Functionally Opposing Roles of Extracellular Signal-Regulated Kinase 1/2 and p38 Mitogen-Activated Protein Kinase in the Regulation of Cardiac Contractility

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Background—Extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (p38-MAPK) have been shown to regulate various cellular processes, including cell growth, proliferation, and apoptosis in the heart. However, the function of these signaling pathways in the control of cardiac contractility is unclear. Here, we characterized the contribution of ERK1/2 and p38-MAPK to the inotropic effect of endothelin-1 (ET-1).

Methods and Results—In isolated perfused rat hearts, infusion of ET-1 (1 nmol/L) for 10 minutes increased contractility and phosphorylation of ERK1/2 and their downstream target p90 ribosomal S6 kinase (p90RSK). Suppression of ERK1/2 activation prevented p90RSK phosphorylation and attenuated the inotropic effect of ET-1. Pharmacological inhibition of epidermal growth factor receptor kinase activity abolished ET-1–induced epidermal growth factor receptor transactivation and ERK1/2 and p90RSK phosphorylation and reduced ET-1–mediated inotropic response. Moreover, inhibition of the p90RSK target Na+/H+ exchanger 1 attenuated the inotropic effect of ET-1. In contrast to ERK1/2 signaling, suppression of p38-MAPK activity further augmented ET-1–enhanced contractility, which was accompanied by increased phosphorylation of phospholamban at Ser-16.

Conclusions—MAPKs play opposing roles in the regulation of cardiac contractility in that the ERK1/2-mediated positive inotropic response to ET-1 is counterbalanced by simultaneous activation of p38-MAPK. Hence, selective activation of ERK1/2 signaling and inhibition of p38-MAPK signaling may represent novel means to support cardiac function in disease. (Circulation. 2008;118:1651-1658.)

Key Words: contractility ■ endothelin ■ mitogen-activated protein kinases ■ signal transduction

The members of the mitogen-activated protein kinase (MAPK) family, extracellular signal-regulated kinase 1/2 (ERK1/2) and p38-MAPK, have been implicated in the development of various pathological states such as cardiac hypertrophy and heart failure because they control cell growth and proliferation.1,2 Initially, ERK1/2 and p38-MAPK signaling were both considered to promote cardiomyocyte hypertrophy in response to G protein–coupled receptor (GPCR) agonists such as angiotensin II and endothelin-1 (ET-1) in cultured cells.3 However, recent studies using transgenic models have defined distinct roles for ERK1/2 and p38-MAPK in the hypertrophic response. Cardiac-specific overexpression of a constitutively active MAPK kinase 1 (MEK1), the upstream regulator of ERK1/2, stimulates concentric left ventricular (LV) hypertrophy without signs of progression toward heart failure.4 In contrast, prolonged inhibition of p38-MAPK activity in mice expressing dominant-negative mutants of MAPK kinase 3 (MKK3) or MKK6, the proximal regulatory kinases of p38-MAPK, facilitates progressive LV hypertrophy, leading to dilation and functional decompensation and suggesting an inhibitory function of p38-MAPK on cardiac growth response.5

Clinical Perspective p 1658

Transactivation of epidermal growth factor receptor (EGFR) has been established as a major mechanism for GPCR agonists to activate MAPKs.6 Stimulation of GPCRs induces metalloproteinase-mediated ectodomain shedding of membrane-anchored proheparin-binding EGF-like growth factor (pro-HB-EGF). Soluble HB-EGF then binds to and activates EGFR, triggering MAPK phosphorylation.6 Recent
studies advocate that EGFR transactivation via HB-EGF shedding represents a vital step for GPCR agonist–induced cardiac hypertrophy in vitro and in vivo.7

In contrast to pathological conditions, the role of MAPKs and EGFR in the regulation of physiological cellular processes in the intact myocardium is not yet well understood. ET-1 is a potent stimulator of cardiac contractility,8–13 acting mainly via the ETα GPCR subtype.14–16 Previous studies demonstrated that stimulation of cardiomyocytes with ET-1 produces a robust increase in ERK1/2, p38-MAPK, and EGFR phosphorylation17,18; to date, however, no information is available on whether these signaling pathways are involved in the inotropic response to ET-1. Therefore, the objective of the present study was to characterize the role of ERK1/2 and p38-MAPK and the potential upstream regulators (eg, EGFR) and downstream effectors of MAPK signaling (eg, Na+–H+ exchange, phospholamban) in the regulation of cardiac contractility stimulated by ET-1 in the intact rat heart.

Methods

A full description of the materials and methods used, including immunoblot analysis and p38-MAPK assay, can be found in the online-only Data Supplement.

Isolated Perfused Rat Heart Preparation

All protocols were reviewed and approved by the Animal Use and Care Committee of the University of Oulu. Male 7-week-old Sprague-Dawley rats (n=112) from the Center for Experimental Animals at the University of Oulu were used. Hearts were excised rapidly, mounted on a Langendorff perfusion system (LF-01, Experimetria Ltd, Budapest, Hungary), and perfused under constant-flow conditions as described previously.12,13,19

Experimental Design

A 40-minute equilibration period and a 5-minute control period were followed by the addition of various drugs to the perfusate for 10 minutes. The concentrations of U0126 (1.5 μmol/L), SB239063 (3 μmol/L), U-73122 (100 nmol/L), GF-109203X (90 nmol/L), AG1478 (1 μmol/L), and zoniporide (1 μmol/L) were selected because they have been demonstrated to suppress ERK1/2,20 p38-MAPK,20 phospholipase C (PLC),21 protein kinase C (PKC),13 and EGFR tyrosine kinase activity22 and to inhibit Na+–H+ exchanger 1 (NHE1).13,23 respectively. At the end of the experiments, the LVs were frozen in liquid nitrogen and stored at −80°C until assayed.

Statistical Analysis

Results are presented as mean±SEM. Two-way repeated-measures ANOVA was used to evaluate the statistical significance of differences among groups for cardiac contractility. When significant differences were detected for the treatment-by-time interactions, a Bonferroni post hoc test was used for specific comparisons. All other parameters were analyzed with 1-way ANOVA followed by Bonferroni post hoc test. Differences were considered statistically significant at the level of P<0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Role of ERK1/2 in the Regulation of Cardiac Contractility

In the isolated perfused rat heart preparation, intracoronary infusion of ET-1 (1 nmol/L) for 10 minutes increased developed tension by 40±2% (Figure 1A), which corresponds to the maximal response based on our previous results.12,13 To determine ERK1/2 activation under our experimental conditions, Western blotting was performed. In agreement with earlier data obtained in cultured neonatal cardiac myocytes,17,24 administration of ET-1 (1 nmol/L) for 10 minutes increased phospho-ERK1/2 levels in isolated perfused adult rat hearts (Figure 1B).

To examine whether activation of ERK1/2 contributes to the positive inotropic action of ET-1, we assessed the effect of U0126, which is a potent specific inhibitor of MEK1/2,19 the upstream regulator of ERK1/2.20 Administration of U0126 (1.5 μmol/L) significantly reduced the levels of phospho-ERK1/2 in the ET-1–stimulated LVs (Figure 1C and 1D). Two-way repeated-measures ANOVA showed significant treatment-by-time interaction (P<0.001) in contractility among the 4 groups. Post hoc analysis revealed that U0126 significantly attenuated the inotropic response to ET-1, the maximal reduction being 57% at the end of 10 minutes’ infusion time (P<0.001; Figure 1A). Infusion of U0126 alone had no effect on contractile force (P=1.0; Figure 1A).

Upstream Activators of ERK1/2 Regulating Cardiac Contractility

Previously, it has been suggested that ET-1 increases cardiac contractility8 and stimulates ERK1/2 phosphorylation via a PKC-dependent pathway in cardiomyocytes.24 To study the
activation of PKC in the adult rat heart, the translocation of PKC isoforms between cytosolic and particulate fraction was determined. In response to ET-1 infusion, no consistent increases in the translocation of PKCα, PKCβ, or PKCε into the particulate fraction were seen in Western analysis (Figure 2A). To assess the contribution of PKC to the effects of ET-1, we used the specific PKC inhibitor GF-109203X.13 Infusion of GF-109203X (90 nmol/L) had no effect on the ET-1–stimulated increase in phospho-ERK1/2 levels (Figure 2B). Moreover, GF-109203X did not alter ET-1–enhanced contractility (P=1.0; Figure 2C). In contrast, the inotropic response to phorbol 12-myristate 13-acetate (PMA; 40 nmol/L), a direct activator of PKC, was markedly reduced by GF-109203X (6.4±1.6% versus 29.2±4.9%, PMA with and without GF-109203X; n=4; P<0.01). In addition, we studied the role of PLC, the upstream activator of PKC. In agreement with the observation obtained using the PKC inhibitor, the potent PLC inhibitor U-7312213,21 (100 nmol/L) failed to alter the positive inotropic effect of ET-1 (P=1.0; Figure 2D). These data suggest that ET-1 increases contractile force through a PLC-PKC–independent pathway.

Recent studies suggest that GPCR agonists can promote the growth of cardiomyocytes via transactivation of EGFR with subsequent activation of MAPKs.22 To examine whether ET-1 transactivates the EGFR, EGFR phosphorylation was measured by immunoprecipitation with anti-EGFR antibody followed by immunoblotting of immunoprecipitates with anti-phosphotyrosine antibody. ET-1 increased total tyrosine phosphorylation of EGFR in the LV (Figure 3A), indicating EGFR transactivation. As shown in Figure 3B, ET-1–induced EGFR tyrosine phosphorylation was abolished by AG1478 (1 μmol/L), a specific EGFR tyrosine kinase inhibitor.22 Moreover, AG1478 significantly reduced ET-1–induced ERK1/2 phosphorylation (Figure 3C and 3D), suggesting that EGFR transactivation is required for the activation of the ERK1/2 cascade. Furthermore, in the presence of AG1478, the inotropic response to ET-1 was significantly suppressed, the maximal reduction being 46% (P<0.001; Figure 3E). Infusion of AG1478 alone had no effect on developed tension (P=1.0; Figure 3E).

**Downstream Targets of ERK1/2 Regulating Cardiac Contractility**

Several lines of evidence suggest that the sarcolemmal NHE1 is a pivotal mediator of the positive inotropic effect of ET-1.8–10,14,16 Accordingly, zoniporide13,23 (1 μmol/L), a potent and selective inhibitor of NHE1, attenuated the ET-1–induced inotropic response by 57% under our experimental conditions (P<0.001), whereas zoniporide alone had no effect on cardiac contractility (P=1.0; Figure 4A). Previously, it has been shown that ERK1/2 and one of its downstream effectors, p90 ribosomal S6 kinase (p90RSK), can phosphorylate and activate NHE1 in response to ET-1 in cardiac myocytes.25 As shown in Figure 4B, ET-1 increased the phospho-p90RSK levels in the membrane fraction. Importantly, both U0126 and AG1478 significantly attenuated ET-1–induced phosphorylation of p90RSK (Figure 4C and 4D), suggesting that p90RSK-mediated activation of NHE1 may be the downstream target of the EGFR–ERK1/2 pathway.

**Role of p38-MAPK in the Regulation of Cardiac Contractility**

Previously, ET-1 has been shown to produce a robust increase in p38-MAPK phosphorylation in primary cultures of cardiac myocytes.3 In agreement, ET-1 infusion for 10 minutes increased phospho-p38-MAPK levels in isolated perfused adult rat hearts (Figure 5A). To assess the involvement of p38-MAPK in the positive inotropic effect of ET-1, we used a novel potent
inhibitor, SB239063. Because p38-MAPK inhibitors, including SB239063, are known to affect the catalytic activity of p38-MAPK rather than the levels of phosphorylated p38-MAPK, a kinase assay that uses ATF-2 as a substrate was performed to confirm the inhibition of p38-MAPK. As shown in Figure 5B and 5C, the ET-1–induced increase in p38-MAPK activity in the LV was abolished by SB239063 (3 μmol/L).

Interestingly, administration of SB239063 augmented the ET-1–induced inotropic response maximally by 42% (P<0.05; Figure 5D). Infusion of SB239063 alone had no effect on developed tension (P=0.1; Figure 5D).

Cross-Talk Between p38-MAPK and ERK1/2 Signaling
Inhibition of p38-MAPK by SB239063 had no effect on ET-1–induced ERK1/2 phosphorylation (Figure 6A). Similarly, administration of U0126 did not affect phospho–p38-MAPK levels (Figure 6B). Interestingly, AG1478 significantly reduced ET-1–induced increases in LV levels of phospho–p38-MAPK (Figure 6C) in addition to its effect on ERK1/2 phosphorylation (Figure 3C). These data suggest that no direct cross-talk exists between ERK1/2 and p38-MAPK signaling. Moreover, EGFR transactivation appears to be involved in the activation of both pathways.

Downstream Targets of p38-MAPK Regulating Cardiac Contractility
Phospholamban is a crucial regulator of cardiac contractility. In its dephosphorylated state, phospholamban binds to and inhibits the activity of sarcoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA2a). Phosphorylation of phospholamban on Ser-16 relieves SERCA2a inhibition and enhances Ca\(^{2+}\) reuptake into the sarcoplasmic reticulum, leading to increased contractility.\(^{26}\) ET-1 significantly increased phospholamban phosphorylation at Ser-16 in the presence of SB239063, although the peptide had no effect on its own (Figure 7A and 7B). Infusion of SB239063 alone did not increase phospholamban phosphorylation significantly (P=0.115; Figure 7B). In addition, U0126 failed to alter the phosphorylation of phospholamban (Figure 7C). These results suggest that p38-MAPK inhibition may enhance the inotropic response to ET-1 by augmenting phospholamban phosphorylation in the myocardium.

Effect of ET-1 on Vascular Tone
Overall, the changes in vascular tone were small. Importantly, inhibition of ERK1/2 or p38-MAPK significantly modified the inotropic response to ET-1 (Figures 1A and 5D) without altering the effect of the peptide on vascular tone (ET-1: from 32.0±1.8 to 38.8±3.3 mm Hg, a 20.6±3.4% increase in perfusion pressure; ET-1 plus U0126: 16.8±2.7%; ET-1 plus SB239063: 18.7±3.8%; P=0.1 versus ET-1 alone). In line with previous observations,\(^{27}\) the PKC inhibitor GF-109203X and PLC inhibitor U-73122 significantly attenuated the vasoconstrictor effect of ET-1 (ET-1: from 32.4±1.0 to 40.3±2.0 mm Hg, a 23.9±2.8% increase; ET-1 plus GF-109203X: 6.0±1.4%; ET-1 plus U-73122: 13.8±1.1%; P<0.001 and P<0.01 versus ET-1 alone, respectively). The other inhibitors had no significant effect on the ET-1–induced increase in perfusion pressure (data not shown).
A growing body of evidence suggests that activation of the MEK1/2–ERK1/2 pathway constitutes an important adaptive mechanism in the myocardium.1,2 ERK1/2 signaling has been reported to confer cardioprotection in vivo against ischemia-reperfusion injury by directly antagonizing myocyte apoptosis.28 Moreover, cardiac-specific overexpression of a constitutively active MEK1 stimulates mild concentric LV hypertrophy associated with enhanced LV function without signs of decompensation over time.4 Consistent with these observations, inhibition of ERK1/2 activation by cardiac-specific expression of a dominant-negative form of Raf-1, the upstream regulator of MEK1/2, results in blunted cardiac hypertrophy, increased apoptosis, and LV dysfunction with a concomitant increase in mortality in response to pressure overload.29 More recently, the requirement of ERK1/2 signaling in stress adaptation has been addressed directly with Erk1−/− and Erk2−/− mice, as well as transgenic mice with inducible expression of an ERK1/2-inactivating phosphatase in the heart (dual-specificity phosphatase 6). Although the hypertrophic growth is not attenuated in these models after long-term pressure overload, selective ablation...
tion of cardiac ERK1/2 signaling predisposes the heart to decompensation and failure in conjunction with an increase in myocyte apoptosis.30 Although systolic function is clearly affected in these transgenic models, it has not yet been established whether ERK1/2 can directly modulate cardiac contractility. In the present study, the GPCR agonist ET-1 produced a rapid increase in LV phospho-ERK1/2 levels, and inhibition of ERK1/2 activation by U0126, a potent MEK1/2 inhibitor, markedly attenuated the ET-1–induced increase in contractile force in the intact rat heart. Hence, our results demonstrate a novel function for MEK1–ERK1/2 signaling whereby it regulates myocardial contractility in addition to influencing cell growth and survival.

Previously, ET-1 has been suggested to increase cardiac contractility8–10,16 and ERK1/2 phosphorylation24 via a PKC-dependent pathway. However, our data indicate that PKC is unlikely to mediate the inotropic effect of ET-1 in the intact adult rat heart. We did not detect translocation of PKCa, PKCd, or PKCe into the particulate fraction after a 10-minute infusion of ET-1, although we cannot exclude the possibility that translocation occurred earlier and the PKC isofoms already returned to the soluble fraction by that time. GF-109203X, a specific PKC inhibitor, did not attenuate the ET-1–stimulated increase in phospho-ERK1/2 levels and the inotropic response to ET-1, although it markedly reduced the inotropic effect of PMA. Furthermore, pharmacological inhibition of PLC, the upstream regulator of PKC, also failed to alter the inotropic effect of ET-1. Of note, GF-109203X and U-73122 significantly attenuated the modest vasoconstrictor effect of ET-1, in line with previous observations,27 indicating that the inhibitors were effective in our experimental system.

Recent advances indicate that EGFR transactivation is an important pathway that links GPCRs and ERK1/2 activation.22 Stimulation of GPCRs induces metalloproteinase-mediated ectodomain shedding of HB-EGF, which can activate EGFR, leading to ERK1/2 phosphorylation via recruitment of the Ras-Raf1-MEK1/2 cascade.6 Inhibition of HB-EGF shedding and EGFR transactivation can prevent GPCR agonist–induced LV hypertrophy and cardiac dysfunction in vivo.7 On the other hand, targeted deletion of HB-EGF results in a severe cardiac phenotype associated with dilated ventricular chambers and diminished cardiac function.31 Although these studies have demonstrated the functional importance of the HB-EGF–EGFR pathway in hypertrophic and developmental growth processes, the relationship between EGFR signaling and cardiac contractility remains unknown. In our experiments, ET-1 increased total tyrosine phosphorylation of EGFR. Because considerable specificity is found between the sites in terms of recruitment of signaling molecules,32 further experiments are warranted to identify the specific sites that have been tyrosine phosphorylated on the EGFR. However, inhibition of EGFR transactivation by the specific EGFR tyrosine kinase inhibitor AG1478 was accompanied by significant attenuation of the ET-1–induced increase in phospho-ERK1/2 levels and the inotropic response to ET-1. Thus, the present data define a previously unrecognized role for EGFR in the regulation of myocardial contractility, acting as a proximal component of MEK1/2–ERK1/2 signaling.

Previous studies suggest that activation of sarcolemmal NHE1 contributes, at least in part, to the positive inotropic effect of ET-1.8–10,14,16 Stimulation of NHE1 can lead to intracellular alkalization and sensitization of cardiac myofilaments to intracellular Ca2+. On the other hand, NHE1–mediated accumulation of intracellular Na+ can indirectly promote a rise in intracellular levels of Ca2+ via a reverse-mode Na–Ca2+ exchanger.53,54 In agreement with previous findings, our data showed that zomiporide, a highly selective inhibitor of NHE1, attenuated the inotropic response to ET-1. Activation of ERK1/2 can result in phosphorylation of the C-terminal regulatory domain of the NHE1, either directly by ERK1/2 itself55 or indirectly through p90RSK.35 p90RSK is located in the cytosol under basal conditions and translocates to the plasma membrane after stimulation where it becomes fully activated.56 Maekawa et al37 have reported recently that expression of a dominant-negative p90RSK abolished oxidative stress–induced activation of NHE1 in cardiomyocytes, providing evidence for the essential role of p90RSK in the regulation of NHE1 activity. In the present study, ET-1 increased phospho-p90RSK levels in the membrane fraction, and both AG1478 and U0126 attenuated it. Therefore, it is conceivable that membrane-associated p90RSK can mediate the effect of ET-1 on NHE1 activity.

The finding that ≈40% of the ET-1–induced positive inotropic effect remained unaffected after inhibition of the EGFR–ERK1/2–NHE1 pathway indicates the existence of additional signaling mechanisms. Phosphoinositide 3-kinase plays an important role in the positive inotropic effect of insulin.58 However, our preliminary results showed that inhibition of phosphoinositide 3-kinase by LY 294002 (3 μmol/L) had no effect on ET-1–enhanced contractility (45.2 ± 5.4% versus 49.7 ± 5%, ET-1 with and without LY 294002; n = 5; P = 1.0). In contrast, ML-7 (1 μmol/L), an inhibitor of myosin light-chain kinase, significantly reduced the inotropic effect of ET-1 (20.7 ± 1.7% versus 43.8 ± 3.7%, ET-1 with and without ML-7; n = 5; P < 0.0001). These results are in line with previous findings31,39 and suggest that myosin light-chain kinase is an important mediator of the inotropic effect of ET-1.

p38-MAPK signaling has long been thought to be associated with various pathological conditions in the heart such as hypertrophy, extracellular matrix remodeling, and cardiac decompensation.2 However, less information is available on the role of p38-MAPK in the regulation of physiological cellular processes in the myocardium. In cultured adult rat cardiomyocytes, activation of p38-MAPK by adenoviral gene transfer of its upstream kinase, MKK3bE, results in the partial inactivation of its downstream targets, resulting in a significant reduction in contractility. Conversely, pharmacological inhibition of the endogenous activity of p38-MAPK increases contractile force in a dose-dependent manner.40 In the present study, ET-1 rapidly increased the activity of p38-MAPK in the intact adult rat heart, and inhibition of the enzyme by its potent inhibitor SB239063 markedly augmented the inotropic response to ET-1, whereas the inhibitor alone failed to alter baseline contractility. These data imply that p38-MAPK has no direct negative effect on contractility in unstressed adult ventricular myocardium, whereas physiological activation of p38-MAPK provides a negative feedback to the ET-1–mediated inotropic response. This agrees with the report that the positive inotropic effect of β2-adrenergic stimulation is considerably enhanced by pharma-
ological inhibition of p38-MAPK in isolated mouse cardiomyocytes.\textsuperscript{41}

Although the concept that p38-MAPK may act as an important regulator of cardiac function is well accepted,\textsuperscript{40–42} the molecular mechanism by which p38-MAPK affects cardiac contractility is still elusive. Previously, it has been suggested that p38-MAPK suppresses ERK1/2 signaling by a mechanism involving protein phosphatases in cardiomyocytes.\textsuperscript{43} However, our results showed that inhibition of p38-MAPK could not further augment ET-1-induced ERK1/2 phosphorylation, ruling out the existence of direct cross-talk between the ERK1/2 and p38-MAPK pathways in the intact heart. Previous observations suggest that p38-MAPK activation may lead to dephosphorylation of phospholamban, a crucial regulator of cardiac contractility. Liu and Hofmann\textsuperscript{44} have shown that adenosine A\textsubscript{1} receptor activation can blunt \textbeta{}-adrenergic–stimulated phospholamban phosphorylation in a p38-MAPK–sensitive manner. Of particular importance was our finding that ET-1 promoted the phosphorylation of phospholamban at Ser-16 in the presence of p38-MAPK inhibition. Phosphorylation of phospholamban relies on SERCA2a inhibition and enhances Ca\textsuperscript{2+} reuptake into the sarcoplasmic reticulum. On subsequent beats, contractility is increased in proportion to the elevation in the size of sarcoplasmic reticulum Ca\textsuperscript{2+} store and the resulting increase in Ca\textsuperscript{2+} release from the sarcoplasmic reticulum.\textsuperscript{26} Therefore, it is tempting to speculate that p38-MAPK may limit increases in contractility via dephosphorylation of phospholamban in the myocardium. Taken together, in the normal heart, the dynamic transient activation of p38-MAPK may have an important homeostatic function by counterbalancing excess inotropic stimulation. Loss of this cardioprotective mechanism during chronic suppression of p38-MAPK signaling may be a pathogenic factor in the progression of heart failure in mice expressing dominant-negative mutants of MKK3 or MKK6.\textsuperscript{5} On the contrary, substantial persistent activation of p38-MAPK signaling also may contribute to the evolution of heart failure by impairing myocardial contractility such as in mice with cardiac-specific expression of MKK3b\textsubscript{e} or MKK6b\textsubscript{e}.\textsuperscript{45} Therefore, cardiac function may be improved by normalization of upregulated p38-MAPK activity in the diseased heart.

Conclusions
We present evidence for the functional importance of ERK1/2 and p38-MAPK in the acute regulation of cardiac contractility in the intact adult rat heart. Our results reveal that MAPKs play opposing roles in that the ERK1/2-mediated positive inotropic response to ET-1 is counterbalanced by simultaneous activation of p38-MAPK. EGFR may act as the upstream regulator and the p90RSK–NHE1 pathway as the downstream effector of ERK signaling. Moreover, p38-MAPK activation may suppress contractility by dephosphorylating phospholamban. Identification of novel signaling pathways that promote cardiomyocyte survival while improving contractile function may offer an attractive approach for treating patients with heart failure. Therefore, further studies are required to test the hypothesis that activation of MEK1/2–ERK1/2 signaling, possessing such beneficial effects, can eventually rescue the failing heart.

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Disclosures
None.

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