The cardiovascular system is a highly complex, well organised system in which signal transduction plays critical physiological and pathophysiological roles. The cellular elements of the heart and vascular wall are equipped with an array of specific receptors and with complex intracellular machinery that facilitates and drives appropriate responses to extracellular stimuli. Understanding the mechanisms through which extracellular stimuli modify the functions of cells in the heart and vascular wall gives valuable insights into how perturbations of signalling systems can cause pathological situations. This knowledge will allow the identification of novel molecular targets for pharmacological intervention and will assist the future development of therapeutic strategies for managing cardiovascular disorders. This brief review will give a general overview of some major intracellular signalling systems operative in cells comprising the heart and vasculature, with particular emphasis on the pleiotropic roles of protein kinases as regulators of cell behaviour.

**SENSING THE SIGNAL: THE ROLE OF G PROTEIN COUPLED RECEPTORS**

Cells must be able to monitor and respond appropriately to changes in their extracellular environment, a process that is often termed “stimulus-response coupling”. Signal transduction (cell signalling) systems allow cells to detect changes in their extracellular milieu and to mount appropriate responses. Although numerous types of receptor systems have evolved to detect extracellular stimuli, the family of receptors that transmit signals through the activation of heterotrimeric GTP binding proteins (G proteins) are important in many different tissues and play prominent roles in cells and tissues of the cardiovascular system. These proteins represent the largest group of cell surface receptors encoded by the mammalian genome (> 1% of human genes), and in the cardiovascular system G protein coupled receptors (GPCRs) are implicated in more or less every regulatory event. Thus, signalling through GPCRs regulates the degree of peripheral arterial resistance, aspects of renal function, the rate and force of myocardial contraction, and cardiac hypertrophy.1 GPCRs involved in normal cardiovascular function include those that respond to angiotensin II (AT₁ receptors), to endothelin-1 (ET₁B receptors), and to epinephrine and norepinephrine (α and β adrenergic receptors). These receptors are expressed on cardiac myocytes, vascular smooth muscle cells (VSMC) and endothelial cells, and signalling through them orchestrates the normal physiological control of vascular tone, heart rate, and contractility. Moreover, since angiotensin II, endothelin-1, and adrenergic agonists promote the growth of cardiomyocytes, stimulate vascular smooth muscle cell (VSMC) proliferation, and modify endothelial cell function, signalling through their receptors can also contribute to the pathological changes exemplified by excessive cardiac hypertrophy, atherosclerosis, and hypertension.

GPCR agonists promote the interaction of their respective receptors with a G protein heterotrimer comprising α, β, and γ subunits (fig1).2 This interaction subsequently promotes exchange of GTP for GDP on the Gα subunit, causes subunit dissociation, and thereby drives the activation or inhibition of one or more effector molecules by the free Gα or Gβγ subunits. These effector molecules, which include enzymes (for example, adenylate cyclases; phospholipases) and ion channels, regulate the generation of second messenger molecules which act through multiple mechanisms to trigger changes in cell function. Therefore, the most important function for second messengers is to regulate the degree of phosphorylation of intracellular proteins, and this is now recognised as the most general regulatory process adopted by eukaryotic cells.3 Protein phosphorylation is a dynamic equilibrium and second messengers can alter the equilibrium by promoting phosphorylation of protein substrates by activating protein kinases, or by reversing this process through protein phosphatases (fig 2). Disease can result from dysregulation of the kinase(s) that trigger the critical phosphorylation events associated with activation of the system or with those that terminate the signal.2
SENSING THE SIGNAL: THE ROLE OF PROTEIN PHOSPHORYLATION

Regulation of the phosphorylation of proteins is a central component of all signal transduction pathways in cells of the cardiovascular system, making these molecules attractive targets for pharmacological intervention. The realization that around 3% of the human genome encodes for kinases and phosphatases, and the growing evidence that mutations and dysregulation of protein kinases play causal roles in human disease further endorses the essential regulatory roles of these cell signalling elements. A highly important feature of protein phosphorylation is its reversible control; protein substrates are phosphorylated by kinases and dephosphorylated by phosphatases (fig 2). Thus, changing kinase activity, phosphatase activity, or both can regulate the extent of phosphorylation of a substrate. The reversible phosphorylation events that are triggered by a ligand binding to its receptor modify protein function, and thus cell behaviour, in numerous ways. For example, such signals can alter the biological activity of a protein by changing its conformation, can disrupt or enhance its interaction with other regulatory molecules, or can change its cellular location.

Protein kinases actually mediate most of the signal transduction in eukaryotic cells. Furthermore, the substrates of protein kinases are often cell specific, which helps to explain why there are distinct effects of different signals in different tissues. These enzymes use adenosine triphosphate (ATP) to donate a phosphate group to particular amino acid residues within their target substrates. Targeting kinases (and phosphatases) to cellular locations close to their substrates also ensures very tight regulation of phosphorylation event. Broadly speaking, kinases can be conveniently

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Figure 1  Basic components of a G protein coupled receptors (GPCR) signalling system. The basic components of a GPCR signalling system are the receptor, a G protein, and an effector molecule. The type of G protein employed, the subunits involved, and the effectors recruited are dependent upon the agonist and the cell type. For example, the AT1 receptor is the principal GPCR through which angiotensin II modifies cardiovascular cell function. In this system, angiotensin II binding to the AT1 receptor activates a G protein known as Goq, which subsequently stimulates activity of the effector molecule phospholipase C (PLC). This enzyme hydrolyses a membrane phospholipid (phosphatidylinositol 4,5-bisphosphate) to generate inositol (1,4,5)-trisphosphate (IP3) and diacylglycerol (DAG). These molecules (termed “second messengers”) respectively raise the intracellular concentration of calcium, and activate protein kinase C. This signalling system is also triggered by activation of the endothelin receptor (ET1B), or by binding of adrenaline (epinephrine) to the β1-adrenoreceptor. In contrast, stimulation of β-adrenergic receptors in the heart or vasculature causes Gs to activate the effector molecule adenylate cyclase, leading to an elevation of the intracellular cyclic AMP concentration and to the consequent activation of cAMP dependent protein kinase (PKA). Termination (down regulation) of GPCR mediated signalling events involves a family of G protein coupled receptor kinases (GRKs). These enzymes phosphorylate activated receptors, promoting their uncoupling from G proteins and initiating their subsequent internalisation.

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divided into three categories based upon the specific amino acid residues that they phosphorylate.

**SERINE/THERONINE KINASES**

Serine/threonine kinases, as their name suggests, phosphorylate either serine or threonine residues within their target proteins. Many members of this subgroup are components of signalling pathways that are essential for normal functioning of the cardiovascular system (fig 3). Protein kinase A (PKA), for example, so called because it is a cyclic AMP (adenosine monophosphate) dependent kinase, plays critical roles in mediating the effects of adrenergic stimulation on the heart and vasculature.8 Similarly, cGMP (guanosine monophosphate) dependent protein kinase (PKG) is a central component of the pathway through which nitric oxide, an endothelial derived vasodilator molecule, decreases vascular tone.9 Protein kinase C is another serine/threonine kinase that is currently receiving a great deal of attention in the cardiovascular field. The protein kinase C (PKC) family comprises 10 isoforms that are divided into three groups based upon their different activation requirements. Members of the conventional PKC family (α, βI, βII, and γ) are calcium dependent and are activated by diacylglycerol (DAG) and phorbol esters. In contrast, enzymes in the so called novel PKC family (δ, ε, η, and θ) are calcium independent, and members of the atypical family (ζ and λ) are not activated by either calcium or DAG.10 Activation of PKCs is important in ischaemic preconditioning of the myocardium, a phenomenon where brief exposure to ischaemia protects against a further ischaemic insult. In particular, PKCe activity is a critical mediator of preconditioning and may protect against myocardial cell death by phosphorylating proteins that regulate the expression of protective genes, or by phosphorylating, and thereby inhibiting, the activities of proteins that promote programmed cell death. In contrast, overexpression of active PKCe can promote pathological hypertrophy. Similarly, PKCβ may be involved in GPCR mediated signalling in normal hearts, but when present in excessive amounts can impair ventricular systolic and diastolic function.11–15

**TYROSINE KINASES**

Protein tyrosine kinases (PTKs) phosphorylate tyrosine residues within proteins. These molecules have been subdivided into two categories, receptor tyrosine kinases (RTKs), of which at least 13 families have been described, and non-receptor PTKs, of which at least nine families are currently defined.16 Growth factor receptors, such as those for epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ErbB-2 are members of the RTK family, and ligand binding in these instances promotes physiological cell growth and proliferation (for example, during wound healing) as well as supporting aberrant cell growth in cancers. These receptors use their intrinsic tyrosine kinase activity to recruit and activate other proteins and hence trigger downstream signalling events that have many similarities to those elicited by activation of GPCRs. Thus, following ligand binding, the RTKs autophosphorylate and the resulting phosphorylated tyrosine residues act as highly selective binding sites for SH2 (Src homology domain 2) containing proteins. Upon recruitment these proteins...
transduce signals through changes in their own enzymatic activity or by recruiting other proteins. Among the SH2 containing proteins are effector molecules (for example, phospholipase C\(_\gamma\)), whose activation leads to further downstream signalling through PKC and mitogen activated protein kinase (MAPK) cascades (see below).

Like GPCRs, RTKs play important roles in cells of the cardiovascular system and are principally involved in initiating signalling events that control cell growth, proliferation, and differentiation. Signalling through ErbB2 in cardiomyocytes, for example, promotes intracellular events that protect against the development of dilated cardiomyopathy. Importantly, patients receiving anti-ErbB2 antibodies as a cancer treatment develop cardiac dysfunction as a side effect, highlighting the critical role of these receptor kinases in regulating normal cardiomyocyte behaviour.17

Among the non-receptor PTKs are the Src, JAK (Janus kinase), and FAK (focal adhesion kinase) families. The Src family comprises eight mammalian members (Src, Yes, Fgr, Fyn, Lck, Lyn, Hck, and Blk) which contain SH2 domains adjacent to their catalytic domain. Since GPCRs do not possess intrinsic tyrosine kinase activity, these receptors trigger activation of many of these non-receptor tyrosine kinases to initiate their intracellular signalling programmes.

PROTEIN KINASE CASCADES: MIXED KINASE SIGNALS

The existence of protein kinase cascades, in which a chain of phosphorylation events occurs, was established 35 years ago with the discovery that PKA phosphorylates and activates phosphorylase kinase in response to elevated cAMP.18 Protein kinase cascades are extremely useful in signal transduction mechanisms as they allow for amplification, feedback, crosstalk, and branching. This, in turn, allows a limited number of enzymes to regulate very precisely a large number of cellular processes. In this respect, the most important group of serine/threonine kinases, upon which many other signals converge, and whose activities regulate numerous events in cells of the cardiovascular system, are the mitogen activated protein kinases.4

The basic assembly of an MAPK cascade comprises three sequential kinases: an MAPK, an MAPK kinase (MKK), and an MAPK kinase kinase (MKKK) (fig 4).19–21 MKKKs are activated either by phosphorylation via MAPK kinase kinase kinases (MKKKKs) or by interaction with small GTP binding proteins of the Ras or Rho families. MKKKs are serine/threonine kinases that phosphorylate and activate their downstream targets.

Figure 3  Pivotal roles for serine/threonine kinases in cells of the cardiovascular system. Serine/threonine kinases are central components of a number of important cell specific signalling pathways operative in, for example, cardiac myocytes and vascular smooth muscle cells. (A) Adrenergic stimulation of cardiomyocytes through \(\beta_1\) adrenoreceptors promotes \(G\)\(_s\) mediated activation of adenylate cyclase, generation of the second messenger cAMP, and activation of cAMP dependent protein kinase (protein kinase A). Once activated, protein kinase A phosphorylates numerous endogenous substrates (many of them ion channels) which facilitate the rate of depolarisation, elevation of intracellular calcium, and the cytoskeletal effects that together culminate in increased myocyte contractility and a raised heart rate. (B) In vascular smooth muscle cells, endothelial derived nitric oxide (NO) directly activates the effector molecule guanylate cyclase (GC) leading to the production of cGMP and direct activation of cGMP dependent protein kinase (protein kinase G). The enzymatic activity of protein kinase G results in the activation of myosin light chain (MLC) phosphatase that dephosphorylates MLC and causes vascular smooth muscle relaxation. Protein kinase G also targets many other substrates (for example, voltage dependent calcium channels; phospholipase C) whose phosphorylation culminates in a reduced intracellular calcium level and hence diminished vessel wall contraction. (C) Preconditioning stimuli in cardiac muscle (for example, brief exposure to ischaemia) cause an NO dependent activation of protein kinase Ce. It is thought that PKCe disables pro-apoptotic proteins and also phosphorylates a number of transcription factors leading to increased expression of protective genes in the myocardium.
Organisation of MAP kinase cascades. MAP kinase cascades are exemplified by the “classical” MAPK cascade. In this signalling pathway, ligand binding to a GPCR triggers activation of the cascade by promoting the generation of second messengers and by recruiting adaptor molecules and non-receptor tyrosine kinases. This results in activation of a MAPK kinase kinase kinase and subsequent phosphorylation and activation of raf, a MAPK kinase kinase. Raf can then phosphorylate the dual specificity kinase MEK (an MAPK kinase) which directly phosphorylates ERK1/2 (a MAPK). Negative feedback then allows for signal damping or desensitisation. Within the “classical” MAPK cascade ERK1/2 promotes the induction of dual specificity MAPK phosphatases (MKP-1 and-2), thus initiating its own deactivation and limiting cellular responses in the absence of continued stimulus input. There is also growing evidence of crosstalk between the different MAPK pathways. For example, it is thought that the proliferative effect of vascular endothelial growth factor on endothelial cells requires the sequential activation of ERK1/2 and JNKs. These studies have been strongly influenced by the availability of selective pharmacological tools that block the MAPKs themselves or target upstream components of the various cascades.
kinase), are unusual in that they recognise and phosphorylate specific threonine and tyrosine residues in their substrates (the MAPks) and are hence known as dual specificity kinases. The final kinases in the three module cascade are the MAPks themselves, which phosphorylate serine/threonine residues in many endogenous substrates. Activation of MAPks often results in their rapid movement to the nucleus. Thus, through their effects on phosphorylation, these kinases directly affect the activities of key cytoplasmic molecules (for example, phospholipase A2 (PLA2) enzymes) and modify acute cellular functions, as well as promoting phosphorylation of nuclear proteins (for example, transcription factors) and thereby exerting more chronic effects by influencing gene expression. Other molecules (‘scaffolds’), that have yet to be fully defined and characterised, facilitate optimal signalling through these pathways by physically linking the kinase components of the various cascades together and therefore maintaining the selectivity and specificity of signal transduction from membrane to nucleus.

The mammalian MAPks are divided into at least five families: ERK1/2 (extracellular regulated kinases), the p38 mapks, the c-jun N-terminal kinases (JNKs), ERK3/4, and ERK5. The most widely studied MAPks of recent years are ERK1/2, which are components of the so called ‘classical’ MAPK cascade. These enzymes were the first MAPks to be identified in mammalian cells as serine/threonine kinases that phosphorylated a component of the cell cytoskeleton following exposure of adipocytes to insulin, another growth factor that uses an RTK as its receptor. Although a key function of ERK1/2 is to control cell proliferation, differentiation, and survival via transcription factor activation, these MAPks have also been implicated in many other acute events in cardiovascular cells, including the release of vasoactive molecules from the endothelium, and vascular smooth muscle cell contraction in resistance vessels. Thus, in endothelial cells ERK1/2 phosphorylates an isoform of the effector molecule PLA2, which cleaves arachidonic acid from membrane phospholipids. Cyclooxygenase enzymes then convert arachidonic acid into prostaglandin H2, which is a substrate for the various synthase enzymes that generate a range of other prostaglandins, including prostacyclin (PGI2). Since PGI2 is a vasodilator, suppresses platelet reactivity, and inhibits vascular smooth muscle cell proliferation, endothelial ERK1/2 activation directly contributes to limiting the degree of vascular smooth muscle contraction, thrombotic events in the vasculature, and smooth muscle cell growth, all of which can occur to excess in a number of cardiovascular disorders including hypertension and atherosclerosis. In vascular smooth muscle, ERK1/2 phosphorylates the high molecular weight form of the contractile regulatory protein caldesmon, suggesting that these kinases are also directly involved in regulating the normal contractile properties of the vascular wall. ERK1/2 and JNK activities are also increased in vessels from hypertensive animals, demonstrating that aberrant expression and activation of these MAPks may also be associated with vessel pathology.

One major function of cardiac myocytes that depends upon ERK1/2 activation is hypertrophic growth. Myocardial hypertrophy is an adaptive process that occurs in response to both physiological and pathological stimuli including angiotensin II, endothelin-1, and catecholamines. All of these mediators, as well as mechanical stress, stimulate ERK1/2 activation in cardiac myocytes and use this pathway to trigger the cytoplasmic and nuclear events that facilitate enhanced protein synthesis and hypertrophic cell growth. Interestingly, another signalling molecule that is thought to be important for hypertrophic growth of myocytes is the phosphatase calcineurin. Calcineurin is a calcium activated phosphatase that catalyses the dephosphorylation of cytoplasmic transcription factors known as NFATs (nuclear factors of activated T cells). In cardiomyocytes, this dephosphorylation event allows movement of NFATs into the nucleus where they cooperate with other transcription factors to drive altered transcription of hypertrophic genes. GPCR ligands that raise intracellular calcium, including angiotensin II, catecholamines, and endothelin-1, can all activate the calcineurin pathway as well as the classical MAPK cascade, thus illustrating how phosphorylation and dephosphorylation events can interact to regulate the hypertrophic phenotype in cardiac muscle. These kinase/phosphatase pathways may be important both for the physiological cardiac hypertrophy observed in the athletic (trained) heart, and for the pathophysiological hypertrophy characteristic of failing hearts with increased workloads. Moreover, recent evidence indicates that calcineurin promotes the release of pro-inflammatory mediators from VSMCs, suggesting that calcineurin mediated dephosphorylation events may also have pathophysiological significance in the vascular wall.

The ERK1/2 pathway is not the only MAPK cascade that has functional significance in the cardiovascular system, and the p38 mapks are also involved in a range of cellular functions. Thus, during inflammation adhesion molecule expression on endothelial cells is necessary for the tethering and transendothelial migration of leucocytes. Expression of these adhesion molecules is highly dependent upon activation of p38 mapk, which phosphorylates the transcription factors required for transcriptional activation of their genes. p38 mapk exists in several isoforms and these may have distinct functions, especially in cardiac tissue. For example, ischaemia/reperfusion activates p38 mapkα but inhibits p38 mapkβ. In addition, activation of p38 mapkα promotes apoptosis of cardiomyocytes whereas p38 mapkβ induces cardiomyocyte hypertrophy. The role of the JNKs has been less well studied but these MAPks are also implicated in cardiac hypertrophy and heart failure.

There is also increasing evidence in cells of the cardiovascular system that GPCRs and RTKs can “talk” to each other to coordinate intracellular signalling events. For example, angiotensin II can directly promote cardiomyocyte growth by “transactivating” the epidermal growth factor (EGF) receptor and therefore triggering the distal ERK1/2-dependent signalling events that are important for the regulation of hypertrophic gene transcription (fig 5). Transactivation of growth factor receptors is now becoming recognised as a novel form of signal transduction utilised by GPCRs. Thus, targeting growth factor receptors and hence the signalling events downstream of receptor activation may prove to be a beneficial means of achieving inhibition of mitogenic signalling in response to a range of GPCRs.

**SUMMARY AND PERSPECTIVES**

Cells involved in regulating homeostasis in the cardiovascular system respond to changes in their local environment by using a range of extracellular receptors, of which the GPCRs are the most important. Signal recognition is transduced into a cellular...
response (physiological or pathological) through intracellular transduction mechanisms that converge on the regulation of the phosphorylation state of intracellular proteins by a range of protein kinase and protein phosphatase enzymes. It seems likely that subtle defects in these mechanisms may lead to a number of cardiovascular pathologies.

This brief description of some signal transduction pathways in the cardiovascular system can only scratch the surface of what are exceedingly complex regulatory mechanisms. The complexity is important because it allows cells to act in concert to maintain homeostasis by responding rapidly to small and fluctuating changes in the incoming environmental signals, while the crosstalk between signalling pathways allows coordinated responses to multiple different and sometimes opposing signals. However, the complexity and crosstalk may also be responsible for chronic pathological pathologies.
changes in the cardiovascular system. These signalling cascades are dynamic, with constant activation and deactivation by protein (de)phosphorylation, allowing the system to achieve equilibrium where cell function is optimum for the prevailing environmental conditions. Under these circumstances small, but chronic, alterations in this complex signalling network could result in a shift in the equilibrium favouring the development of pathological conditions such as, for example, cardiac hypertrophy. The existence of families of kinases and phosphatases and the realisation that individual members of a family may play opposing physiological roles is a particularly challenging concept that must inform future therapeutic development.

The good news is that our understanding of the signal transduction pathways in the cardiovascular system has increased enormously over the past two decades. The identification of protein kinases and phosphatases as key elements in these pathways make them attractive molecular targets for future drug development. In particular, the intimate involvement of the MAPK family of enzymes (and their associated phosphatases) in physiological and pathological cardiovascular processes suggests that they may offer useful therapeutic targets for preventing or reversing aberrant cell growth in failing hearts. Our increasingly detailed understanding of the inner mechanisms of cells comprising the cardiovascular system may soon lead to targeted and tailored therapies for previously ill defined disorders.

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A comprehensive review detailing the complexities underlying receptor mediated signalling in the heart and vessels. This review provides good coverage of the various G protein coupled receptors operative in vascular and cardiac cells, the interactions between them, and how this crosstalk regulates functional outcome.


This article reviews the specific roles of two families of scaffolding molecules involved in organising G protein coupled signalling systems.


A detailed review of G proteins and G protein mediated signalling.


An excellent review covering all the basic aspects of G protein activation along with details of the diverse signalling pathways linked to activation of G protein coupled receptors.


A brief historical perspective on the discovery of protein phosphorylation and dephosphorylation as important regulatory mechanisms in eukaryotic cells.


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A review of the PKA pathway in cardiac myocytes and the roles of scaffolding proteins (AKAPs) in regulating activation of PKA mediated phosphorylation events.


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A short informal review on the potential dual role of cGMP dependent protein kinases as regulators of tone in normal vessels, and of the phenotypic changes associated with vascular smooth muscle cells in diseased vessels.


A brief but informative commentary on PKC isozymes. This article is accompanied by a poster insert that details the mechanisms involved in PKC activation.


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