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Forum Minireview

Calmodulin and Cyclic ADP-Ribose Interaction in Ca^{2+} Signaling Related to Cardiac Sarcoplasmic Reticulum: Superoxide Anion Radical-Triggered Ca^{2+} Release

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ABSTRACT

Reactive oxygen species (ROS) are often shown to damage cellular functions. The targets of oxidative damage depend on the nature of ROS produced and the site of generation. In contrast, ROS can also regulate signal transduction. In this case, ROS may either induce or enhance events, which lead to forward directions of cellular signaling. The consequences of regulation of signal transduction can be observed in physiological processes such as muscle contraction. Here, we discuss the concentration-dependent effects of superoxide anion radical ($\cdot O_2^-$) on Ca^{2+} release from the cardiac sarcoplasmic reticulum (SR). Recent studies suggest that the ADP-ribosyl cyclase pathway, through its production of cyclic adenosine 5'-diphosphoribose (cADPR), may control Ca^{2+} mobilization in cardiac muscle cells. $\cdot O_2^-$ has dual effects that are concentration dependent. At low concentrations (nearly nanomolar levels), $\cdot O_2^-$ induces Ca^{2+} release by stimulating synthesis of cADPR, which requires calmodulin for sensitization of ryanodine-sensitive Ca^{2+}-release channels (RyRC). At these low concentrations, $\cdot O_2^-$ is responsible for regulation of cellular signal transduction. At higher concentrations (micromolar levels), $\cdot O_2^-$ produces a loss in the function of calmodulin that is to inhibit RyRC. This results in an increase in Ca^{2+} release, which is linked to cell injury. The difference in the functions of low and high concentrations of $\cdot O_2^-$ may result in two distinct physiological roles in cardiac muscle Ca^{2+} signaling. Antiox. Redox Signal. 2, 47–54.

REACTIVE OXYGEN SPECIES AND CELL INJURY AND REGULATION REPERTOIRE

CELLULAR REDOX HOMEOSTASIS determines minute-to-minute alterations in cellular integrity (Engelhardt, 1999). In addition potentially to mediating direct structural and functional damage to carbohydrates, lipids, proteins, and nucleic acid, oxygen radicals affect such protean processes as cellular stress responses (Huang *et al.*, 1994; Polla *et al.*, 1996), intracellular signaling (Lander *et al.*, 1995; Berlett *et al.*, 1996), membrane perturbation and depolarization (Orrenius *et al.*, 1992), nuclear transcription factor regulation (Flohe *et al.*, 1997), genomic redox-responsive element alterations (Gaudu *et al.*, 1997), vascular tone maintenance (Todoki *et al.*, 1992; Wada and Okabe, 1997; Mizukawa and Okabe, 1997; Norisue *et al.*, 1997), and even apoptosis (Hansson *et al.*, 1996) and/or cell lysis (Geeraerts *et al.*, 1991).

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Endogenous as well as exogenous alteration in the flux of oxygen radicals can have profound influences on the initiation, course, and extent of cellular perturbation induced by the full spectrum of disease.

Sources of oxyradical stress are numerous: Univalent electron bleed from the mitochondrial electron transport chain occurs as part of normal respiration but is enhanced in the setting of ischemia-reperfusion, sepsis, and direct mitochondrial damage (Nohl and Jordan, 1986). Phagocyte activation leads to induction of the respiratory burst and specifically NADPH oxidoreductase, which leads to microexplosions of superoxide anion ($^{\cdot}O_2^-$) production, which can be further metabolized to a variety of other toxic compounds including hydrogen peroxide (H_2O_2), hydroxyl radical ($HO^{\cdot}$), hypochlorous acid, and chloroamines (Chanock *et al.*, 1994). Although such species represent key elements in a normal host inflammation defense system, inadvertent release of such compounds into the host milieu would be expected to augment autoinjury. In the setting of ischemia-reperfusion, xanthine dehydrogenase, which normally utilizes $NADP^+$ as an electron acceptor, is converted to xanthine oxidase with the corresponding capacity to utilize oxygen as an electron acceptor. During the ischemic period, high-energy phosphate bonds are hydrolyzed to extract every morsel of chemical energy available, and, as a result, there is an accumulation of the purine catabolites xanthine and hypoxanthine. Subsequently during reperfusion, with reintroduction of oxygen back into the system, there is a burst of $^{\cdot}O_2^-$ as well as H_2O_2 production (Granger, 1988). It should be appreciated that the conversion of xanthine dehydrogenase to xanthine oxidase can also occur as an aspect of inflammation secondary to exposure of enzyme to proteases such as neutrophil elastase. Eicosanoid metabolism represents another potent source of oxyradicals (Okabe *et al.*, 1985; Kukreja *et al.*, 1986). Specifically, during the conversion of prostaglandin G_2 to prostaglandin H_2 there is stoichiometric production of $^{\cdot}O_2^-$. Moreover, a number of other reactions in both the lipoxygenase as well as cyclooxygenase pathways produce highly reactive peroxy lipid intermediates. A number of other important sources for the production of $^{\cdot}O_2^-$ also exist, including various other electron transport chains (*e.g.*, cytochrome P_{450}), autoxidation reactions, and redox cycling (Cross and Jones, 1991).

Although respiration allows efficient production of ATP, the price paid for this aerobic efficiency is constant bombardment by reactive oxygen species (ROS). Accordingly, it is not surprising that the body has evolved a number of sophisticated, interrelated antioxidant mechanisms to maintain redox homeostasis within the cell. These antioxidant compounds may be classified into high-molecular-weight species, which include the enzymes superoxide dismutase, catalase, and glutathione peroxidase, and lower-molecular-weight species, including α-tocopherol, ascorbic acid, uric acid, bilirubin, glutathione (and related sulfhydryl congeners including lipoic acid), and β-carotene (Zimmerman, 1995).

ROS can be generated in response to interactions between various ligands such as hormones, growth factors, cytokines, and their receptors, and ligand-mediated signal transduction has been able to be blocked by antioxidants (Suzuki *et al.*, 1997). Further, ROS can cause Ca^{2+}-dependent activation of stress-activated protein kinase/C-Jun amino-terminal kinase classified into the MAP kinase family (Inanami *et al.*, 1999). Therefore, ROS may not be merely damage-causing agents, but may also be mediators of physiological functions such as by serving as second messengers.

Two principal pathways of Ca^{2+} release from the sarcoplasmic reticulum (SR) of excitable and nonexcitable cells have been described: One pathway is dependent on the second messenger, D-*myo*-inositol 1,4,5-trisphosphate (IP_3) and a second pathway is regulated by Ca^{2+} and sensitive to caffeine and ryanodine (Galione *et al.*, 1991; McPerson and Campbell, 1993). In addition to promoting IP_3 formation, agonists can also induce pathways that activate the ryanodine-sensitive Ca^{2+}-release channel (RyRC) (Stauderman and Murawsky, 1991). During cardiac muscle excitation-contraction coupling, this channel is activated in response to an increase in intracellular Ca^{2+} (*i.e.*, Ca^{2+}-induced Ca^{2+}-release). Furthermore, the β-nicoti-

namide-adenine dinucleotide (β-NAD^+) metabolite, cyclic adenosine 5′-diphosphoribose (cADPR), may also function as an additional Ca^{2+}-mobilizing messenger (Dargie *et al.*, 1990). It is the purpose of the present paper to convince the readers that one of the roles of $^{\cdot}O_2^-$ anion radical in cardiac muscle is to regulate $Ca_2{}^+$-signal transduction by modulating cADPR actions on the SR.

ROS AND SR FUNCTION

The rise in cytoplasmic Ca^{2+}, identified first as the trigger of muscle contraction (Heilbrunn and Wiercinski, 1947), is now recognized as a universal signal that controls numerous processes in all eukaryotic cells. The similar recognition that Ca^{2+} is stored in and released from both the SR of muscle (Ebashi and Endo, 1968) and the endoplasmic reticulum (ER) of nonmuscle cells (Somlyo, 1984; Pozzan *et al.*, 1994) led to major questions still being asked about the identity of the molecular mechanisms of Ca^{2+} release from the SR/ER (Somlyo and Somlyo, 1994; Berridge, 1997). Release of Ca^{2+} from the SR/ER can be triggered by the binding of the second messenger IP_3 to the IP_3 receptor/Ca^{2+} release channel (for review, see Berridge, 1993). It also can be mediated by the RyRC in response to a surface membrane action potential during the excitation-contraction coupling in cardiac and skeletal muscle.

Depending upon concentrations, ryanodine can either stimulate or inhibit Ca^{2+} efflux from isolated cardiac (Okabe *et al.*, 1991) and skeletal (Meissner, 1986a) SR membrane vesicles. These effects are consistent with single-channel experiments where micromolar concentrations of ryanodine "lock" the channel into a reduced-conductance, high-open probability (P_o) state, and millimolar concentrations lead to irreversible channel closure (Lai *et al.*, 1989; Kawakami and Okabe, 1998).

A study (Mészáros *et al.*, 1993) suggests that cADPR can release intracellular Ca^{2+} in a variety of mammalian cells including cardiac myocytes. An isoform of ADP-ribosyl cyclase, the enzyme responsible for cADPR synthesis, has been purified from the ovotestis of the marine mollusc *Aplysia californica* (Lee and Aarhus, 1991), and subsequently cloned (Glick *et al.*, 1991). A homologous enzyme with dual ADP-ribosyl cyclase and cADPR hydrolase activities is widely expressed in the plasma membrane of mammalian cells (Rusinko and Lee, 1989) and is similar or identical to the human leukocyte antigen CD38 (States *et al.*, 1992). CD38 has been cloned from human insulinoma (Takasawa *et al.*, 1993) and rat pancreatic islets (Koguma *et al.*, 1994). Expression of CD38 in CDS1 cells leads to cADPR-sensitive Ca^{2+} release (Summerhill *et al.*, 1993).

At present, there is much interest in the possibility that cADPR may be an endogenous regulator of one or more isoforms of the RyRC. However, cADPR may not bind directly to RyRC but to accessory proteins, probably calmodulin, that may couple cADPR to channel activation (Lee *et al.*, 1994). Consistent with this notion, 8-amino-cADPR, which acts as a selective cADPR antagonist, does not block caffeine- or ryanodine-induced Ca^{2+} release (Walseth and Lee, 1993).

ROS have been shown to stimulate Ca^{2+} signaling by increasing the cytosolic Ca^{2+} concentration, suggesting a possible physiological role of ROS in the regulation of Ca^{2+} signaling. The exact source of Ca^{2+} release in response to ROS remains controversial, and precise molecular targets of ROS have not yet been defined. Enhanced Ca^{2+} transport through Ca^{2+} channels as well as the inhibition of Ca^{2+} pumps occur in the presence of ROS, and these macromolecules may be possible target sites of ROS to elicit Ca^{2+} signaling. The cardiac RyRC is redox-sensitive and has become an excellent model to understand how biological molecules may be regulated by redox reactions. The RyRC complex consists of ryanodine receptor, FK506-binding protein, and other associated molecules such as triadin, junctin, calsequestrin, and calmodulin (Coronado *et al.*, 1994; Zhang *et al.*, 1997). We have studied the influence of ROS on RyRC in cardiac junctional SR preparations. Selective activation of RyRC by $^{\cdot}O_2^-$ was found to depend on the presence of calmodulin and calmodulin was identified as a functional mediator of $^{\cdot}O_2^-$-triggered Ca^{2+} release through the RyRC (Kawakami and Okabe, 1998).

SUPEROXIDE ANION RADICAL AND MODULATION OF Ca^{2+} RELEASE

Calmodulin

Calmodulin is a ubiquitous Ca^{2+}-binding protein. Seiler *et al.* (1984) first observed that calmodulin was associated with high-molecular-weight proteins in the SR, later identified as the RyRC. Calmodulin inhibited Ca^{2+}-, caffeine-, and AMP-induced Ca^{2+} releases from the cardiac and skeletal muscle SR. The concentration of calmodulin required to inhibit 50% of the Ca^{2+} release was ~0.1–0.2 μmol/liter (Meissner, 1986b). The inhibitory action of calmodulin was observed in the absence of ATP, suggesting that calmodulin-dependent kinases were not involved. In single-channel experiments performed with skeletal or cardiac channels, 2 μmol/liter calmodulin reversibly decreased channel P_o. The action was Ca^{2+} dependent and ATP independent. A strong argument against an essential role for calmodulin in RyRC inactivation is that we noted only a partial reduction of the Ca^{2+} release rate by calmodulin (Kawakami and Okabe, 1998). This observation leads us to propose that a predominant role of calmodulin in excitation-contraction coupling may be modulation of RyRC function.

Evidence has been accumulated to support the requirement of calmodulin for the Ca^{2+}-releasing activity of $^{\cdot}O_2^-$ (Okabe *et al.*, 1987, 1989, 1991; Kawakami and Okabe, 1998). It was also suggested that $^{\cdot}O_2^-$ can activate RyRC by displacing calmodulin from the SR. This effect is observed at higher concentrations of $^{\cdot}O_2^-$ (micromolar levels) (Kumasaka *et al.*, 1999), possibly due to degradation of calmodulin molecules. However, at lower concentrations of $^{\cdot}O_2^-$ (nearly nanomolar levels), calmodulin stimulates Ca^{2+} release elicited by $^{\cdot}O_2^-$ (Kumasaka *et al.*, 1999), suggesting that calmodulin may sensitize the Ca^{2+} release mechanism of endogenous RyRC stimulator(s) that can be activated by $^{\cdot}O_2^-$ anion radicals.

Cyclic ADP-ribose

cADPR is a novel candidate for the mediator of Ca^{2+} release from intracellular Ca^{2+} stores (Dargie *et al.*, 1990). A functional role for cADPR as a mediator of RyRC has not been established in many tissues, although the enzymatic machinery for its synthesis is present. The enzyme responsible for synthesizing cADPR has been found in the heart (Walseth *et al.*, 1991) by monitoring the ability to synthesize cADPR from β-NAD^+ in the sea urchin homogenate Ca^{2+}-release system (Lee and Aarhus, 1991). Furthermore, nuclear magnetic resonance (NMR) and mass spectroscopic analyses have identified the active principle in these extracts as cADPR (Ruskino and Lee, 1989). Basal levels of cADPR in cardiac muscle estimated to be between 100 and 200 nmol/liter. Mészáros *et al.* (1993) reported that cADPR increases the P_o of cardiac RyRC incorporated into planar phospholipid bilayers. On the basis of these results, it has been claimed that cADPR can trigger the release of Ca^{2+} from the SR in cardiac cells at resting (diastolic) $[Ca^{2+}]$ (Mészáros *et al.*, 1993). It has been reported that cADPR had no apparent effect in intact rat ventricular myocytes (Guo *et al.*, 1996), although this may be a temperature-related effect (Iino *et al.*, 1997). It appears that an action of cytosolic cADPR to activate cardiac RyRC may be influenced by temperature, leading to a possible explanation of the failure to detect actions of cADPR in some previous experiments.

Analogues of β-NAD^+ in which various groups have been substituted at the 8-position of the adenine ring are also substrates for ADP-ribosyl cyclases, yielding the corresponding 8-substituted cADPR (Walseth and Lee, 1993). These analogues have been demonstrated to be competitive antagonists of cADPR-induced Ca^{2+} release and to compete with [^{32}P]cADPR binding at the sea urchin egg microsomal binding site (Walseth and Lee, 1993). Of these, 8-amino-cADPR is the most potent antagonist. $^{\cdot}O_2^-$ radicals at low concentrations were shown to stimulate calmodulin-, β-NAD^+-, and cADPR-sensitive and 8-amino-cADPR-inhibitable decrease in SR Ca^{2+} uptake rate (by increasing Ca^{2+} efflux through RyRC) in heart homogenate (Kumasaka *et al.*, 1999). In addition, when the homogenate was incubated with $^{\cdot}O_2^-$ (at concentrations near nanomolar levels), conversion of β-NAD^+ into cADPR was also stimulated (Kumasaka *et al.*, 1999). Therefore,

cardiac muscle homogenates possess ADP-ribosyl cyclase activity, and $^{\cdot}O_2^-$ can stimulate Ca^{2+} release from the SR by increasing cADPR synthesis. The cardiac SR immediately upon addition of authentic cADPR, but not β-NAD^+, did exhibit Ca^{2+} release stimulation, implying that the SR by itself does not possess ADP-ribosyl cyclase activity.

The ability of cADPR to stimulate RyRC appears to depend on calmodulin, because the effect of cADPR was enhanced by calmodulin in native SR vesicles, however, cADPR lost its ability in EGTA-washed calmodulin-depleted SR vesicles (Kumasaka *et al.*, 1999).

CONCLUSIONS

In recent years much progress has been made in our understanding of the mechanisms regulating intracellular Ca^{2+} homeostasis. The Ca^{2+}-induced Ca^{2+} release mechanism involves gating of the RyRC by increased intracellular Ca^{2+}, which in turn releases Ca^{2+} from the SR. Recent work suggests that the ADP-ribosyl cyclase pathway through its production of cADPR may control Ca^{2+} mobilization in cells. $^{\cdot}O_2^-$ anion radicals, which can interact with certain molecules with sufficient selectivity, may play a role in cell signaling processes.

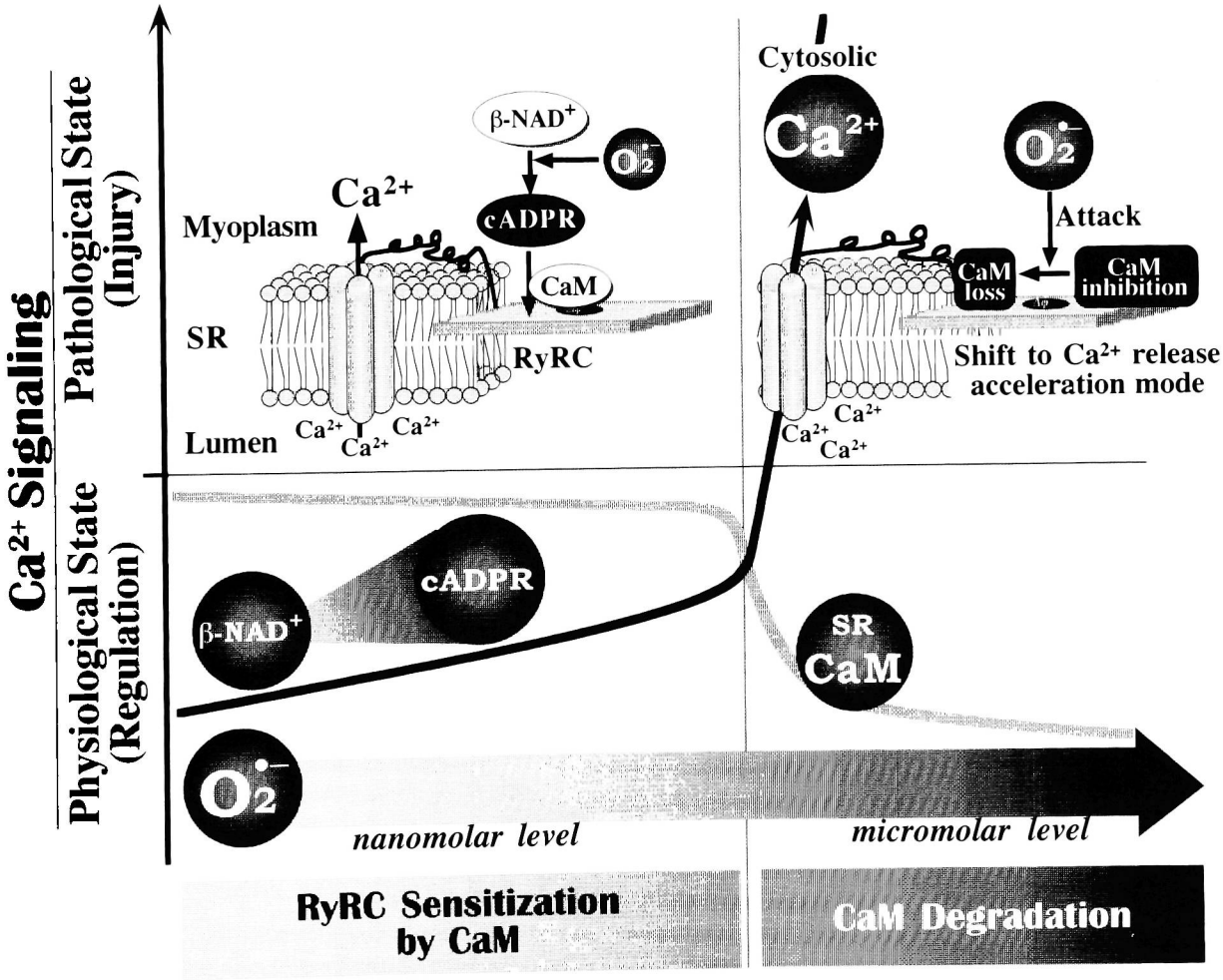

FIG. 1. Working model for Ca^{2+}-signaling *via* the RyRC triggered by $^{\cdot}O_2^-$ anion radicals, and the distinction between cell regulation and injury with respect to the concentration of $^{\cdot}O_2^-$. Two phases of $^{\cdot}O_2^-$-induced Ca^{2+} release (cADPR-dependent and in response to the loss in function of calmodulin) from cardiac SR are depicted. $^{\cdot}O_2^-$ radicals can elicit different responses depending on its concentrations. We postulate a two-step process of the effect of $^{\cdot}O_2^-$; one is cADPR synthesis stimulation that can activate the Ca^{2+}-release mechanism when it is in a sensitized state by the presence of calmodulin (at physiological $^{\cdot}O_2^-$ concentration levels), and another is the direct calmodulin interaction by which $^{\cdot}O_2^-$ radicals produce a loss in inhibitory function of calmodulin (at higher $^{\cdot}O_2^-$ concentrations) thereby inducing pathological Ca^{2+} release.

$^{\cdot}O_2^-$ radicals have dual effects on stimulation of cardiac RyRC that are concentration dependent. $^{\cdot}O_2^-$ at low concentrations induces Ca^{2+}release (physiologically) by stimulating synthesis of cADPR whose action requires calmodulin. At higher concentrations, $^{\cdot}O_2^-$ produces a loss in function of calmodulin, thereby increasing Ca^{2+} release (Fig. 1). Experiments are yet needed to determine the concentration-dependent mechanisms of $^{\cdot}O_2^-$ for physiology of Ca^{2+} mobilization and cADPR-mediated Ca^{2+}-signaling in myocardium. It is important to distinguish between physiological regulation and cell damage with respect to the concentrations of $^{\cdot}O_2^-$ anion radicals.

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ABBREVIATIONS

cADPR, Cyclic adenosine 5′-diphosphoribose; ER, endoplasmic reticulum; H_2O_2, hydrogen peroxide; $HO^{\cdot}$, hydroxyl radical; IP_3, D-*myo*-inositol 1,4,5-trisphosphate; β-NAD^+, β-nicotinamide-adenine dinucleotide; $^{\cdot}O_2^-$, superoxide anion radical; P_o, open probability; ROS, reactive oxygen species; RyRC, ryanodine-sensitive Ca^{2+}-release channel; SR, sarcoplasmic reticulum.

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