ANG II and cardiac myocyte contractility: p38 is not stressed out!

Abdelkarim Sabri1 and Pamela A. Lucchesi2

1Cardiovascular Research Center, Temple University, Philadelphia, Pennsylvania; and 2Department of Pharmacology, Louisiana State University Health Sciences Center, New Orleans, Louisiana

MITOGEN-ACTIVATED PROTEIN KINASES (MAPK) are implicated in the regulation of many cellular processes in cardiac myocytes, including hypertrophy, apoptosis, and excitation-contraction coupling. At least four major subfamilies have been identified in cardiac tissue, including the extracellular signal-regulated kinase 1 and 2, c-Jun-NH2-terminal kinase, “big” MAPK, and p38. In the heart, p38 is activated by a wide variety of contractile and hypertrophic agonists, chemokines, and reactive oxygen species (ROS) (11). Initial work in cultured neonatal and adult cardiac myocytes associated p38 phosphorylation with myocyte hypertrophy and apoptosis (see Ref. 15 for a recent review). Studies using pharmacological inhibitors and genetic manipulation suggest that p38 activation may actually be detrimental in vivo. p38 activation occurs during pressure overload-induced cardiac hypertrophy (17) and in human heart failure (4). Cardiac-specific overexpression of p38 in transgenic mice results in left ventricular remodeling and contractile dysfunction (12). Although these studies focused on stress-activated p38 signaling in cardiac myocyte growth and apoptosis, emerging evidence points to a role for p38 in regulating cardiac myocyte contractility. Studies by Xiao’s group (13) using adenosine-mediated expression of MKK3 were the first to demonstrate a negative inotropic effect of p38 in adult cardiac myocytes. Subsequent studies reported a role for p38 in the negative inotropic effect of HIV gp120 protein (9).

ANG II is a well-characterized inotropic and hypertrophic agonist that activates p38 via ANG II type 1 receptor (AT1R)-dependent signaling to tyrosine kinases, protein kinase C (PKC), and MKK3/6. More recently, NAD(P)H oxidase-dependent production of ROS has been shown to activate p38 via the redox-sensitive apoptosis signal-regulated kinase 1 (ASK-1) and MKK3/6 (8). In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Palomeque et al. (14) provide exciting evidence for a role of NAD(P)H oxidase-independent p38 activation in ANG II-induced negative inotropy in cardiac myocytes. The authors used a combination of pharmacological and genetic tools to carefully delineate the pathway that lies between AT1R activation and decreased myofilament Ca2+ sensitivity. The effects of ANG II are mediated by tyrosine kinase- and PKC-dependent p38 activation that does not involve NAD(P)H oxidase stimulation because neither the NAD(P)H oxidase inhibitor diphenyleneiodonium nor the ROS scavenger 4,5-dihydroxy-1,3-benzedisulfonic acid had any effect on the negative inotropic actions of ANG II or p38 phosphorylation. Using both lucigenin and 5-(6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate, the authors determined that ANG II did not increase ROS production during the time period in which the negative inotropic effects of ANG II were observed (20 min), although ANG II did increase ROS production at 60 min. This was somewhat surprising given the results from numerous studies that place the NAD(P)H oxidase between AT1R activation and p38. Wenzel et al. (19) reported that ANG II-induced p38 activation was blocked by diphenyleneiodonium chloride and by antisense downregulation of NAD(P)H oxidase subunits, although the time course for ANG II-dependent ROS production was not measured. Kimura et al. (10) demonstrated that NAD(P)H oxidase inhibition with apocynin blocked ANG II-induced p38 activation and ischemic preconditioning. ANG II-induced hypertrophy and p38 activation in vivo are suppressed in mice genetically deficient in gp91phox (2) or in the redox-sensitive ASK-1 (8). Additional studies in gp91phox−/− mice may provide more definitive proof of ANG II-induced p38 activation that is independent of NAD(P)H oxidase dependent signaling.

The reasons for these discrepancies are unclear. It may be that the temporal activation of p38 by ANG II consists of an acute stimulation in a redox-independent manner and a sustained activation that requires ROS production. Support for this possibility comes from the finding that many studies measured ANG II-mediated superoxide production in cardiac cells at least 60 min to 4 h after AT1R stimulation (7, 16). Although these time points are appropriate for measuring sustained activation of MAP kinases and subsequent hypertrophic growth or induction of apoptotic pathways, they may not account for the acute activation of signaling cascades involved in the regulation of contractility. It is also possible that distinct p38 isoforms are activated by oxidative stress-dependent and -independent pathways. For example, proapoptotic and anti-hypertrophic effects are attributed to p38α activation, whereas p38β activation appears to mediate an antiapoptotic, hypertrophic effect (18).

The mechanisms by which ANG II and p38 decrease cardiac myocyte contractility were not completely identified in this study, although it was clear that changes in the amplitude or duration of the Ca2+ transient were not involved. The authors convincingly demonstrate that ANG II-induced, p38-dependent decreases in contractility were due to altered myofilament Ca2+ sensitivity. Similar results for p38 were also reported by Liao et al. (13). The reduced Ca2+ sensitivity appears to be independent of both changes in intracellular pH (3, 13, 14) and troponin I phosphorylation (13). One putative mechanism is p38-dependent phosphorylation of heat shock proteins (HSP) 27 and αB-crystallin and their subsequent translocation to sarcomeric or cytoskeletal structures (1, 6). Support for this notion comes from a study by Dana et al. (5) demonstrating that p38-dependent HSP27 phosphorylation in ischemic preconditioning requires both PKC and tyrosine kinases. On the other hand, recent work by Hofmann’s laboratory (3) suggests that p38-mediated reductions in force development in adult cardiac myocytes is not associated with decreased myofilament Ca2+ sensitivity but was associated with HSP27 translocation.

Address for reprint requests and other correspondence: P. A. Lucchesi, Dept. of Pharmacology, LSU Health Sciences Center, 1901 Perdido St., P7–1 New Orleans, LA 70112-1393 (e-mail plucch@lsuhsc.edu).

to the myofilament fraction. Whether similar processes occur in the negative inotropic response to ANG II and p38 remains to be determined.

In summary, the study by Palomeque et al. (14) provides new evidence that ANG II regulates cardiac myocyte contractility via a p38 MAPK-dependent process that does not require NAD(P)H oxidase activation. These results add new conceptual information on MAPK signaling cascades involved in the regulation of myofilament Ca^{2+} sensitivity and cardiac contractility. A more thorough understanding of the events that translate p38 activation to negative inotropic responses may have important therapeutic implications for certain pathophysiological conditions such as heart failure and ischemia-reperfusion injury.

REFERENCES


