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

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Abstract

Various protein kinases including protein kinase A (PKA), Ca2+-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 Ca2+-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; Ca2+-calmodulin kinase; Phosphoinositide 3-kinase; MAP kinase; Extracellular regulated protein kinase; p38-MAP kinase; Cardiac hypertrophy; Arrhythmias; Cardiac function.

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
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.12,13 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), Ca²⁺-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 metabolism15-17 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

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

PPARα, 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;
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 hydrolyze 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. Upon binding of cyclic AMP to regulatory subunits, dissociation and release of active regulatory monomers occur for the transduction of signal. There are four types of PKA – RIα, PKA-IIα, PKA-IIβ and PKA-Iβ, which are expressed in cardiomyocytes. 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 contractility. Several studies addressing the interaction of PKA with sarcoplasmic reticulum (SR), at phospholamban (PLB) and ryanodine receptor 2 (RyR2, 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. 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. PKA was also shown to phosphorylate and stimulate the activity of RyR2 to release Ca^{2+} from the SR Ca^{2+}-stores. PKA-dependent SR phosphorylation following β-AR stimulation has also been observed to produce an increase in the leakage of SR Ca^{2+}. 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. Moreover, stimulation of cardiomyocytes by β-AR is associated with phosphorylation of both myosin C protein and troponin I (cTnI) by PKA in thick myofilaments and thin myofilaments, respectively. It has also been reported that cTnI 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.
facilitated by PKA phosphorylation, this assembly of proteasome is also blocked upon PKA inhibition. It is noteworthy that PKA inhibition has been reported to play a role in decreasing apoptosis in cardiomyocytes. Furthermore, PKA inhibition was shown to exert cardioprotective effect during ischaemic injury and promote growth hormone induced cardioprotection during ischaemia reperfusion as well. 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. CaMK exists in four isoforms which are encoded by highly related genes α, β, γ and δ. 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. 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. 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. 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 myocardiun, which is associated with the development of hypertrophic and apoptotic cardiomyopathy. 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. 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. 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. 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 and this effect of CaMKII was also demonstrated to play a role in arrhythmias in a mouse model of heart failure. 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.
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 Ca2+-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 in the heart.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 coworkers89 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 PKC 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 Ca2+-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.87,99 Additionally, Boyle

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 Ca2+-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 Ca2+ and diacylglycerol (DAG) to express their activities and have α, βI, βII and γ isoforms. The novel ones are activated by DAG, independent of Ca2+ and exhibit δ, ε, η and θ isoforms. Atypical ones respond to phosphoinositide-dependent kinase-1, independent of Ca2+ 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 Ca2+-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 coworkers89 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 PKC 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 Ca2+-cycling proteins.83,94-97

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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 function114, 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, 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
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 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 epoxycosatrienoic 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. Additionally, contractile defects have been reported in cardiac myocytes lacking PI3K subunit p110α. 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. 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. 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 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 Ca²⁺ status (Ca²⁺ depletion and Ca²⁺ repletion) occur. 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. Nonetheless, inhibition of p38-MAPK has been reported to be cardioprotective against ischaemic damage. Otsu and co-workers 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. It was reported that rats treated with selective p38-MAPK inhibitors showed a decrease in angiotensin II-induced ROS production, hypertension and cardiac hypertrophy. 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. Li et al 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. Although most of the regulatory actions of JNK are similar to those of p38-MAPK, the effects of JNK and p38 inhibitors on cardiac dysfunction in hamsters are opposite to each other. 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 ERK1 and ERK2 belong to MAPK family of serine-threonine specific protein kinases. 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. 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. 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. Activation of ERK1/2 upon the induction of pressure overload has been reported to promote cardiomyocyte survival. 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. It should be also pointed out that prolonged activation of ERK1/2 has been demonstrated to result in the development of heart failure 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. It should be noted that both p38-MAPK and JNK are activated by the ischaemic insult whereas the effects of ischaemia-reperfusion on ERK1/2 activities are controversial. In fact, inhibition of ERK1/2 has been reported to enhance ischaemia-reperfusion injury as well as apoptosis. Furthermore, ERK1/2 signal transduction pathway has been reported to
induce compensated cardiac hypertrophy. Not only the effects of ERK1/2 activation on apoptosis are opposing to those p38K-JNK, ERK1/2 signal transduction pathways have been reported to play an antiapoptotic role in the cell survival. 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.

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Conflict of interest

None.
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