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Redox Regulation of Cardiac Muscle Calcium Signaling

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ABSTRACT

Signal transduction for cardiac muscle contraction is regulated by the Ca^{2+}-induced Ca^{2+}-release mechanism. Redox reactions by biological oxidants and antioxidants have been shown to alter the kinetics of Ca^{2+}-induced Ca^{2+} release. We postulate that altered kinetics of Ca^{2+}-induced Ca^{2+} release may divert the contractile pool of Ca^{2+} to elicit excitation-transcription coupling. We provide evidence that redox reactions regulate excitation-transcription coupling by showing that membrane depolarization may activate the GATA4 transcription factor only when the cells are pretreated with hydrogen peroxide. Therefore, redox regulation of the ryanodine receptor may serve as a mechanism to determine whether the contractile pool of Ca^{2+} should signal gene transcription during excitation-contraction coupling. Antiox. Redox Signal. 2, 65–71.

INTRODUCTION

SIGNAL TRANSDUCTION for contraction of cardiac and skeletal muscle is initiated by depolarization of the sarcolemma, leading to the increased cytosolic concentration of Ca^{2+}, which, in turn, serves as a second messenger for eliciting contraction in the process called excitation-contraction coupling. In cardiac muscle, signal transduction for excitation-contraction coupling is controlled by the Ca^{2+}-induced Ca^{2+}-release mechanism (Fabiato, 1983). This process starts with the entry of Ca^{2+} through the voltage-dependent sarcolemmal L-type Ca^{2+} channel, binding of Ca^{2+} to a site on the ryanodine receptor (RyR; Ca^{2+}-release channel), leading to the release of Ca^{2+} from the sarcoplasmic reticulum (SR) (Nabauer *et al.*, 1989; Cleemann and Morad, 1991). The large and transient release of Ca^{2+} from the SR is then sensed by troponin C, resulting in actin– myosin interactions. Muscle relaxation occurs as Ca^{2+} leaves the cytosol via either Ca^{2+}-ATPase to be stored in the SR or by extruding it from the cell via the sarcolemmal Na^{+}-Ca^{2+} exchanger. As the muscle cycles form beat-to-beat between contraction and relaxation multiple times per minute, Ca^{2+} signaling must be precisely regulated to allow for the plasticity of cardiac function.

The Ca^{2+} release apparatus of cardiac and skeletal muscle appear to be closely related with molecular entities composed of the RyR and a complex of functionally associated proteins such as triadin, junctin, FK506-binding protein, and calmodulin. Luminal Ca^{2+} bind-

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ing proteins such as calsequestrin provide for the large Ca^{2+} storage capacity of the SR and may, in part, regulate the RyR activity. Studies of fractionated SR vesicles and the purified RyRs incorporated into lipid bilayers suggest that the Ca^{2+} release process is under redox regulation as described in articles presented in this Forum. Intramolecular interactions within the RyR tetramer as well as intermolecular interactions between RyR and triadin have been shown to depend, in part, on the redox state.

REDOX REGULATION OF Ca^{2+}-INDUCED Ca^{2+} RELEASE

Reactive oxygen species (ROS) and their generating systems including xanthine + xanthine oxidase (Goldhaber *et al.*, 1989), xanthine + xanthine oxidase + iron-loaded transferrin (Butron *et al.*, 1990), hydrogen peroxide (H_2O_2) (Goldhaber *et al.*, 1989; Goldhaber and Liu, 1994), H_2O_2 + Fe^{3+}-nitrilotriacetate (Corretti *et al.*, 1991; Josephson *et al.*, 1991), and photoactivation of rose bengal (Shattock *et al.*, 1991) have been shown to cause attenuation of cardiac muscle contraction. This attenuation, however, is usually preceded by a transient augmentation of twitch amplitude as well as cytosolic Ca^{2+}. Studies in whole-cell-clamped rat ventricular myocytes have further indicated that calcium current (I_{Ca})-gated Ca^{2+} release is under redox regulation and that glutathione (GSH) may play a critical role in this regulatory process. For instance, it was shown that H_2O_2 enhances Ca^{2+} channel-gated Ca^{2+} release from the SR and this augmentation requires thiol reductants, GSH, or dithiothreitol (DTT) (Suzuki *et al.*, 1998). As shown in Fig. 1, H_2O_2 enhanced the efficacy of Ca^{2+}-induced Ca^{2+} release ($\Delta[Ca^{2+}]_i/I_{Ca}$) in rat ventricular myocytes dialyzed with the solution containing GSH. The requirement for oxidants and reductants in the enhancement of the Ca^{2+}-induced Ca^{2+}-release mechanism in the cellular system suggests that thiol-disulfide interchange or exchange reactions regulate Ca^{2+} release from the SR by converting the disulfide structure to another thiol through sequential reduction (by GSH) and oxidation (by H_2O_2) reactions. This is consistent with the earlier proposal by Abramson and Salama (1988, 1989) that intramolecular thiol-disulfide interchange reactions in skeletal muscle within the Ca^{2+}-release channel open or close the channel. The lack of biochemical evidence that reductants regulate oxidant-mediated Ca^{2+} channel activation can be explained by the notion that the thiol-disulfide exchange may occur between the RyR and triadin (or some other functional proteins) not present in many of the isolated systems.

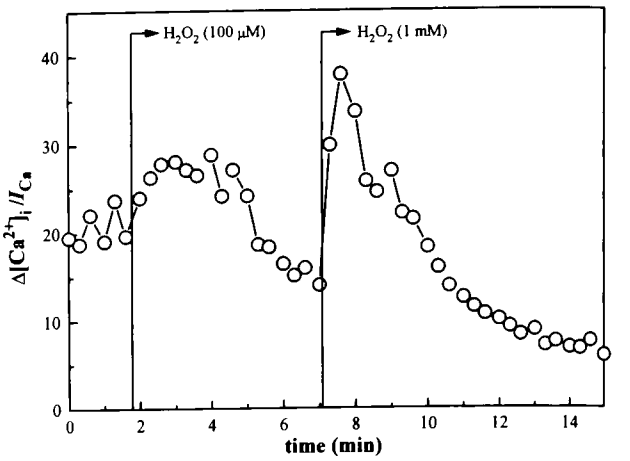

FIG. 1. H_2O_2 enhances efficacy of Ca^{2+}-induced Ca^{2+} release in myocyte dialyzed with GSH. Whole-cell-clamped rat ventricular myocyte dialyzed with (in m*M*) 110 CsCl, 30 TEA-Cl, 5 MgATP, 10 HEPES, 0.2 cAMP, 0.2 K_5fura-2, 1 EGTA, and 2 GSH was exposed to H_2O_2 (100 μM and 1 m*M*). Voltage-dependent $\Delta[Ca^{2+}]_i/I_{Ca}$ was monitored every 20 sec and expressed in (n*M*)/(pA/pF). (Reprinted from Suzuki *et al.*, 1998, with permission.)

It is also intriguing to note that GSH may play a key role in calmodulin regulation of the Ca^{2+}-induced Ca^{2+}-release mechanism (Suzuki *et al.*, 1999a). For instance, exposure of whole-cell-clamped rat ventricular myocytes dialyzed with Fura-2 (0.1 m*M*) to a calmodulin inhibitor W-7 caused enhancement of the efficacy of I_{Ca}-induced Ca^{2+} release at negative potentials (Fig. 2), suggesting that calmodulin may suppress the I_{Ca}-induced Ca^{2+} release mechanism in a voltage-dependent manner (Suzuki *et al.*, 1999a). This phenomenon could be observed only when cells were dialyzed with internal solutions not containing GSH. In sharp contrast, the addition of physiological concentrations of GSH into the dialysis solution prevented the W-7-induced effects on I_{Ca}-gated Ca^{2+} release, suggesting that cellular re-

dox status may be important in calmodulin regulation of Ca^{2+}-induced Ca^{2+} release and that redox reactions may play critical regulatory roles in determining the kinetics of Ca^{2+} release of the SR.

CARDIAC MUSCLE EXCITATION-TRANSCRIPTION COUPLING

In addition to its critical role as a second messenger for muscle contraction, Ca^{2+} can also cause diverse biological actions including cell proliferation, hypertrophy, differentiation, and apoptosis. Recently, the concept that Ca^{2+} may differentially affect various signaling mechanisms has gained significant attention (Berridge, 1997). Kinetics of Ca^{2+} influx into the cytosolic space may be a determinant of such diverse actions of Ca^{2+}. Consistent with this idea, Dolmetsch *et al.* (1997) demonstrated that the differential activation of signaling pathways for gene transcription occurs depending on the amplitude and duration of Ca^{2+} responses. For instance, while NF-κB and JNK are activated by a large transient cytosolic Ca^{2+} rise, NFAT and p44/42 MAP kinase (ERK) pathways are activated by lower and sustained Ca^{2+} rises. The route of entry into the cytosol has also been reported to be a determinant of the differential regulation of Ca^{2+} for various biological outcomes (Ghosh and Greenberg, 1995). For example, Ca^{2+} influx through the L-type channels, but not through the Na^{+}-Ca^{2+} exchanger, appears to be the dominant trigger of Ca^{2+} release from the SR in cardiac myocytes (Sham *et al.*, 1995). Furthermore, Ca^{2+}-mediated signaling may diverge into various transcription factors through differential activation of Ras and MAP kinase which, in turn, converge back at the level of c-*fos* promoter (Johnson *et al.*, 1997). More recently, the role of Ca^{2+} oscillations in controlling gene expression has been confirmed (Dolmetsch *et al.*, 1998; Li *et al.*, 1998).

It is important to determine whether the contractile pool of Ca^{2+} may also stimulate gene expression in cardiac muscle and, if so, whether cellular redox status may serve as a determinant of such regulatory pathway. How can diverse Ca^{2+} signals specifically elicit muscle contraction during excitation-contraction coupling? Are there situations where the Ca^{2+}-signaling of excitation-contraction coupling is diverted to signal excitation-transcription coupling? We hypothesize that alterations of Ca^{2+} release kinetics conferred through the redox regulation of SR proteins may serve as sensors for recognizing the contractile pool of Ca^{2+} as transcriptional signals.

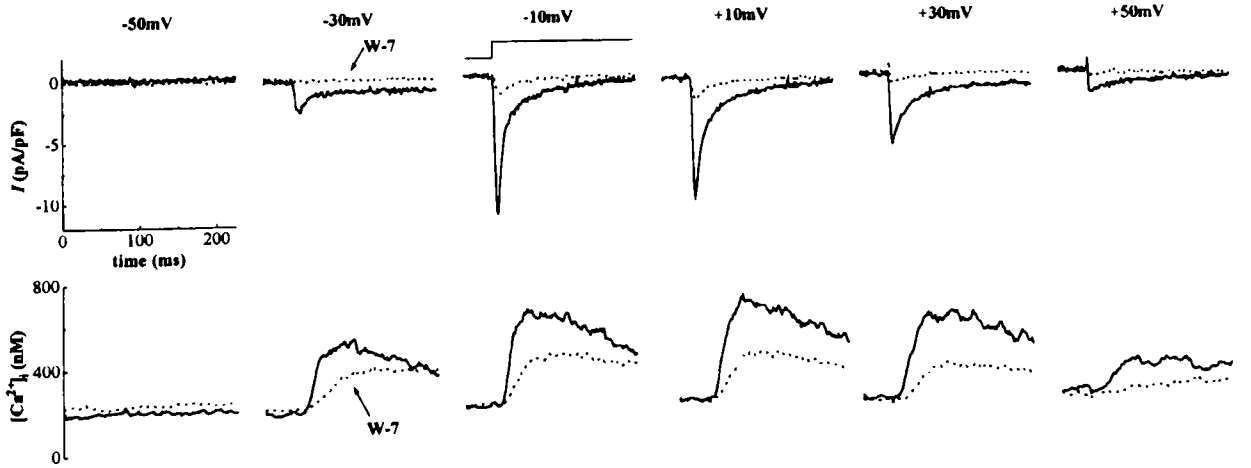

FIG. 2. Effects of W-7 on Ca^{2+} channel-gated Ca^{2+} release. Whole-cell-clamped rat cardiac myocytes dialyzed with the internal solution composed of (in m*M*) 110 CsCl, 30 TEA-Cl, 5 MgATP, 10 HEPES, 0.2 cAMP, and 0.1 K_5fura-2 were perfused with Tyrode's solution containing 2 m*M* $CaCl_2$ and 0.2 m*M* $BaCl_2$, and Ca^{2+} currents (I_{Ca}) and Ca^{2+} transients were generated by depolarization to various potentials. **Upper panel.** Representative traces of I_{Ca} generated by depolarization from −50 mV to potentials indicated. **Lower panel.** Representative traces of corresponding Ca^{2+} transients. Solid line traces represent before W-7 exposure, whereas dotted line traces are after W-7 (20 μ*M*) exposure for 2 min. (Reprinted from Suzuki *et al.*, 1999a, with permission.)

Although the kinetics of Ca^{2+}-induced Ca^{2+} release from the SR are normally characterized as rapid and transient (Fig. 3A), deviations from such rapid kinetics have been consistently observed under a number of experimental conditions. For example, cardiac adaptation in senescence is characterized by prolonged Ca^{2+} activation of contractile proteins, leading to a prolonged force-bearing capacity. This is mediated by a prolongation of the cytosolic Ca^{2+} transient (Fig. 3B), due to a reduced rate of Ca^{2+} sequestration by the SR (Lakatta and Orchard, 1985). More severe cardiac hypertrophy is accompanied by inefficient Ca^{2+}-induced Ca^{2+} releases with slower and smaller releases (Fig. 3C) (Gomez *et al.*, 1997; Jones *et al.*, 1998). Such altered kinetics of Ca^{2+}-induced Ca^{2+} release may be related to redox status of the cell as both senescence and cardiac hypertrophy/failure have been shown to be accompanied by altered cellular redox state (Singh *et al.*, 1995; Muscari *et al.*, 1996). Studies of isolated cardiac myocytes have also shown that redox reactions can indeed alter I_{Ca}-induced Ca^{2+} transients. As discussed above, it is generally observed that oxidants elicit a transient augmentation of Ca^{2+}-induced Ca^{2+} release (Fig. 3D) followed by decreased Ca^{2+} transients (Fig. 3E). Furthermore, myocytes with intracellularly incorporated high concentrations of reduced thiols such as GSH (10 m*M*) and DTT (2 m*M*) exhibit attenuated Ca^{2+}-induced Ca^{2+} release (Fig. 3F). Therefore, alterations of cellular redox state occurring during aging, cardiac hypertrophy, heart failure, and ischemia-reperfusion injury could lead to altered kinetics of Ca^{2+}-induced Ca^{2+} release, which may upregulate excitation-transcription coupling during the cardiac cycle.

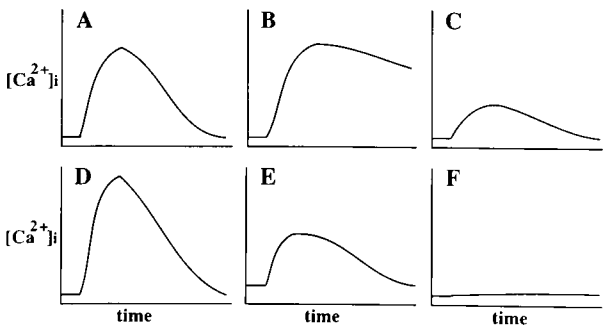

FIG. 3. Depolarization-induced Ca^{2+}-release transients in cardiac myocytes. A. Normal myocytes. **B.** Senescent myocyte (Lakatta, 1993). **C.** Hypertrophied myocytes (Gomez *et al.*, 1997; Jones *et al.*, 1998). **D.** Myocytes exposed to H_2O_2 for 1 min (Goldhaber and Liu, 1994). **E.** Myocytes exposed to H_2O_2 for 5 min (Goldhaber and Liu, 1994). **F.** Myocytes with intracellularly incorporated DTT (Suzuki *et al.*, 1998).

Are there signaling circuits between the SR and the nucleus? In cultured neonatal rat ventricular myocytes, electrical stimulation has been shown to elicit induction of atrial natriuretic factor (ANF) and myosin light chain-2 gene expression (McDonough and Glembotski, 1992). ANF expression by electrical stimulation was shown to be inhibited by nifedipine or W-7, suggesting the involvement of the dihydropyridine (DHP) receptor and calmodulin (McDonough and Glembotski, 1992). Further studies implicate a critical role for calmodulin-dependent protein kinase II (McDonough *et al.*, 1994), JNK, c-*jun*, serum response factor, and Sp1 in this signaling cascade (McDonough *et al.*, 1997).

Recently, Molkentin *et al.* (1998) have demonstrated that adult transgenic mouse hearts expressing constitutively active mutant of calcineurin (Ca^{2+}-dependent protein phosphatase) develop cardiac hypertrophy, suggesting that, in adult cardiac muscle, Ca^{2+} can elicit gene expression. Moreover, overexpression of calsequestrin (the Ca^{2+}-binding protein of the SR) also induces cardiac hypertrophy in transgenic mice (Jones *et al.*, 1998), directly implicating the existence of a signaling pathway between the Ca^{2+}-signaling cascade and the nucleus. Studies by Molkentin *et al.* (1998) have identified an important cardiac muscle signaling pathway through the Ca^{2+}-calcineurin-NFAT3-GATA4 pathway in which Ca^{2+}/calmodulin-activated calcineurin dephosphorylates NFAT3, allowing it to migrate into the nucleus to promote protein–protein interactions with GATA4, thus activating GATA-mediated gene transcription. Because NFAT is activated by slow and sustained Ca^{2+} influx (Dolmetsch *et al.*, 1997), activation of such noncontractile pathways for Ca^{2+} may result in cardiac hypertrophy. Indeed, in calsequestrin-overexpressing hearts, it was found that Ca^{2+} release and uptake kinetics in response to depolarization signals were extremely slower and more sustained compared to normal rapidly

decaying Ca^{2+} transients (Jones *et al.*, 1998). In such mice, we found that DNA-binding activities of GATA and NFAT were upregulated (Suzuki *et al.*, 1999b), suggesting the possibility that altered kinetics of Ca^{2+}-induced Ca^{2+} release may elicit excitation-transcription coupling.

REDOX REGULATION OF EXCITATION-TRANSCRIPTION COUPLING

To provide evidence that altered kinetics of depolarization-induced Ca^{2+} release by oxidation of the SR Ca^{2+}-release apparatus diverts the contractile pool of Ca^{2+} to signal the excitation-transcription coupling cascade, effects of oxidants on depolarization-induced gene transcription were investigated in cultured cardiac myocytes. In neuronal cells, KCl depolarization signals have been shown to elicit cell growth signals such as the activation of MAP kinase and serum response factor (Rosen *et al.*, 1994). In sharp contrast, depolarization of cultured cardiac myocytes with 50 m*M* KCl did not elicit cell growth signaling, suggesting that cardiac myocytes have developed signaling mechanisms to suppress the excitation-transcription coupling cascade during normal excitation-contraction coupling events. However, when myocytes were pretreated with oxidants such as H_2O_2, KCl exposure activated the DNA-binding activity of GATA4 (Fig. 4), consistent with the idea that oxidant-mediated alterations of Ca^{2+}-induced Ca^{2+} release may divert the contractile pool of Ca^{2+} to elicit excitation-transcription coupling (Fig. 5).

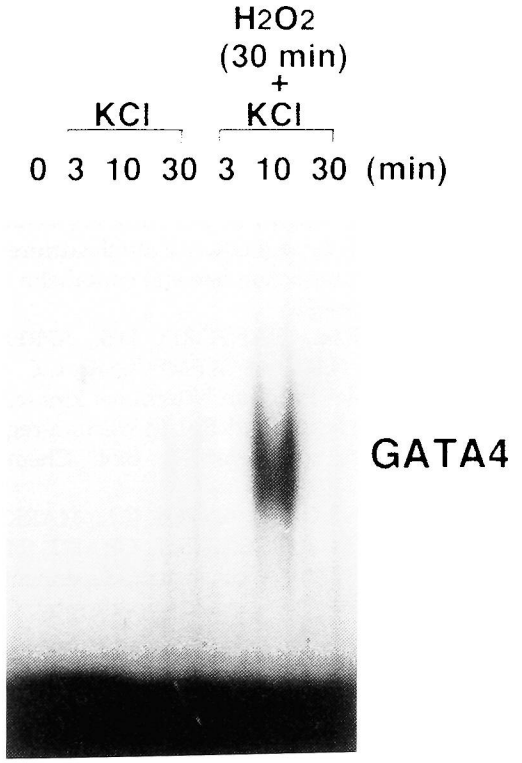

FIG. 4. H_2O_2 treatment elicits KCl depolarization-induced GATA4 activation. Treatment of cardiac myocytes with 50 m*M* KCl for 3, 10, or 30 min did not induce GATA4 activation. GATA4 was activated when cells were pretreated with H_2O_2 (100 μM) for 30 min and then treated with KCl for 10 min.

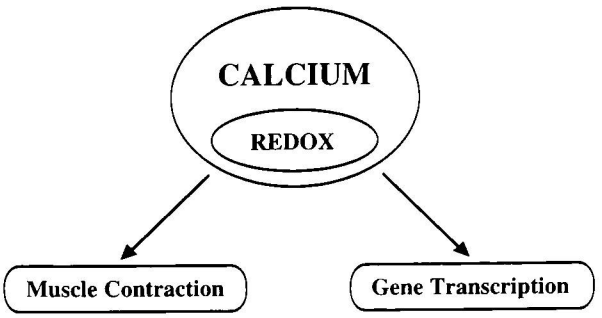

FIG. 5. Scheme depicting redox regulation of Ca^{2+} signaling for cardiac muscle contraction and gene transcription.

It has been proposed that biological oxidants may serve as signaling molecules (Suzuki *et al.*, 1997). Specifically, the potential roles of ROS as second messengers have been demonstrated in a variety of biological systems. The second messenger theory implicates the requirement of oxidants in a given signal transduction pathway. In addition to such roles of ROS, we propose that biological oxidants regulate divergence/convergence mechanisms within the signal transduction network. Specifically, in cardiac myocytes, ROS appear to divert Ca^{2+} signaling of the contractile pathway to the gene transcription pathway by altering the specificity of Ca^{2+} signaling.

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ABBREVIATIONS

ANF, atrial natriuretic factor; DTT, dithiothreitol; GSH, glutathione, reduced form; H_2O_2, hydrogen peroxide; I_{Ca}, Ca^{2+} current; ROS, reactive oxygen species, RyR, ryanodine receptor; SR, sarcoplasmic reticulum.

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