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Voltage-gated Ca^{2+} entry and ryanodine receptor Ca^{2+}-induced Ca^{2+} release in preglomerular arterioles

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Fellner SK, Arendshorst WJ. Voltage-gated Ca^{2+} entry and ryanodine receptor Ca^{2+}-induced Ca^{2+} release in preglomerular arterioles. *Am J Physiol Renal Physiol* 292: F1568–F1572, 2007. First published December 26, 2006; doi:10.1152/ajprenal.00459.2006.—We have previously shown that in afferent arterioles, angiotensin II (ANG II) involves activation of the inositol trisphosphate receptor (IP_3R), activation of adenine diphosphoribose (ADPR) cyclase, and amplification of the initial IP_3R-stimulated release of cytosolic Ca^{2+} ($[Ca^{2+}]_i$) from the sarcoplasmic reticulum (SR) (Fellner SK, Arendshorst WJ. *Am J Physiol Renal Physiol* 288: F785–F791, 2004). The response of the ryanodine receptor (RyR) to local increases in $[Ca^{2+}]_i$ is defined as calcium-induced calcium release (CICR). To investigate whether Ca^{2+} entry via voltage-gated channels (VGCC) can stimulate CICR, we treated fura 2-loaded, freshly isolated afferent arterioles with KCl (40 mM; high KCl). In control arterioles, peak $[Ca^{2+}]_i$ increased by 165 ± 10 nM. Locking the RyR in the closed position with ryanodine (100 μM) inhibited the $[Ca^{2+}]_i$ response by 59% ($P < 0.01$). 8-Br cADPR, a specific blocker of the ability of cyclic ADPR (cADPR) to sensitize the RyR to Ca^{2+}, caused a 43% inhibition. We suggest that the lower inhibition by 8-Br cADPR ($P = 0.02$, ryanodine vs. 8-Br cADPR) represents endogenously active ADPR cyclase. Depletion of SR Ca^{2+} stores by inhibiting the SR Ca^{2+}-ATPase with cyclopiazonic acid or thapsigargin blocked the $[Ca^{2+}]_i$ responses to KCl by 51% (P not significant vs. ryanodine or 8-Br cADPR). These data suggest that about half of the increase in $[Ca^{2+}]_i$ induced by high KCl is accomplished by activation of CICR through the ability of entered Ca^{2+} to expose the RyR to high local concentrations of Ca^{2+} and that endogenous cADPR contributes to the process.

renal microcirculation; cyclic adenine diphosphoribose; afferent arteriole

CALCIUM-INDUCED CALCIUM RELEASE (CICR) is classically defined as the response of the ryanodine receptor (RyR) to a local increase in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$). An abrupt increase in $[Ca^{2+}]_i$, following activation of the inositol trisphosphate receptor (IP_3R) (2, 16) activates the RyR, and in conjunction with cyclic ADPR (cADPR), further increases $[Ca^{2+}]_i$ to augment the original signal (13, 35). We have previously shown that angiotensin II (ANG II) stimulation of isolated, fresh afferent arterioles causes the activation of the IP_3R, a burst of $[Ca^{2+}]_i$, and subsequent release of Ca^{2+} from the sarcoplasmic reticulum (SR) via the RyR (10). We have further shown that stimulation of adenine diphosphoribose cyclase (ADPR cyclase) and the formation of cADPR act to enhance CICR (10).

Many, if not all G protein-coupled receptor constrictor agonists of preglomerular resistance vessels result in mobilization of Ca^{2+} from the SR and in Ca^{2+} entry via voltage-gated L-type channels (VGCC), store-operated (SOC), and possibly receptor-operated (ROC) Ca^{2+} entry channels (4, 6, 12, 26). Whereas the interactions of some Ca^{2+} mobilization and entry pathways have been studied in several cell types, there are only a few studies regarding the role of CICR in resistance vessels in general or the renal microcirculation in particular. In β-escin-permeabilized renal arterial smooth muscle cells, tetracaine, a blocker of the RyR, inhibited the $[Ca^{2+}]_i$ response to cADPR by 70% (30).

Given that the trigger for CICR is thought to be a local increase in $[Ca^{2+}]_i$ near the RyR, we asked the question whether Ca^{2+} entry via VGCC would similarly result in CICR. It is likely that the SR is spatially close to the plasma membrane, thus affording a local or microdomain of increased $[Ca^{2+}]_i$ to activate the RyR (1, 24). In bovine coronary arteries, KCl and Bay K8644 dose dependently cause vasoconstriction (14). Nicotinamide, an inhibitor of ADPR cyclase, blocks the vasoconstriction by ~70%. 8-Br cADPR, a cell-permeant inhibitor of the action of cADPR on the RyR, inhibits the $[Ca^{2+}]_i$ response to high KCl in bovine coronary vascular smooth muscle cells (VSMC) (34). A study in the isolated, perfused hydronephrotic kidney showed that stimulation of voltage-dependent Ca^{2+} entry channels with Bay K8644 causes oscillations in the diameter of the afferent arteriole. These oscillations are obliterated by the SR Ca^{2+}-ATPase inhibitor thapsigargin or by treatment with ryanodine (10 μM) (29). These data suggest that a functional RyR and adequate SR Ca^{2+} stores are required for oscillations to occur. In the rat tail artery, nicotinamide reduces the vasoconstrictive response to high KCl (19). Closing of the RyR with ryanodine (30 μM) inhibits the $[Ca^{2+}]_i$ response to membrane depolarization (−30 mV) in cerebral VSMC (21). Ryanodine (100 μM) and ruthenium red, an inhibitor of the RyR, diminish the Ca^{2+} response to KCl in pancreatic β cells, supporting a role for CICR in Ca^{2+} signaling in these cells (23). An examination of the of L-type and N-type VGCC in PC12 cells demonstrated the participation of the RyR and CICR following stimulation with Bay K8864 (31).

We investigated the potential contribution of CICR to the global $[Ca^{2+}]_i$ response of membrane depolarization with KCl in afferent arterioles. To block the function of the RyR, we pretreated vessels with a high concentration of ryanodine. We utilized the specific inhibitor 8-Br cADPR to antagonize the effect of endogenous cADPR. To further define the contribution of CICR to the $[Ca^{2+}]_i$ response to high KCl, we depleted SR Ca^{2+} stores with thapsigargin or with cyclopiazonic acid (CPA).

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METHODS

All studies were approved by and performed in compliance with the guidelines and practices of the University of North Carolina at Chapel Hill Institutional Animal Care and Use Committee.

Preparation of fresh afferent arterioles. We used the magnetized polystyrene microsphere-sieving technique as previously described in our laboratory to isolate afferent arterioles (<20 μm in diameter) from 5-wk-old (90–125 g) Sprague-Dawley rats maintained in the Chapel Hill Colony (8, 11). PBS, with the following composition (in mM) 137 NaCl, 4.1 KCl, 0.66 KH_2PO_4, 3.4 Na_2HPO_4, 2.5 $NaHCO_3$, 1.0 $MgCl_2$, and 5 glucose, was adjusted daily to pH 7.4 at 4, 23, and 34°C. The vessel segments in PBS containing 0.1% BSA were treated with collagenase type IV (374 U/mg, 5–7 μg/ml, Worthington) for 18 min at 34° C. Arterioles were loaded with fura 2-AM (3 μM) and 0.1% BSA for 50 min at 23°C in the dark. After the arterioles were washed with PBS, the suspension was kept in Ca^{2+} (1.1 mM)-containing buffer on ice.

Measurement of $[Ca^{2+}]_i$. We measured $[Ca^{2+}]_i$ as previously described (10, 11). Afferent arterioles were identified by their morphology and measured diameter of 15–20 μm. As well, we required visualization of microspheres in the lumen of the afferent arteriole or in the proximal branch of an interlobular artery from which it arose to exclude the possibility that the vessel was an efferent arteriole. A segment of an afferent arteriole was centered in a small window of the optical field that was free of glomeruli or tubular fragments. Some arterioles were sampled close to a branch point whereas others were in the straight, midportion of the vessel. Occasionally, an arteriole was still attached to a glomerulus and was studied a short distance away. Hence, there is heterogeneity of sampling sites along the vessel.

The VSMC were excited alternately with light of 340- and 380-nm wavelength from a dual-excitation wavelength Delta-Scan equipped with dual monochronometers and a chopper (Photon Technology International). After signals were passed through a barrier filter (510 nm), fluorescence was detected by a photomultiplier tube. Signal intensity was acquired, stored, and processed by an IBM-compatible Pentium computer and Felix software (Photon Technology International). Background subtraction was performed in all studies. There was no interruption in the recording during the addition of reagents to the chamber. A video camera projected images of afferent arterioles onto a video monitor, permitting visualization of contraction of vessel segments.

We have previously demonstrated that application of fura 2 and drugs on the abluminal side of the afferent arteriole results in no detectable contribution to the $[Ca^{2+}]_i$ signal from endothelial cells (8).

Reagents. We purchased KCl, CPA, ryanodine, 8-Br cADPR, and thapsigargin from Sigma (St. Louis, MO), fura 2-AM from Molecular Probes (Eugene, OR), and magnetized microspheres from Spherotech (Libertyville, IL).

Statistics. The data are presented as means ± SE. Each data set was derived from afferent arterioles originating from at least three separate experiments, two rats (4 kidneys) per experiment. Individual arterioles were studied only once and then discarded. Paired data for arterioles before and after agonist stimulation were tested with Student's paired *t*-test. Unpaired *t*-tests were employed for comparisons of responses between two groups.

RESULTS

KCl stimulates an increase in $[Ca^{2+}]_i$. Addition of KCl (40 mM) to the bath causes an immediate increase in $[Ca^{2+}]_i$ in afferent arterioles. This concentration of KCl was used in all experiments. Previous work from our laboratory shows that nifedipine totally blocks the $[Ca^{2+}]_i$ response to 50 mM KCl in afferent arterioles (25). Two patterns of responses are seen: a minimal peak plateau or more pronounced peak plateau configuration (Fig. 1, *A* and *B*). Given the heterogeneity of afferent arteriolar sampling sites (near or distant from the glomerulus), it is not surprising that the responses may vary. Based on the methods employed in our study, the baseline $[Ca^{2+}]_i$ is 126 ± 8, the peak 291 ± 16, and the plateau 220 ± 15 nM ($n = 34$, $P < 0.01$, both). The peak difference in $[Ca^{2+}]_i$ from baseline is thus 165 ± 10 nM.

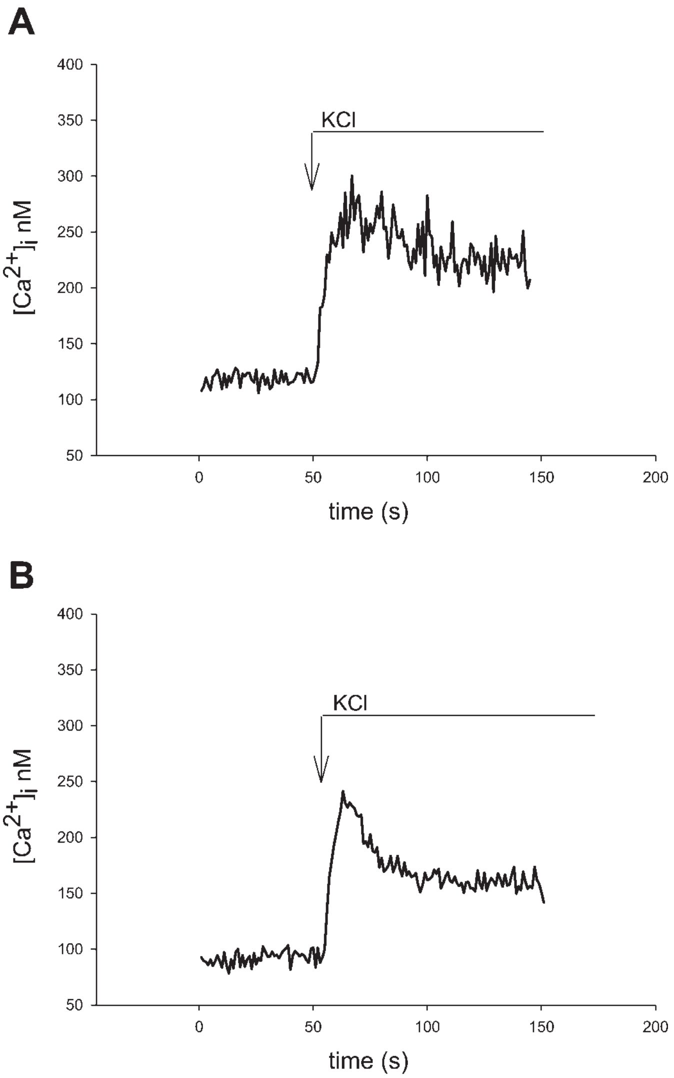

Fig. 1. Cytolsolic Ca^{2+} concentration ($[Ca^{2+}]_i$) response of isolated afferent arterioles to KCl (40 mM). Representative tracings (*A* and *B*) show 2 typical responses, a square wave or a peak-plateau configuration.

Blockade of the RyR diminishes the $[Ca^{2+}]_i$ response to KCl. At high concentrations (>10 μM), ryanodine locks the RyR in the closed position (5, 28). To evaluate the contribution of CICR via the RyR to the $[Ca^{2+}]_i$ response to KCl, we pretreated afferent arterioles with ryanodine (100 μM). We have previously shown that this concentration of ryanodine does not alter baseline $[Ca^{2+}]_i$ (10). In the presence of ryanodine, the peak $[Ca^{2+}]_i$ response to KCl is an increase of 68 ± 14 nM (59% inhibition, $n = 8$, $P < 0.01$ vs. control, Fig. 2). These data clearly indicate that activation of RyR participates in the global $[Ca^{2+}]_i$ response to KCl-induced depolarization in afferent arterioles.

Role of endogenous cADPR in CICR. To assess the participation of endogenous cADPR in the generation of CICR, we

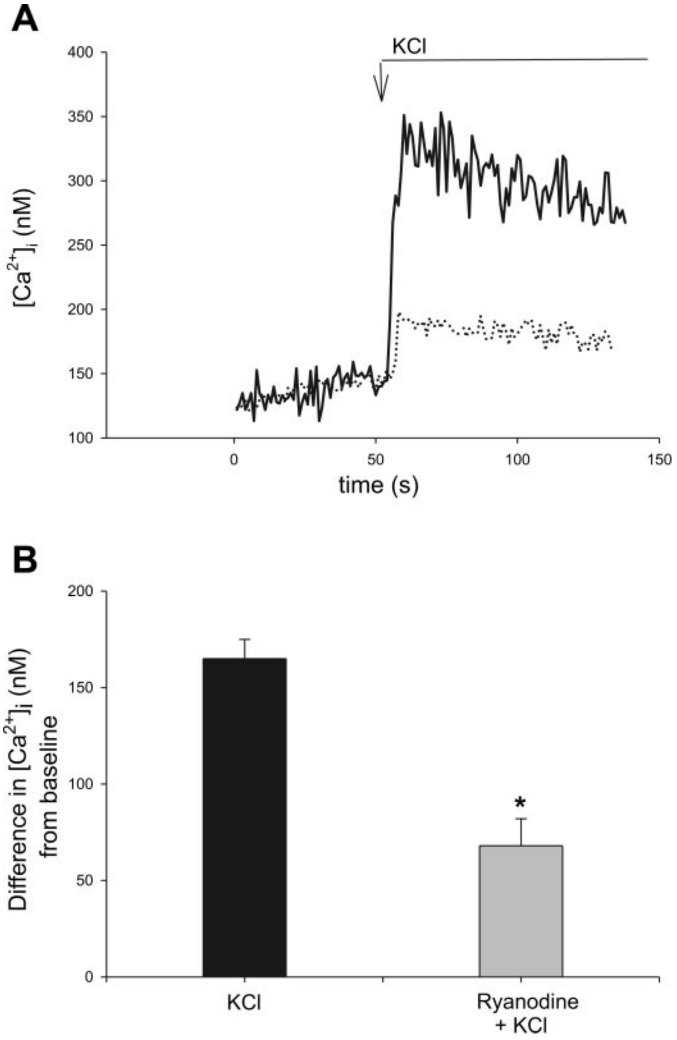

Fig. 2. $[Ca^{2+}]_i$ response to KCl (40 mM) in the presence and absence of ryanodine (100 μM). *A*: representative tracing of the inhibitory effect of ryanodine. *B*: summary data of peak $[Ca^{2+}]_i$ responses. $^*P < 0.01$.

used the cell-permeant, specific antagonist 8-Br cADPR. In the presence of the inhibitor, KCl causes an increase in $[Ca^{2+}]_i$ of 94 ± 7 nM (43% inhibition, $n = 14$, $P < 0.01$ vs. control, $P = 0.02$ vs. ryanodine group, Fig. 3). These data further confirm that the $[Ca^{2+}]_i$ response to KCl involves CICR.

Depletion of SR Ca^{2+} stores. Inhibition of the SR Ca^{2+}-ATPase, by preventing refilling of the SR Ca^{2+} storage pool, depletes the SR of Ca^{2+} and also results in a modest increase in $[Ca^{2+}]$ because of the failure to return $[Ca^{2+}]_i$ to the SR. Thus, even if the RyR is activated, there will be a diminished ability of CICR to occur. We treated afferent arterioles with CPA or with thapsigargin (10 μM, both). There is a relatively small increase in $[Ca^{2+}]_i$ during the 2 min following addition of either inhibitor (37 ± 2 and 22 ± 8 nM, respectively, $n = 6$ for each). Following the addition of KCl, the increase in $[Ca^{2+}]_i$ was reduced to 72 ± 14 and 90 ± 8 nM, respectively (56 and 46% inhibition, mean 51% inhibition, $P < 0.01$ vs. control, Fig. 4). These values are not different from the ryanodine or the 8-Br cADPR data sets ($P > 0.22$ and $P = 0.40$, respectively). Thus any pharmacological interference with the function of CICR in these arterioles causes an ~50% reduction in $[Ca^{2+}]_i$ response. Said another way, CICR is responsible for at least half of the $[Ca^{2+}]_i$ response to KCl-induced membrane depolarization in afferent arterioles.

DISCUSSION

We show for the first time that Ca^{2+} responses to KCl-induced depolarization of afferent arteriolar VSM depends in large measure (~50%) on the ability of entered Ca^{2+} to activate CICR via the RyR. It has long been known that Ca^{2+} entry via VGCC is the major mechanism for Ca^{2+} entry and for contraction of afferent arterioles but considerably less so of cortical efferent arterioles (4, 7, 17). What is not known is the extent to which VCGG interacted with other $[Ca^{2+}]_i$-generating pathways in these resistance vessels.

Utilizing KCl (40 mM) to depolarize afferent arteriolar segments, we note that there is some variation in the configuration of the $[Ca^{2+}]_i$ response. Some vessels were sampled closer to the glomerulus and others close to a branch point. It has previously been shown that branching points of renal resistance vessels are enriched in L-type calcium channels (15). If one assumes that the initial influx of Ca^{2+} is respon-

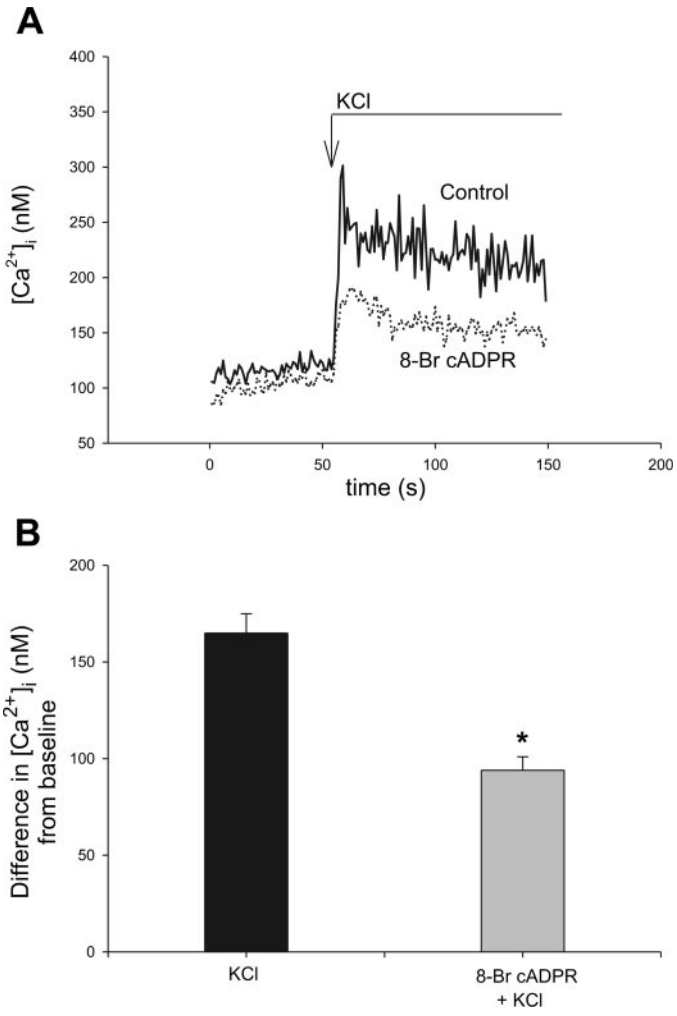

Fig. 3. Inhibitory effect of 8-Br cyclic adenine diphosphoribose (cADPR) on the $[Ca^{2+}]_i$ response to KCl (40 mM) in afferent arterioles. *A*: typical tracings demonstrating the reduction in the $[Ca^{2+}]_i$ response in the presence of 8-Br cADPR. *B*: summary data. $^*P < 0.01$ vs. control.

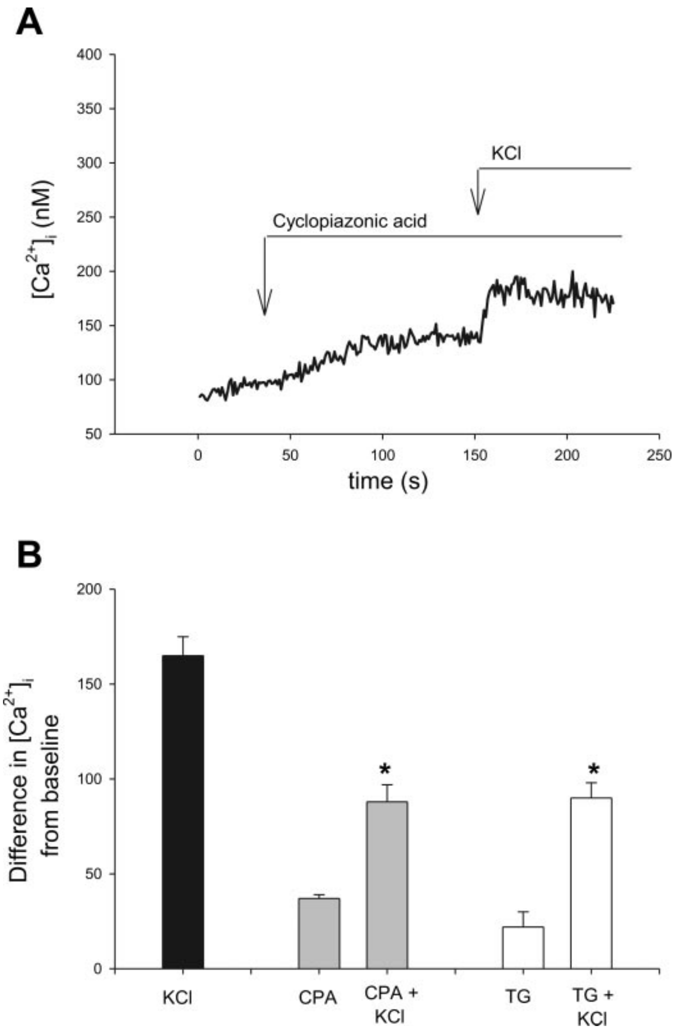

Fig. 4. Depletion of sarcoplasmic reticulum (SR) Ca^{2+} stores with the inhibitors of the SR Ca^{2+}-ATPase cyclopiazonic acid (CPA) or thapsigargin (TG). *A*: representative tracing of the slow rise of $[Ca^{2+}]_i$ following CPA and reduction of the $[Ca^{2+}]_i$ response to KCl (40 mM). *B*: summary data showing that both CPA and TG result in a reduced $[Ca^{2+}]_i$ response to KCl-induced depolarization.

sible for the triggering of CICR, and that both processes then operate together, the density of L-type calcium channels might influence the relationship between the peak and the plateau phase of the response. There is no information on whether there are differences in the distribution of RyRs in renal resistance vessels. Other laboratories have noted similar variations in the $[Ca^{2+}]_i$ response to KCl in preglomerular vessels (3, 32).

Over the past several years, we have explored the role of the ADPR cyclase, cADPR, and RyR pathways in afferent arteriolar VSM (8, 10, 11). Our working model proposes that ANG II and ET-1 activate NAD(P)H oxidase to produce superoxide, which then causes dimerization of ADPR cyclase, the more active form of the enzyme (36, 37). cADPR, by binding to FK binding proteins (FKBP) associated with the RyR, frees the RyR from the inhibitory effect of FKBP and thus greatly enhances the sensitivity of the RyR to Ca^{2+} (33). Our studies provide data to support a linkage between ANG II- or ET-1-induced formation of superoxide and nearly immediate increases in $[Ca^{2+}]_i$ via cADPR and CICR.

A question raised by the current study is the contribution of endogenous levels of cADPR to $[Ca^{2+}]_i$ signaling. We show that antagonism of the effect of cADPR on the RyR with maximally inhibitory concentrations of 8-Br cADPR (10) causes a 43% inhibition of the $[Ca^{2+}]_i$ response to KCl. This contrasts with the 76% inhibition by 8-Br cADPR in ANG II-induced increases in $[Ca^{2+}]_i$ (11). That the extent of inhibition by 8-Br cADPR is less than that achieved by ryanodine suggests, as anticipated, that KCl does not stimulate the formation of cADPR via ADPR cyclase (22). We have no reason to believe that opening of L-type VGCC leads to the formation of superoxide or to the activation of ADPR cyclase. Thus 8-Br cADPR is likely blocking endogenously produced cADPR in the afferent arteriole. There appears to be a detectable basal level of superoxide in unstimulated VSMC. Aortic VSMC has a resting level of superoxide that is almost doubled after the addition of ANG II. Diphenyliodonium not only blocks ANG II-induced formation of reactive oxygen species (ROS) but also diminishes basal ROS (27). In our studies of ANG II- and ET-1-stimulated formation of superoxide, measured with tempo 9 AC, we noted the presence of basal levels of superoxide as well (8, 11). In vivo renal blood flow studies show that apocynin, a blocker of NAD(P)H oxidase, and tempol, a superoxide dismutase mimetic, cause an increase in basal renal blood flow (20). These data strongly suggest that endogenous production of superoxide contributes to basal renal blood flow.

Heretofore, investigators have not implicated "oxidative stress" or changes in ROS as playing a role in the Ca^{2+} signal generated by activation of VGCC. Our new data suggest that in VSMC, when superoxide levels are increased, there will be increased formation of cADPR and enhancement of CICR from the RyR. When one considers the Ca^{2+} signaling pathways involved in the myogenic response (18), the possibility that ischemia or oxidative stress may augment the $[Ca^{2+}]_i$ response to VGCC activation becomes very relevant. As well, the response to ANG II and other constrictor agonists to stimulate Ca^{2+} entry via VGCC in the renal microcirculation would be enhanced. Our growing knowledge of the role of ROS in vascular function may assist us in understanding the pathogenesis of hypertension and subsequent renal damage.

One lesson we have learned from our studies of Ca^{2+} signaling in afferent arteriolar VSMC is that there are complex and exquisite interconnections among each of these mechanistic pathways. No one of them stands alone. We have previously shown that activation of the RyR in preglomerular VSMC causes sufficient depletion of SR Ca^{2+} stores to stimulate SOC (9). Thus activation of VGCC may result in SOC as a consequence of RyR-related CICR.

In summary, we show that about half of the $[Ca^{2+}]_i$ response to KCl-induced depolarization in afferent arterioles is brought about by the effect of entered Ca^{2+} stimulating CICR. Such an increase in $[Ca^{2+}]_i$ in the microdomain between the plasma membrane and the SR would result in "linked Ca^{2+} transport" (24). We also demonstrate the importance of endogenous levels of ADPR cyclase in CICR.

GRANTS

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