing effect of p38 MAP kinase and JNK inhibitors on the development of heart failure in the cardiomyopathic hamster. Cardiovasc Res 2006;69:888–98.
173. Li Z, Ma JY, Kerr I, Chakravarty S, Dugar S, Schreiner G, et al. Selective inhibition of p38α MAPK improves cardiac function and reduces myocardial apoptosis in rat model of myocardial injury. Am J Physiol Heart Circ Physiol 2006;291:H1972–7.
174. Malhotra A, Kang BP, Opawumi D, Belizaire W, Meggs LG. Molecular biology of protein kinase C signaling in cardiac myocytes. Mol Cell Biochem 2001;225:97–107.
175. Muslin AJ. MAPK signaling in cardiovascular health and disease: Molecular mechanisms and therapeutic targets. Clin Sci 2008;115:203-18.
176. Stefanovsky VY, Pellitier G, Hannan R, Gagonon Kugler T, Rothblum LI, Moss T. An immediate response of ribosomal transcription to growth factor stimulation is mediated by ERK phosphorylation of UBF. Mol Cell 2001;81:1063-73.
177. Heft MA, Harder BA, Eppenberger H. Schaub MC Signaling pathways in cardiac myocycte hypertrophy. J Mol Cell Cardiol 1997;29:2873-92.
178. Shao Q, Takeda N, Temsah R, Dhalla KS, Dhalla NS. Prevention of hemodynamic changes due to myocardial infarction by early treatment with imidapril. Cardioasc Pathol 1996;1:180-6.
179. Weinberg EO, Schoen FJ, George D, Kagaya Y, Douglas

PS, Litwin SE, et al. Angiotensin converting enzyme inhibitors prolong survival and modifies the transition to heart failure in rats with pressure overload hypertrophy due to ascending aortic stenosis. Circulation 1994;90:1410-22.
180. Haq S, Choukroun G, Lim H, Tymitz KM, del Monte F, Gwathmey J, et al. Differential activation of signal transduction pathways in human hearts with hypertrophy versus advanced heart failure. Circulation 2001;103:670-7.
181. Yano M, Kim S, Izumi Y Yamanaka S, Iwao H. Differential activation of cardiac c-jun amino-terminal kinase and extracellular signal-regulated kinase in angiotensin II-mediated hypertension. Circ Res 1998;83:752-60.
182. Yoshida K, Yoshiyama M, Omura T, Nakamura Y, Kim S, Takeuchi K, et al. Activation of mitogen-activated protein kinases in the nonishemic myocardium of an acute myocardial infarction in rats. Jpn Circ J 2001;65:808-14.
183. Knight R, Buxton D. Stimulation of c-jun kinase and mitogen-activated protein kinase by ishemia and reperfusion in the perfused rat heart. Biochem Biophys Res Commun 1996;218:83-8.
184. Behrends M, Schulz R, Post H, Alexandrov A, Belosjorow S, Michel MC, et al. Inconsistent relation of MAPK activation to infarct size reduction by ischemic preconditioning in pigs. Am J Physiol Heart Circ Physiol 2000;279:H1111-9.
185. Bogoyevitch MA, Gillespie-Brown J, Ketterman AJ, Fuller SJ, Ben-Levy R, Ashworth A, et al. Stimulation of the stress-activated mitogen-activated protein kinase subfamilies in perfused heart. p38/RK mitogen-activated protein kinases and c-jun N-terminal kinases are activated by ischemia/reperfusion. Circ Res 1996;79:162-73.
186. Yue TL, Wang C, Gu JL, Ma XL, Kumar S, Lee JC, et al. Inhibition of extracellular signal-regulated kinase enhances ischemia/reoxygenation-induced apoptosis in cultural cardiac myocyctes and exaggerates reperfusion injury in isolated perfused heart. Circ Res 2000;86:692-9.
187. Bueno OF, De Windt LJ, Tymitz KM, Witt SA, Kimball TR, Klevitsky R, et al. The MEKI-ERK½ signaling pathway promotes compensated cardiac hypertrophy in transgenic mice. EMBO J 2000;19:6341-50.
188. Xia, Z, Dickens M. Raingeaud J, Davis RJ, Greenberg ME, Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis. Science 1995;270:1326-31.
189. Horiuchi M, Akishita M, Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. Hypertension 1999;33:613-21.