Burn injury decreases myocardial Na-K-ATPase activity: role of PKC inhibition

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Horton JW, Tan J, White DJ, Maass DL. Burn injury decreases myocardial Na-K-ATPase activity: role of PKC inhibition. Am J Physiol Regul Integr Comp Physiol 293: R1684–R1692, 2007. First published July 18, 2007; doi:10.1152/ajpregu.00219.2007.—Cardiomyocyte sodium accumulation after burn injury precedes the development of myocardial contractile dysfunction. The present study examined the effects of burn injury on Na-K-ATPase activity in adult rat hearts after major burn injury and explored the hypothesis that burn-related changes in myocardial Na-K-ATPase activity are PKC dependent. A third-degree burn injury (or sham burn) was given over 40% total body surface area, and rats received lactated Ringer solution (4 ml·kg⁻¹·% burn⁻¹). Subgroups of rats were killed 2, 4, or 24 h after burn (n = 6 rats/time period), hearts were homogenized, and Na-K-ATPase activity was determined from ouabain-sensitive phosphate generation from ATP by cardiac sarcolemmal vesicles. Additional groups of rats were studied at several times after burn to determine the time course of myocyte sodium loading and the time course of myocardial dysfunction. Additional groups of sham burn-injured and burn-injured rats were given calphostin, an inhibitor of PKC, and Na-K-ATPase activity, cell Na⁺, and myocardial function were measured. Burn injury caused a progressive rise in cardiomyocyte Na⁺, and myocardial Na-K-ATPase activity progressively decreased after burn, while PKC activity progressively rose. Administration of calphostin to inhibit PKC activity prevented both the burn-related decrease in myocardial Na-K-ATPase and the rise in intracellular Na⁺ and improved postburn myocardial contractile performance. We conclude that burn-related inhibition of Na-K-ATPase likely contributes to the cardiomyocyte accumulation of intracellular Na⁺. Since intracellular Na⁺ is one determinant of electrical-mechanical recovery after insults such as burn injury, burn-related inhibition of Na-K-ATPase may be critical in postburn recovery of myocardial contractile function.

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the postburn period. Burn-injured rats did not display discomfort or pain, moved freely about the cage, and consumed food and water within 15 min after recovery from isoflurane anesthesia. Sham burn-injured rats also received identical regimens of analgesics (buprenorphine) throughout the study period.

**Protein extraction.** Protein extraction of sarcolemmal membranes from rat heart tissue fractionation was carried out as described by Fuller et al. (19). All procedures were performed at 4°C. Rat heart tissue was homogenized with a glass homogenizer in buffer containing (in mM) 20 HEPES, 250 sucrose, 2 EDTA, and 1 MgCl₂, pH 7.4. To isolate a purified sarcolemmal/particulate (SLP) fraction, the resulting homogenate was centrifuged at 10,000 rpm for 20 min. The supernatant containing partially purified SLP fraction was centrifuged again for 30 min at 20,000 rpm, and the resulting pellet was suspended in lysis buffer. This SLP fraction contained sarcolemmal membranes as well as other subcellular components that do not contain Na-K-ATPase, including sarcoplasmic reticulum, nuclei, residual myofilaments, and mitochondria.

**Measurement of PKC activity.** PKC activity was measured in myocardial membrane with a PKC assay kit (Upstate Biotechnology, Lake Placid, NY). Following the manufacturer’s protocol, [γ-32P]ATP (6,000 Ci/mmol stock solution) was used in this study. The reaction mixture included 2.5 μl of reaction buffer, 2.5 μl of PKC substrate, 2.5 μl of freshly sonicated PKC lipid activator, and 50 μg of sample protein. The reaction was initiated by adding 7 μl of the Mg²⁺-ATP cocktail containing [γ-32P]ATP, followed by incubation. The reaction was stopped by transferring 25 μl of the reaction mixture onto the center of a P81 paper square (provided in the assay kit from Upstate Biotechnology). The assay squares were then washed three times for 5 min each with 0.75% phosphoric acid. Finally, the assay squares were washed once with acetone for 3 min and then transferred into scintillation vials; 5 ml of scintillation cocktail was added, and samples were counted with a scintillation counter. PKC activity was calculated as picomoles of phosphate per microgram of protein according to the manufacturer’s suggested protocol.

**Na-K-ATPase methods.** Na-K-ATPase activity was measured in triplicate by the inorganic phosphate (Pi) released from ATP as described by Tsakiris (52). Cardiac sarcolemmal membrane protein (50 μg) was used to measure total ATPase activity (Na,K,Mg-dependent ATPase and Mg²⁺-dependent ATPase activity). The incubation medium contained (in mM) 120 NaCl, 20 KCl, 1 K-EDTA, 240 sucrose, 4 MgCl₂, and 50 Tris·HCl, pH 7.4, in a final volume of 200 μl. The reaction was initiated by addition of ATP to a final concentration of 3.0 mM. Ouabain-insensitive Mg-ATPase was assayed under the same conditions after addition of 2 mM ouabain and without NaCl and KCl. The reaction was initiated by adding ATP at 37°C and stopped after an incubation period of 15 min by addition of 60 μl of an ice-cold mixture of 1% ammonium molybdate in 0.9 M H₂SO₄ (7, 52, 53). Released Pi was colorimetrically measured at 390 nm by the method of Chen and colleagues (10). ATPase activity of these preparations ranged from 0.8 to 1.5 U/mg protein according to the manufacturer’s suggested protocol.

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Isolated heart perfusion. To examine the time course of cardiac contraction and relaxation responses to burn injury in the absence of calpain therapy, subgroups of rats were anticoagulated with sodium heparin (200 U; Elkins-Sinn, Cherry Hill, NJ) and decapitated 2, 4, 8, 12, 24, 48, or 72 h or 8 days after burn over 40% TBBSA (n = 7–9 rats/time period). To examine the effects of PKC inhibition on myocardial performance, additional burn-injured rats (and sham-injured rats) treated with calphostin or vehicle after injury were anticoagulated and killed 24 h after burn injury, a time when myocardial defects were maximal after burn injury. The heart from each experimental animal was rapidly removed and placed in a petri dish containing ice-cold (4°C) Krebs-Henseleit bicarbonate-buffered solution (in mM: 118 NaCl, 4.7 KCl, 21 NaHCO₃, 1.25 CaCl₂, 1.2 MgSO₄, 1.2 KH₂PO₄, and 11 glucose). All solutions were prepared

**Study 1**

SD Rats

- **Sham Burn**
- **Burn**

Rats killed and

1) PKC and Na,K-ATPase activities measured 2, 4, 24 hrs post burn or post sham burn (5-6 rats/group/time period)
2) Myocyte Na⁺ and LV function measured 2, 4, 8, 12, 24, 48, 72 hrs or 8 days post burn (11-14 rats/group/time period)

**Study 2**

SD Rats

- **Sham Burn**
- **Burn**

- **Sham Burn**
  - given vehicle (saline)
- **Sham Burn**
  - given calphostin (0.1 mg/kg)
- **Burn**
  - given vehicle (saline)
- **Burn**
  - given calphostin (0.1 mg/kg)

Rats killed and

1) PKC and Na,K-ATPase activities measured 2, 4, 24 hrs post burn (4-5 rats/group/time period)
2) Myocyte Na⁺ and LV function measured 24 hrs post burn (11-13 rats/group)

Fig. 1. Summary of experimental study design. SD, Sprague-Dawley; PKC, protein kinase C; LV, left ventricular.
each day with demineralized, deionized water and bubbled with 95% 
O₂-5% CO₂ (pH 7.4, PO₂ 550 mmHg, Pco₂ 38 mmHg). A cannula placed 
in the ascending aorta was connected via glass tubing to a 
buffer-filled reservoir for perfusion of the coronary circulation at a 
constant flow rate. Hearts were suspended in a temperature-controlled 
chamber maintained at 38°C, and a constant flow pump (Ismatec, 
model 7335-30, Cole-Parmer Instrument, Chicago, IL) was used to 
maintain perfusion of the coronary artery (ml/min) by retrograde 
perfusion of the aortic stump cannula. Coronary perfusion pressure 
was measured, and effluent was collected to confirm coronary flow 
rate. Contractile function was assessed by measuring intraventricular 
pressure with a water-filled latex balloon attached to a polyethylene 
tube and threaded through the apex of the left ventricular chamber. 
Peak systolic left ventricular pressure (LVP) was measured with a 
Statham pressure transducer (model P23ID, Gould Instruments, Ox-
nard, CA) attached to the balloon cannula, and the rates of LVP rise 
(+dP/dt) and fall (−dP/dt) were obtained with an electronic differ-
entiator (model 7P20C, Grass Instruments, Quincy, MA) and recorded 
(Grass model 7DWL8P). Left ventricular developed pressure was 
calculated from peak systolic LVP and left ventricular end-diastolic 
pressure. Data from the Grass recorder were input into a Dell Pentium 
computer, and a Grass PolyVIEW Data Acquisition System was used 
to convert acquired data into digital form.

Cardiac myocyte isolation. After burn injury (or sham burn), 
animals from each experimental group (n = 4–6 rats/group) were 
heparinized, blood samples were collected, and rats were decapitated;
hearts were harvested and placed in a petri dish containing ice-cold 
heart medium [in mM: 113 NaCl, 4.7 KCl, 0.6 KH₂PO₄, 0.6 
NaHPO₄, 1.2 MgSO₄, 12 NaHCO₃, 10 KHC₂O₃, 20 n-glucose, 10 
HEPES; 30 taurine, 2.0 carnitine, and 2.0 creatine with 0.5× minimum 
essential medium (MEM) and amino acids (50×, GIBCO/BRL 
mini-M, to a final concentration of 1,000 μM). After the final pelleting step the supernatant was removed, and the pellet was resuspended in MEM (prepared by adding 10.8 g of 1× MEM (Sigma M-1018), 11.9 m 
NaHCO₃, 10 mM HEPES, and 10 ml penicillin-streptomycin, 100×, 
GIBCO/BRL 1540-122 with 950 ml of MilliQ water); total volume 
was adjusted to 1 liter. At the time of MEM preparation, the medium 
was bubbled with 95% O₂-5% CO₂ for 15 min and the pH was 
adjusted to 7.1 with 1 M NaOH. The solution was then filter sterilized 
and stored at 4°C until use. At the final concentration of calcium, the 
cardiomyocyte cell number was calculated and myocyte viability was 
determined.

Measurement of myocyte Na⁺ levels. Myocytes were pipet-
ted into microtitr plates at 5 × 10⁴ cells·ml⁻¹·well⁻¹ (12-well cell 
culture cluster, Corning, Corning NY) and incubated for 18 h (CO₂ 
incubator at 37°C). Supernatants were collected to measure myocyte-
secreted TNF-α, IL-1β, IL-6, and IL-10 (rat ELISA, Endogen, 
Woburn, MA). We previously examined (22) the contribution of 
cardiac myocytes isolated at several times after injury; LVP, left ventricular 
pressure; +dP/dtmax, maximum rise in LVP; −dP/dtmax, maximum fall in LVP. *Significant difference from sham burn at P < 0.05 (ANOVA, multiple-
comparison procedure).
(SBFI) for 1 h at room temperature in the dark. Myocytes were then suspended in 1.0 mM calcium-containing MEM and washed to re-

P

time point (difference between vehicle-treated burn and calphostin-treated burn at each
time consistent with significant myocyte Na

time course of myocyte sodium accumulation and time

cardiac contractile dysfunction. Burn injury caused a progressive rise in cardiac myocyte Na

time course studies examining cardiac contractile function

RESULTS

All values are means ± SE. PKC, protein kinase C; MAP, mean arterial pressure; HR, heart rate; Hct, hematocrit; HCO3, serum bicarbonate; O2 Sat, oxygen saturation; Ca2+, serum ionized calcium; Na+, serum ionized sodium. *Significant difference from sham burn at P < 0.05. (ANOVA, multiple comparison procedure); †significant difference from burn + vehicle (group 3 vs. group 4) at P < 0.05.
after burn, but LVP measured 8 days after burn failed to return to values measured in sham burn-injured rats (P < 0.05).

Myocardial PKC activity and Na-K-ATPase activity. In this study, vehicle-treated burn injury caused a progressive rise in myocardial PKC activity in tissue harvested 2, 4, or 24 h after burn over 40% TBSA (Fig. 2). This progressive change in PKC activity was paralleled by a progressive decrease in Na-K-ATPase activity 2, 4, and 24 h after burn (Fig. 3).

Administration of calphostin, a specific inhibitor of PKC, after burn injury attenuated the burn-related increases in myocardial PKC (Fig. 2) and blunted the burn-related decrease in Na-K-ATPase activity during the postburn period also attenuated the burn-related accumulation of Na\(^+\) by cardiomyocytes.

Effects of burn injury on hemodynamic and metabolic function. All animals survived the experimental period. Twenty-four hours after burn injury, mean arterial blood pressure was lower in group 3 (burn injury + vehicle; 112 ± 8 mmHg) compared with that measured in sham burn-injured rats (group 1; 151 ± 5 mmHg; P < 0.002). Metabolic acidosis occurred after vehicle-treated burn injury, as indicated by the increase in whole blood lactate (3.3 ± 0.4 mM) compared with values measured in sham burn-injured rats (2.2 ± 0.3 mM; P < 0.04). Hematocrit levels fell 24 h after burn injury, likely because of the aggressive fluid resuscitation (Table 2). Plasma cytokines were significantly elevated 24 h after vehicle-treated burn injury (group 3) compared with values measured in sham burn-injured rats (group 1; P < 0.05). While administration of calphostin in burns (group 4) improved mean arterial blood pressure and improved metabolic acidosis compared with values measured in vehicle-treated burns (group 3), these values did not return to the levels measured in sham burn-injured rats. Calphostin administration after burn injury lowered plasma cytokine levels compared with values that were measured in vehicle-treated burns (P < 0.05), but plasma cytokine levels in calphostin-treated burns remained above those measured in sham burns (P < 0.05; Table 2).

Effects of burn injury and calphostin on cardiac inflammation. Burn injury produced significant pro- and anti-inflammatory responses in the myocardium, as indicated by increased secretion of TNF-\(\alpha\), IL-1\(\beta\), IL-6, and IL-10. Calphostin therapy after burn injury attenuated cardiac myocyte secretion of the proinflammatory cytokines TNF-\(\alpha\) (Fig. 4A), IL-1\(\beta\) (Fig. 4B), and IL-6 (Fig. 4C), as well as the anti-inflammatory cytokine IL-10 (Fig. 4D).

Effects of calphostin treatment on cardiac myocyte Na\(^+\) levels and myocardial function. As shown in Fig. 5, the burn-related rise in myocyte Na\(^+\) levels measured 24 h after vehicle-treated burn injury was significantly attenuated by calphostin treatment of burns (P < 0.05). The attenuation of cardiomyocyte Na\(^+\) overload and restoration of intracellular Na\(^+\) homeostasis in calphostin-treated burns was associated with improved myocardial contraction and relaxation in group 4 compared with left ventricular performance measured in vehicle-treated burn (group 3; P < 0.05). Left ventricular developed pressure (LVP) and ±dP/dt responses (Table 3) were measured in all four experimental groups as the hearts were perfused at constant preload, constant heart rate, and constant coronary flow rate. Additional studies included in vitro perfusion of the heart 24 h after burn injury (Langendorff approach), providing further evidence of cardiac contractile depression as indicated by the reduced LVP and ±dP/dt responses to incremental increases in either preload (Fig. 6A) or increases in perfusate Ca\(^{2+}\) (Fig. 6B). Hearts harvested from calphostin-treated burn-injured rats generated significantly greater levels of LVP and ±dP/dt at all levels of left ventricular preload (Fig. 6A) and better left ventricular performance in response to incremental increases in perfusate Ca\(^{2+}\) (Fig. 6B) compared with values generated by hearts harvested from vehicle-treated burn-injured rats (P < 0.05).

DISCUSSION

The present study confirmed that administration of a specific PKC inhibitor, calphostin, attenuated the burn-related increase in myocardial PKC activity. Furthermore, calphostin attenuated burn-related myocardial contraction and relaxation defects, and this improved myocardial performance was associated with increased Na-K-ATPase activity and significant attenuation of the burn-related increase in cardiomyocyte intracellular Na\(^+\) loading. These data are consistent with our
chamber, an ion transport system that couples cellular Na⁺ accumulation in postburn myocardial dysfunction was provided by the time course data in the present study. There was no cardiac contractile depression 2 h after burn, when there was little change in myocyte intracellular Na⁺ levels. However, progressive Na⁺ accumulation was followed by progressive myocardial contraction and relaxation defects. These data suggest that Na⁺ accumulation by the cardiac myocyte likely initiated a cellular signaling cascade that perhaps includes increased myocyte inflammation, as indicated by increased myocyte secretion of TNF-α, IL-1β, and IL-6, culminating in myocardial contractile depression. Pharmacological interventions that limit the rise in intracellular Na⁺ have been shown to reduce myocardial injury and improve myocardial performance in several experimental models (12, 26, 37, 43). Since the Na-K-ATPase exchanger is the primary regulator of sodium efflux from the cell, a pharmacological agent that increases Na-K-ATPase activity should promote Na⁺ efflux from the cell, limit injury-related Na⁺ accumulation, and provide organ protection (13). Data from the present study support this hypothesis with increased myocardial Na-K-ATPase activity after calphostin treatment of burn injury paralleled by reduced myocyte Na⁺ levels, reduced myocardial inflammation, and improved cardiac contractile performance.

While the Na-K-ATPase transporter plays a pivotal role in regulating cellular ionic homeostasis through its transmembrane transport of Na⁺ and K⁺, Na-K-ATPase function is modulated in several cell types by phosphorylation by either PKA or PKC (3, 8, 17, 27, 32). In this regard, PKC activity has been shown to inhibit Na-K-ATPase activity in noncardiac tissue by phosphorylating the enzyme, decreasing affinity of the Na-K-ATPase for sodium, and producing a decrease in activity of the enzyme (4, 6, 28, 59). However, the present study is the first, to our knowledge, to suggest that burn-related changes in myocardial Na-K-ATPase activity are PKC dependent. In our study, the PKC inhibitor calphostin increased myocardial Na-K-ATPase activity after burn injury, and these data are consistent with studies by Lundmark and colleagues (29), who described that chelerythrine increased Na-K-ATPase activity after ischemic injury in isolated rat hearts. While increased PKC activity after burn injury in our study was paralleled by a fall in Na-K-ATPase activity and impaired cardiac function,

### Table 3. Stabilization of perfused heart at constant left ventricular volume (preload), constant coronary flow rate, and constant heart rate

<table>
<thead>
<tr>
<th></th>
<th>Group 1: Sham + Vehicle</th>
<th>Group 2: Sham + Calphostin</th>
<th>Group 3: Burn + Vehicle</th>
<th>Group 4: Burn + Calphostin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVP, mmHg</td>
<td>93 ± 4</td>
<td>90 ± 4</td>
<td>61 ± 3 *</td>
<td>89 ± 3 †</td>
</tr>
<tr>
<td>+dP/dmax, mmHg/s</td>
<td>2.055 ± 1.120</td>
<td>1.910 ± 0.74</td>
<td>1.170 ± 0.67 *</td>
<td>1.788 ± 0.65 †</td>
</tr>
<tr>
<td>−dP/dmax, mmHg/s</td>
<td>1.725 ± 1.26</td>
<td>1.640 ± 0.67</td>
<td>0.989 ± 0.52 *</td>
<td>1.542 ± 0.92 †</td>
</tr>
<tr>
<td>DPmax, mmHg/s</td>
<td>1.792 ± 1.93</td>
<td>1.600 ± 1.14</td>
<td>0.986 ± 0.51 *</td>
<td>1.572 ± 0.68 †</td>
</tr>
<tr>
<td>Time to peak pressure, ms</td>
<td>85.6 ± 1.9</td>
<td>97.2 ± 3.6</td>
<td>94.3 ± 2.4</td>
<td>105.5 ± 5.0 †</td>
</tr>
<tr>
<td>Time to 90% relaxation, ms</td>
<td>83.7 ± 1.3</td>
<td>101.0 ± 5.6</td>
<td>92.6 ± 5.5</td>
<td>102.8 ± 5.2 †</td>
</tr>
<tr>
<td>Time to +dP/dmax, ms</td>
<td>56.3 ± 1.3</td>
<td>51.0 ± 5.6</td>
<td>56.1 ± 1.4</td>
<td>59.2 ± 4.6</td>
</tr>
<tr>
<td>Time to −dP/dmax, ms</td>
<td>56.8 ± 1.6</td>
<td>58.2 ± 0.9</td>
<td>54.0 ± 1.1</td>
<td>59.2 ± 3.3</td>
</tr>
<tr>
<td>Coronary perfusion pressure, mmHg</td>
<td>55.0 ± 2.8</td>
<td>51.2 ± 5.4</td>
<td>56.3 ± 5.6</td>
<td>46.5 ± 4.1</td>
</tr>
<tr>
<td>Coronary vascular resistance, mmHg</td>
<td>11.0 ± 0.6</td>
<td>10.3 ± 1.1</td>
<td>11.3 ± 1.1</td>
<td>9.3 ± 0.8</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>262 ± 16</td>
<td>258 ± 3</td>
<td>263 ± 9</td>
<td>253 ± 6</td>
</tr>
</tbody>
</table>

All values are means ± SE. DPmax developed pressure at 40 mmHg. *Significant difference from respective sham group at P < 0.05. †Significant difference in group 4 (calphostin-treated burns) compared to values measured in group 3 (vehicle-treated burns) at P < 0.05.
increased PKC activity has been associated with both protective and detrimental effects. While PKC translocation from the cytosol to the cell membrane has been shown to play a role in ischemic preconditioning (33, 46), PKC inhibition has been shown to lessen myocardial injury and dysfunction, and these beneficial effects were linked to downregulation of proinflammatory responses (23, 25). Similarly, PKC inhibition has been shown to afford cardioprotection in models of coronary occlusion (25).

While burn-related PKC activation likely contributed to the progressive decrease in myocardial Na-K-ATPase in our study, other factors should be considered. Alterations in membrane lipid content clearly alter the function of membrane-bound enzymes (38). In this regard, Pierce and Dhalla (39) described an association between increased cholesterol content of the sarcolemmal membranes and a decrease in a sarcolemmal Na-K-ATPase activity. Similarly, feeding a cholesterol-enriched diet increased sarcolemmal cholesterol content and depressed Na-K-ATPase activity in adult rats (35). The rise in plasma cholesterol and triglycerides that occurs after burn injury may provide another mechanism by which burn injury alters Na-K-ATPase activity (9, 24, 56). Alternatively, increased proinflammatory activities after burn injury as indicated in our study by a rise in plasma and tissue TNF-α, IL-1β, and IL-6 levels may exert direct inhibitory effects on Na-K-ATPase enzymatic activity, promoting myocyte accumulation of sodium and cellular injury. We showed previously (44) that increased myocyte secretion of TNF-α and IL-1β parallel a rise in myocyte sodium.

Several limitations of the present study must be considered. The changes in myocardial Na-K-ATPase, cardiac myocyte

Fig. 6. A: LV developed pressure (LVP) and maximum rate of rise and fall of LVP (±dP/dt max) responses to increases in left ventricular volume or preload assessed 24 h after burn. B: LVP and ±dP/dt max responses to increases in perfusate Ca²⁺ in all experimental groups. All values are means ± SE. *Significant difference from respective sham group (P < 0.05, ANOVA, Student-Newman-Keuls).
Na⁺ levels, myocyte cytokine secretion, and left ventricular function paralleled one another, but do not indicate causality. We proposed that burn injury initiates a sequence of events that include increased PKC activity, which in turn impaired Na-K-ATPase expression and activity, promoting a subsequent rise in myocyte Na⁺. The rise in cellular Na⁺ likely triggered local inflammatory responses, culminating in impaired left ventricular function. Our finding that calphostin (a PKC inhibitor) improved Na-K-ATPase expression and pump activity, lowered myocyte Na⁺, and improved left ventricular function supports this proposal. However, calphostin may have directly altered cytokine secretion by myocytes, improving cardiac function regardless of calphostin’s effects on either PKC or Na-K-ATPase activity or myocyte Na⁺ levels. Other limitations include the fact that calphostin may have altered several aspects of cellular function in other organs as well as in the heart. While the administration of calphostin in vivo after major burn injury allowed us to examine several aspects of the burn-related sequelae (cell signaling, inflammation, as well as organ or heart function), this in vivo approach was complicated by the potential effects of calphostin on many cell types and organ systems.

In summary, burn injury over 40% of the total body surface area in adult rats increased myocardial PKC activity and decreased Na-K-ATPase activity. These biochemical changes were paralleled by cardiac myocyte accumulation of sodium and myocardial contraction and relaxation deficits that were evident by 12 h after burn. Administration of calphostin, a specific PKC inhibitor, increased postburn myocardial Na-K-ATPase activity, decreased burn-related myocardial sodium overload, and improved myocardial performance. These data suggest that burn-related changes in Na-K-ATPase activity promoted sodium accumulation by the myocyte, which likely initiated a cellular signaling cascade that culminated in myocardial contractile depression. Our data further suggest that inhibition of PKC activity after burn injury provides cardiac protection by preventing myocyte sodium loading that occurs via the PKC-related decrease in Na-K-ATPase activity.

GRANTS

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