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Targeting Protein Kinase C Beta II to Reduce Myocardial Ischemia–Reperfusion Injury

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Abstract

Myocardial infarction (MI) remains a leading cause of morbidity and mortality worldwide and is most commonly caused by coronary artery occlusion. Although restoration of coronary blood flow is essential to preserve viable myocardium, reperfusion paradoxically induces additional injury through mechanisms involving reactive oxygen species (ROS) generation and inflammation, collectively termed myocardial ischemia–reperfusion (MIR) injury. Protein kinase C beta II (PKCβII) has emerged as a potential therapeutic target in MIR because of its role in regulating oxidative and inflammatory signaling pathways; however, the relative effects of PKCβII activation versus inhibition remain incompletely defined. Accordingly, we evaluated a selective cell-permeable PKCβII inhibitor (YT-003) and a selective PKCβII activator using complementary in vitro and ex vivo MIR models.

Rat polymorphonuclear leukocytes (PMNs) were pretreated with selective PKCβII modulators and chemically stimulated to generate superoxide (SO) to assess ROS-generating capacity. Human umbilical vein endothelial cells (HUVECs) underwent hypoxia and reoxygenation, with treatment given at the onset of reoxygenation, and viability was assessed. Isolated rat hearts underwent global ischemia followed by reperfusion in a Langendorff preparation, with treatment administered at reperfusion onset; cardiac functional recovery and infarct size were measured.

YT-003 significantly reduced PMN-derived SO release, improved HUVEC survival after hypoxia–reoxygenation, decreased myocardial infarct size, and increased left ventricular functional recovery compared with controls. In contrast, the selective PKCβII activator did not significantly alter outcomes in any of the experimental models.

These findings indicate that selective PKCβII inhibition with YT-003 is protective in complementary in vitro and ex vivo MIR models. The activator data indicate a lack of efficacy for this particular peptide, rather than excluding a protective role for PKCβII activation more generally. These results are hypothesis-generating and require confirmation in clinically relevant in vivo models before the therapeutic potential of PKCβII inhibition after MI can be defined.

Abbreviations

Diacylglycerol (DAG); Dimethyl sulfoxide (DMSO); Endothelial nitric oxide synthase (eNOS); Human umbilical vein endothelial cells (HUVECs); Ischemia–reperfusion (I/R); Left ventricular developed pressure (LVDP); Left ventricular end-diastolic pressure (LVEDP); Left ventricular end-systolic pressure (LVESP); Mitochondrial permeability transition pore (mPTP); Myocardial infarction (MI); Myocardial ischemia–reperfusion (MIR); Myristic acid (Myr); Myristic acid- and Tat-conjugated PKCβII inhibitor (YT-004); Myristoylated PKCβII activator, N-Myr-SVEIWD (PKCβII+); Myristoylated PKCβII inhibitor, N-Myr-SLNPEWNET (YT-003); Nicotinamide Adenine Dinucleotide Phosphate Oxidase 2 (NOX-2); Nitric oxide (NO); Phorbol 12-myristate 13-acetate (PMA); Polymorphonuclear leukocytes (PMNs); Protein kinase C beta II (PKCβII); Rate of decrease in left ventricular pressure (dP/dtmin); Rate of increase in left ventricular pressure (dP/dtmax); Reactive oxygen species (ROS); Receptor for activated C kinase 1 (RACK1); Standard error of the mean (SEM); Superoxide (SO); Trans-activator of transcription peptide (Tat); Tumor necrosis factor-alpha (TNFα)

Introduction

Myocardial infarction (MI) remains a leading cause of morbidity and mortality worldwide and represents a substantial healthcare burden [1-3]. In the United States alone, more than 750,000 MIs occur annually, often resulting in significant, long-term cardiovascular complications among survivors [4,5]. MI is most commonly caused by partial or complete occlusion of a coronary artery. Current clinical interventions focus on rapidly restoring coronary blood flow to salvage ischemic myocardium. Although reperfusion limits overall infarct size, it paradoxically induces additional tissue injury known as myocardial ischemia–reperfusion (MIR) injury. MIR injury can account for up to 50% of total final infarct size, highlighting it as a critical and under-addressed therapeutic target [6,7]. Despite its clinical significance, only one FDA-approved therapy currently exists for MIR injury [8].

Protein kinase C beta II (PKCβII), a calcium and diacylglycerol (DAG)-dependent serine/threonine kinase, emerged as a potential mediator of MIR injury through its established roles in inflammatory signaling and cellular stress responses [6,7,9-13]. PKCβII expression is elevated in patients with ischemic cardiomyopathy, and pharmacologic inhibition of PKCβII has been shown to improve cardiac function in multiple experimental models of MIR injury [14-18]. Prior work has suggested that low-level, long-term PKCβ expression during adulthood may improve postischemic recovery in mice [19]. However, whether acute selective PKCβII activation during reperfusion is protective, neutral, or harmful remains incompletely defined. The present study addresses this question by directly comparing the effects of PKCβII activation and inhibition

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within identical MIR injury models.

Our laboratory has developed a selective PKCβII inhibitor, YT-003 (Young Therapeutics), which blocks PKCβII-mediated production of reactive oxygen species (ROS). ROS play a central role in MIR injury by promoting oxidative damage, impairing vascular function, and amplifying inflammatory signaling pathways [20,21]. PKCβII is a known upstream regulator of ROS generation during ischemia–reperfusion. PKCβII activation is initiated early during reperfusion by the release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNFα) [22]. TNFα and other pro-inflammatory cytokines bind to their respective cytokine receptors and activate intracellular signaling pathways that converge on PKCβII activation. In parallel, reperfusion-associated agonists acting through G-protein–coupled receptors stimulate phospholipase C, increasing intracellular Ca^{2+} and diacylglycerol (DAG), which further promote PKCβII activation (Figure 1) [23-26]. Activated PKCβII binds to the receptor for activated C kinase 1 (RACK1) and is translocated to the plasma membrane, where it phosphorylates $p47^{phox}$, promoting assembly of NADPH oxidase 2 (NOX-2) [27-29]. NOX-2 subsequently generates superoxide radicals that contribute directly to MIR injury.

In addition to regulating NOX-2–dependent ROS generation, PKCβII also contributes to mitochondrial oxidative stress during reperfusion (Figure 1). Following activation, PKCβII can phosphorylate the redox adaptor protein p66Shc, causing it to enter the mitochondria where it facilitates the oxidation of reduced cytochrome c and generation of hydrogen peroxide [30-32]. This increase in mitochondrial ROS has been linked to opening of the mitochondrial permeability transition pore (mPTP), loss of mitochondrial integrity, and initiation of cell injury pathways associated with ischemia–reperfusion damage [33-35]. Together, these findings suggest that PKCβII amplifies reperfusion injury through both NOX-2 signaling and mitochondrial ROS production. (Figure 2) summarizes basal PKCβII signaling and the divergent effects of YT-003 and our PKCβII activator. YT-003 is designed to bind RACK1 and impair RACK1-dependent localization of activated PKCβII to membrane-associated signaling complexes, thereby limiting downstream ROS production (Figure 2). In prior work, YT-003 significantly and concentration-dependently reduced superoxide release from isolated rat polymorphonuclear leukocytes (PMNs), increased nitric oxide production in rat aortic segments, and improved functional recovery in an ex vivo rat heart MIR model [12]. Our PKCβII activator was designed as a pseudo-RACK sequence to promote an active-like PKCβII conformation that facilitates RACK1 interaction and membrane-associated localization (Figure 2) [29].

Based on this mechanistic framework and prior findings, we predicted that YT-003 would replicate our previously observed cardioprotective effects by significantly decreasing PMN SO release, improving endothelial cell survival after hypoxic stress, reducing cardiac infarct size, and improving left ventricular function in an ex vivo rat heart MIR model [12]. Conversely, we hypothesized that PKCβII activation would produce the opposite effects, resulting in increased PMN superoxide release, decreased endothelial cell survival, larger infarct size, and impaired functional recovery.

Methods

All experimental protocols were performed in accordance with

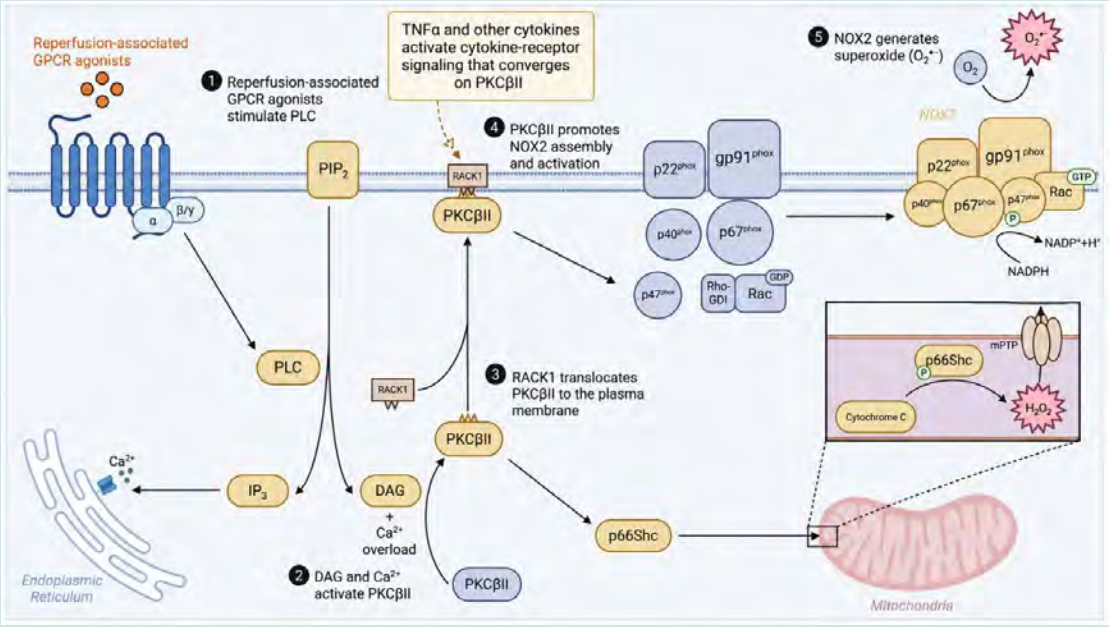

Figure 1: Proposed PKCβII-mediated ROS signaling during myocardial ischemia–reperfusion, showing convergent cytokine-receptor and GPCR signaling to PKCβII, NOX2 activation, and mitochondrial ROS production.

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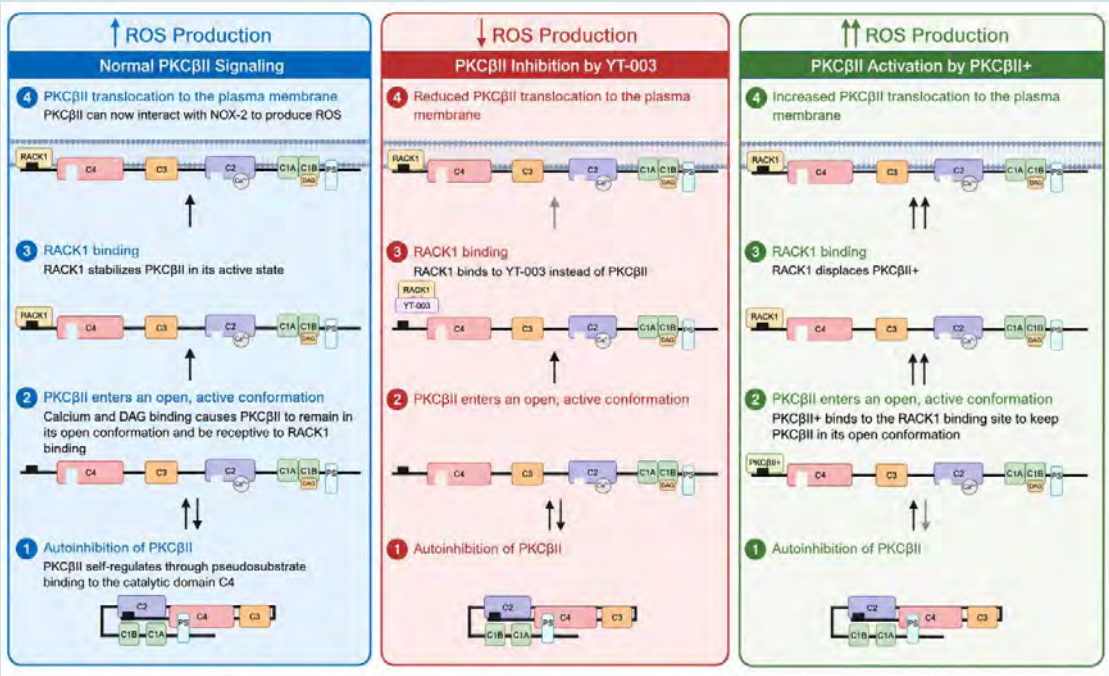

Figure 2: Proposed model comparing basal PKCβII signaling, YT-003–mediated inhibition of RACK1-dependent PKCβII localization, and the predicted effects of PKCβII+ on PKCβII activation and ROS production.

the institutional policies of the Philadelphia College of Osteopathic Medicine, and all animal procedures were additionally approved by the Institutional Animal Care and Use Committee.

Drug Conjugation

Our PKCβII inhibitor peptide (SLNPEWNET) and PKCβII activator peptide (SVEIWD) were used to assess the effects of PKCβII inhibition and activation, respectively. Each peptide was tested in its native, unconjugated form and conjugated to myristic acid (Myr), an endogenous fatty acid that enhances cell membrane permeability, to determine whether myristoylation improved intracellular delivery. YT-003 denotes the myristoylated PKCβII inhibitor N-Myr-SLNPEWNET. A scrambled version of YT-003 (N-Myr-WNPESLNTE) was synthesized and used as a control. In the figures and tables, the myristoylated PKCβII activator (N-Myr-SVEIWD) is designated PKCβII+, the unconjugated activator peptide as Native PKCβII+, and the unconjugated inhibitor peptide as Native PKCβII−; the myristoylated inhibitor is designated YT-003 throughout. All peptides were tested at a final concentration of 20 μM in 0.4% dimethyl sulfoxide (DMSO). The PMN assay evaluated the native and myristoylated PKCβII inhibitor and activator peptides, as well as scrambled YT-003. The HUVEC assay evaluated YT-003 and the myristoylated PKCβII activator (PKCβII+), whereas the isolated-heart experiments evaluated YT-003, scrambled YT-003, and PKCβII+. Previous concentration–response studies of YT-003 in PMN superoxide (SO) release and ex vivo rat MIR hearts were reported by Omiyi et al. (2005) and Lipscombe et al. (2015) [12,16].

Rat PMN SO Release

Male Sprague-Dawley rats (350–400 g, Charles River Laboratories, Springfield, MA) were housed in a 12-h light/12-h dark cycle in a temperature-controlled room. Animals had ad libitum access to food and water. All procedures were conducted in accordance with animal handling protocol A21-002. Rats were placed under anesthesia with 2.5% isoflurane and injected intraperitoneally with 16 mL of 0.5% glycogen to induce rat peritonitis and subsequent PMN recruitment. After 18 h, rats were re-anesthetized with 2.5% isoflurane, and PMNs were harvested by peritoneal lavage as previously described [36]. PMN yield and viability were assessed by trypan blue exclusion.

PMA-induced superoxide release was measured spectrophotometrically using a previously published ferricytochrome c reduction assay [37]. For each assay, a 900-μL reaction mixture was prepared containing 450 μL of 0.25% ferricytochrome c solution, 5 × 10^6 PMNs, 2 μL of the designated treatment, and molecular-grade water. Dimethyl sulfoxide (DMSO, 0.4%) was used as the vehicle control. Reaction mixtures were transferred to cuvettes, placed in a spectrophotometer, and incubated for 15 min at 37 °C. Baseline absorbance was recorded at 550 nm. PMNs were then activated by adding 100 μL of a 100 nM phorbol 12-myristate 13-acetate (PMA) stock to a final concentration of 10 nM, and absorbance was recorded every 30 s for 390 s. Three treatment groups and one vehicle control were analyzed simultaneously. Only assays in which vehicle-control absorbance increased by greater than 0.300 absorbance units were included in the final analysis.

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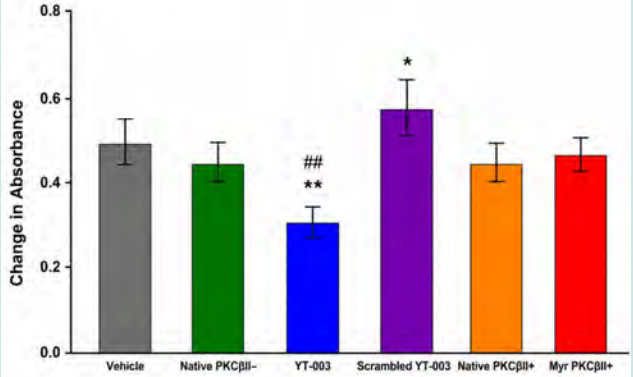

Figure 3: Superoxide production in PMA-stimulated isolated rat PMNs, showing that YT-003 significantly reduced superoxide release compared with vehicle and scrambled YT-003 controls; data are mean ± SEM, *p < 0.05 and **p < 0.01 versus vehicle control, ##p < 0.01 versus scrambled YT-003, n = 6 independent experiments.

HUVEC Hypoxia–Reoxygenation Assay

Human umbilical vein endothelial cells (HUVECs) from a single donor were obtained from Lonza (Walkersville, MD) and cultured in endothelial cell growth medium on 0.2% gelatin-coated 96-well plates. Culture medium was supplemented with 2% fetal bovine serum and EBM-2 BulletKit components (Lonza, CC-3162). Cells were passaged no more than 5 times and grown to approximately 80% confluence under normoxic conditions (21% O_2, 5% CO_2, 85% relative humidity, 37 °C). Culture medium was replaced every 48 h.

For the hypoxia–reoxygenation assay, HUVECs were placed in a modular incubator chamber and exposed to hypoxic conditions (1% O_2, 5% CO_2, and balanced N_2) for 24 h. Cells were then returned to normoxic conditions for 24 h, with drug treatment administered at the onset of reoxygenation. Cell viability was assessed at the end of the reoxygenation period using a WST-8 tetrazolium-based colorimetric assay, and absorbance was measured at 450 nm using a microplate reader. Results were normalized to normoxic control conditions.

Rat MIR Model

Male Sprague-Dawley rats (275–325 g, Charles River Laboratories, Springfield, MA) were housed in identical conditions to those described for the PMN SO experiments. Rats were anesthetized via an intraperitoneal injection of pentobarbital (60 mg/kg) and heparin (1000 units). The heart was subsequently excised and immediately perfused with Krebs buffer at 37 °C at a constant pressure of 80 mmHg using a Langendorff perfusion apparatus. Baseline cardiac parameters were recorded during a 15-min stabilization period by placing a SPR-425 catheter (Millar Instruments, Inc., Houston, TX) into the left ventricle. The heart was then subjected to 30 min of global ischemia by stopping perfusion, followed by 50 min of reperfusion during which perfusion was restored. The designated drug treatment or vehicle control (0.4% DMSO) was delivered during the first 5 min of reperfusion at a rate of 1 mL/min. Heart rate, left ventricular end-systolic pressure (LVESP), left ventricular end-diastolic pressure (LVEDP), the rate of increase in left ventricular pressure (dP/dt_{max}), and the rate of decrease in left ventricular pressure (dP/dt_{min}) were recorded at 5-min intervals throughout the reperfusion period. Data were acquired and stored using a PowerLab/8Sp data acquisition system (AD Instruments, Colorado Springs, CO). Left ventricular developed pressure (LVDP) was calculated as the difference between LVESP and LVEDP.

At the conclusion of the reperfusion period, the heart was removed from the Langendorff apparatus and placed in a −20 °C freezer for 30 min. The hearts were then sectioned perpendicular to their long axis into seven 2-mm slices and incubated for 5 min at 37 °C in 1% 2,3,5-triphenyltetrazolium chloride dissolved in 0.2 M Tris buffer (pH 7.4). Following incubation, the slices were fixed in 4% paraformaldehyde. Viable tissue stained red, whereas infarcted tissue appeared pale. Percent infarction was determined by separating the infarcted from the viable tissue and calculating the ratio of the infarcted tissue weight to the total slice weight.

Statistical Analysis

All data are presented as mean ± SEM. Normally distributed data were analyzed using ANOVA followed by post hoc pairwise comparisons using the Games-Howell test. Non-normally distributed data were analyzed using the Kruskal-Wallis test followed by Wilcoxon rank-sum pairwise comparisons with Bonferroni correction. Values of $p < 0.05$ were considered statistically significant. Statistical symbols, significance thresholds, and the corresponding comparison groups are defined in the individual figure legends and table footnote.

Results

PKCβII Inhibition Reduces Superoxide Release in Isolated PMNs

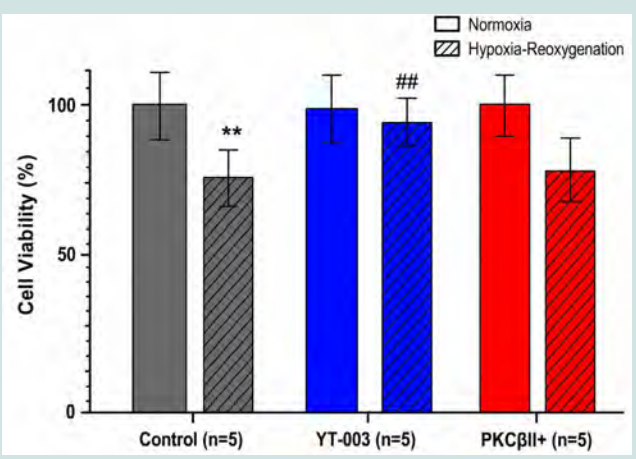

Figure 4: HUVEC viability under normoxic conditions or following hypoxia–reoxygenation with YT-003 or a myristoylated PKCβII activator, showing significant preservation of viability by YT-003 compared with the hypoxia–reoxygenation control; **p = 0.004 versus normoxic control and ##p = 0.0087 versus hypoxia–reoxygenation control.

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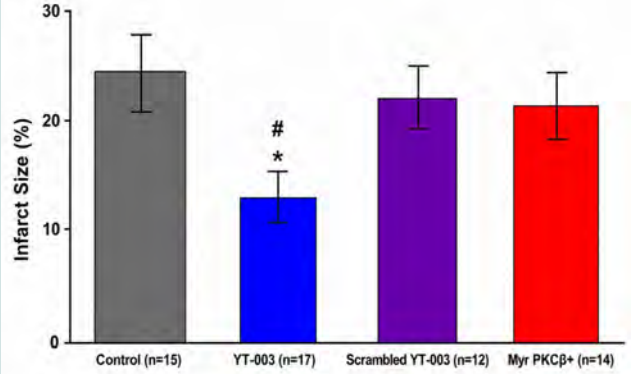

Figure 5:Myocardial infarct size in isolated rat hearts following ex vivo ischemia–reperfusion; data are mean ± SEM, and YT-003 significantly reduced infarct size versus control (*p = 0.026) and scrambled YT-003 (#p = 0.019).

Superoxide (SO) production was measured in isolated rat polymorphonuclear leukocytes (PMNs) to determine whether PKCβII activation or inhibition alters reactive oxygen species generation after PMA stimulation (Figure 3). Superoxide release is expressed as the change in absorbance at 550 nm recorded 390 s after PMA stimulation. Neither the native PKCβII inhibitor (0.43 ± 0.02, n = 22) nor the native PKCβII activator (0.43 ± 0.04, n = 15) significantly altered SO release compared to the vehicle control (0.46 ± 0.02, n = 74). In contrast, PMNs treated with YT-003 exhibited a marked reduction in SO release at 390 s (0.30 ± 0.02, n = 27). This reduction was significant compared with vehicle control (p = 0.000012), the native PKCβII inhibitor (p = 0.0043), and scrambled YT-003 (p = 0.00028). The myristoylated PKCβII activator did not significantly alter SO production (0.44 ± 0.02, n = 26). Notably, treatment with scrambled YT-003 resulted in a significant increase in SO release (0.58 ± 0.05, n = 22) relative to vehicle-treated controls (p = 0.016).

KCβII Inhibition Improves Endothelial Cell Viability in a Hypoxia–Reoxygenation Model

Endothelial cell survival following ischemic stress was assessed using a hypoxia–reoxygenation model in human umbilical vein endothelial cells (HUVECs). For each condition, n = 5 represents five measurements obtained in five independent experiments. Exposure to 24 h of hypoxia followed by 24 h of reoxygenation significantly reduced HUVEC viability to 79.0 ± 8.7% of the normoxic control (n = 5; p = 0.004; (Figure 4). Administration of YT-003 at the onset of reoxygenation significantly improved endothelial viability (94.7 ± 6.8%, n = 5, p = 0.0087). In contrast, treatment with the myristoylated PKCβII activator did not significantly improve cell viability, which remained approximately 81.4 ± 9.7% (n = 5, p = 0.81).

PKCβII Inhibition Reduces Infarct Size in an Ex Vivo Rat MIR Model

To determine whether PKCβII modulation influences myocardial tissue injury, isolated rat hearts were subjected to 30 min of global ischemia followed by 50 min of reperfusion in an ex vivo myocardial ischemia–reperfusion model. Hearts treated with YT-003 at the onset of reperfusion exhibited a significantly smaller infarct size (13.0 ± 1.8%, n = 17) compared to DMSO-treated controls (24.3 ± 3.5%, n = 15, p = 0.026) and hearts treated with scrambled YT-003 (22.0 ± 1.9%, n = 12, p = 0.019) (Figure 5). In contrast, treatment with the myristoylated PKCβII activator did not significantly alter infarct size (21.4 ± 2.6%, n = 14, p = 1.0).

PKCβII Inhibition Improves Left Ventricular Functional Recovery During Reperfusion

YT-003 treatment significantly improved left ventricular functional recovery during reperfusion. YT-003 significantly increased dP/dt_{max} compared with vehicle control from 10 min to the end of reperfusion, except at 20 min (Figure 6A). YT-003 also significantly increased dP/dt_{max} compared to scrambled YT-003 from 10 min to the end of reperfusion and compared to the PKCβII activator from 25 min to the end of reperfusion. In addition, YT-003 significantly increased LVDP compared to vehicle control at 5 min and from 30 min to the end of reperfusion, to scrambled YT-003 from 5 min to the end of reperfusion, and to the PKCβII activator from 25 min to the end of reperfusion (Figure 6B). Interestingly, scrambled YT-003 significantly reduced LVDP compared with control between 20 and 40 min of reperfusion. The myristoylated PKCβII activator did not significantly improve dP/dt_{max}, LVDP, or any other cardiac parameters compared to vehicle control under the conditions examined (Figure 6) (Table 1). Heart rate did not differ significantly between any groups (Table 1).

Discussion

Summary of Major Findings

Our study compared the effects of PKCβII activation and inhibition on MIR injury. YT-003 significantly decreased SO release from isolated rat PMNs and improved HUVEC viability in a hypoxia–reoxygenation assay. In an ex vivo rat heart MIR model, YT-003 significantly reduced infarct size and significantly improved left ventricular functional recovery during reperfusion. In contrast, the myristoylated PKCβII activator did not significantly alter PMN SO release, HUVEC viability, heart infarct size, or left ventricular functional measures.

PKCβII in PMNs

PMNs are a well-established contributor to MIR injury. At the site of injury, PMNs release reactive oxygen species (ROS), platelet-activating factor, and extracellular matrix-degrading proteases, and amplify the inflammatory response through the release of pro-inflammatory cytokines that promote additional PMN recruitment [38,39]. Previous studies using animal MIR injury models found that leukocytes were recruited to the site of injury and began infiltrating

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Table 1: Cardiac functional parameters at baseline and after 50 min of reperfusion in an ex vivo isolated rat-heart model of myocardial ischemia–reperfusion, showing that YT-003 significantly improved left ventricular function compared with control and scrambled YT-003; data are mean ± SEM, with *p < 0.05 and **p < 0.01 versus control and #p < 0.05 and ##p < 0.01 versus scrambled YT-003.

Cardiac Parameter	Time point	Control (n = 15)	YT-003 (n = 17)	Scrambled YT-003 (n = 12)	PKCβII+ (n = 14)
dP/dt_{min} (mmHg/s)	Initial	-1697±65	-1702±58	-1657±45	-1631±54
	Final	-773±89	-1061±83##	-433±66	-643±65
dP/dt_{max} (mmHg/s)	Initial	2444±56	2388±47	2411±51	2390±50
	Final	815±107	1535±106**##	513±76	860±118
LVEDP (mmHg)	Initial	8.8±0.5	8.3±0.9	7.0±0.7	8.0±0.6
	Final	62.1±3.7	41.6±4.4*##	68.5±1.2	58.4±3.5
LVESP (mmHg)	Initial	104±3	100±3	99±2	98±2
	Final	103±4	111±4#	91±3*	96±3
LVDP (mmHg)	Initial	94±2	92±3	92±2	89±2
	Final	41±6	69±5**##	23±4	38±5
Heart Rate (bpm)	Initial	283±7	278±5	272±7	274±8
	Final	265±7	248±5	311±37	253±10

post-ischemic tissue within the first hour of reperfusion [40,41]. Based on these observations, treatments were administered at the beginning of reperfusion to limit downstream inflammatory injury.

Our PKCβII modulators were designed to target PKCβII's NOX-2-mediated ROS generation (Figure 1). The present findings suggest that inhibiting PKCβII signaling significantly reduces PMN-derived ROS production. However, PKCβII also regulates multiple signaling pathways that contribute to neutrophil chemotaxis and inflammatory cell trafficking [42,43]. During reperfusion, PMNs are recruited to the site of injury by pro-inflammatory cytokines, such as interleukin-6, interleukin-8, and TNFα, released from the reperfused myocardium [44,45]. Therefore, PKCβII may influence not only PMN ROS production, but also PMN recruitment and trafficking to ischemic tissue. In a previous study using our ex vivo rat heart MIR model, in which PMNs were delivered at the onset of reperfusion along with the drug treatment, PKCβII inhibition reduced the number of PMNs that infiltrated and adhered to cardiac tissue at the end of reperfusion, supporting this mechanism. In that same study, adding PMNs to the heart worsened LVDP recovery, and PKCβII inhibition reversed this effect, consistent with our in vitro findings that PKCβII inhibition reduced PMN SO release [12]. Interestingly, we did not observe a significant effect with the PKCβII activator in isolated PMNs or in the rat heart model [12].

PKCβII in Endothelial Cells

Endothelial cells lining the cardiac vasculature are important mediators of MIR injury. In the present study, PKCβII inhibition improved HUVEC viability following hypoxia–reoxygenation, suggesting a protective effect on endothelial cells under ischemia-like stress. Endothelial cells also produce nitric oxide (NO), which promotes vasodilation, limits ROS-mediated injury, and reduces PMN adhesion and accumulation, all of which may attenuate MIR injury [46,47]. We previously showed in isolated rat aortic segments that PKCβII inhibition increased NO release [12]. In a rat model of obesity-associated insulin resistance, another group found that PKCβII activation reduced eNOS expression, one of the main sources of NO, by inhibiting Akt phosphorylation [48]. PKCβII inhibition has also been shown to restore vessel relaxation responses and calcium-activated potassium channel activity in isolated mouse coronary arteries [49]. Collectively, these findings suggest that PKCβII inhibition may improve endothelial viability under hypoxic stress and preserve endothelial function during ischemia–reperfusion injury, at least in part through maintenance of NO signaling.

PKCβII in MIR Injury

As previously mentioned, our lab has focused on PKCβII's mechanism of ROS production through NOX-2. The present results demonstrate that targeting this pathway significantly reduces total SO release, decreases myocardial damage, and improves cardiac performance during reperfusion. PKCβII also contributes to mitochondrial ROS production (Figure 1). PKCβII has been shown to activate the redox adaptor protein p66Shc, promoting its mitochondrial translocation, where it facilitates hydrogen peroxide generation through oxidation of reduced cytochrome c [31,32]. Increased mitochondrial ROS has been associated with opening of the mPTP, and prolonged mPTP opening can contribute to irreversible cellular injury [33-35]. Although this pathway has not been fully defined in PMNs or cardiomyocytes in the context of MIR injury, selective PKCβ inhibition has been reported to reduce p66Shc-driven superoxide production, suggesting that PKCβII's role in MIR injury may include mitochondrial damage [50-52]. YT-003 likely does not interact with this pathway since PKCβII's interaction with p66Shc is currently believed to occur independently of RACK1.

PKCβII Activation Versus Inhibition

The literature regarding PKCβII activation remains limited and mixed. One study suggests that PKCβII activation may induce a preconditioning effect, as constitutive PKCβII expression has been shown to increase cardiomyocyte contractility in young mice

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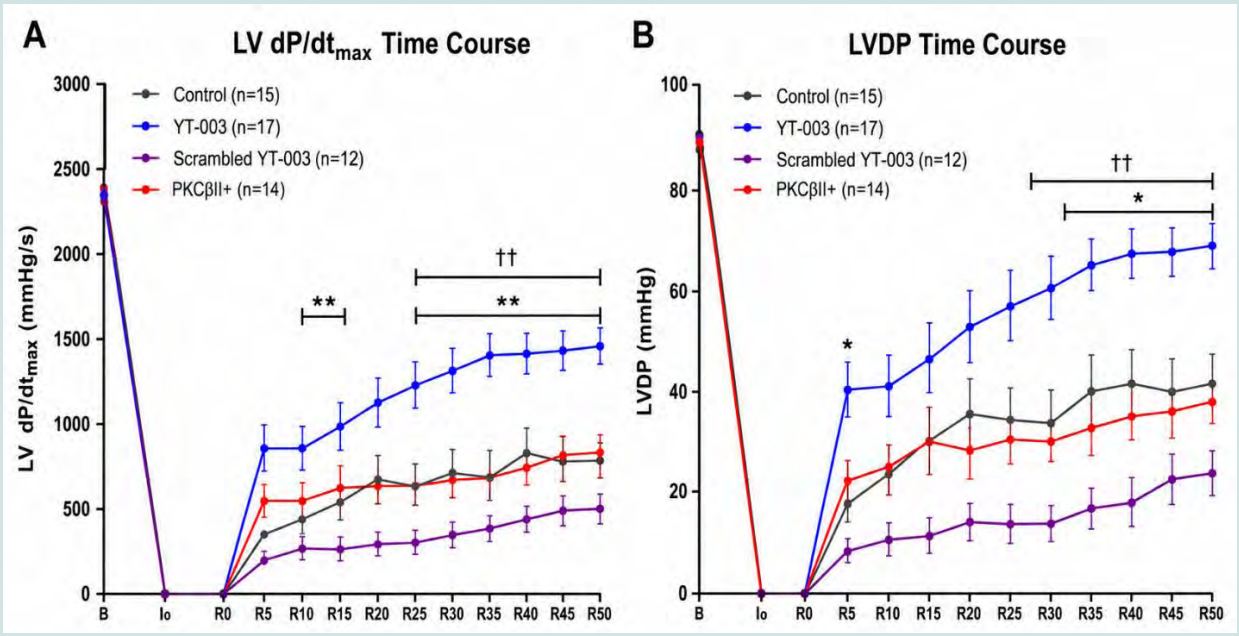

Figure 6:Left ventricular functional recovery in isolated rat hearts following ex vivo ischemia–reperfusion, showing that YT-003 improved dP/dtmax (A) and LVDP (B) during reperfusion compared with control and PKCβII+; B, baseline; I0, onset of ischemia; R0, onset of reperfusion; *p < 0.05 and **p < 0.01 versus control; ††p < 0.01 versus PKCβII+.

[19]. However, another group showed that prolonged PKCβII overexpression is associated with cardiomyocyte necrosis, calcium deposition, and maladaptive hypertrophy effects, and these changes were mitigated by PKCβII inhibition [53]. In the present study, our PKCβII activator caused no significant differences in any of our experimental models. This null result should be interpreted with caution, because several explanations unrelated to the biology of PKCβII activation could account for it. First, intracellular delivery may have been insufficient. Although the activator was myristoylated using the same strategy that enhanced the intracellular efficacy of YT-003, cellular uptake and cytosolic availability were not directly measured, and delivery efficiency cannot be assumed to be equivalent for two peptides of different sequences, charges, and lengths. Second, the single concentration tested (20 μM) was selected based on prior concentration–response work with the inhibitor; no concentration–response relationship was established for the activator, so a subthreshold exposure cannot be excluded. Third, the duration of action may have been inadequate, since the compound was delivered only during the first 5 min of reperfusion and its persistence in the cell was not determined. Finally, the activator may not have engaged PKCβII as predicted or may not have stabilized the active conformation sufficiently to enhance RACK1-dependent translocation. Because target engagement was not confirmed by an independent readout, such as PKCβII translocation or substrate phosphorylation, the present data establish a lack of efficacy of this specific activator peptide under these conditions rather than an absence of any protective effect of PKCβII activation. Future pharmacodynamic and target-engagement studies will be required to define the extent, timing, and duration of PKCβII activation produced by this compound.

In contrast, far more studies have investigated the inhibition of PKCβII. PKCβII expression was elevated in cardiomyocytes from patients with ischemic and dilated cardiomyopathy [14,54]. Several different animal studies have shown that PKCβII inhibition reduces MIR injury [15,17,18]. Our results show that YT-003 is cardioprotective and are consistent with the current literature on PKCβII inhibition. The scrambled YT-003 peptide provided unexpected results. It increased SO production in the PMN assay and depressed cardiac function in the ex vivo experiment, without significantly affecting infarct size. Because the scrambled sequence carries the same amino acid composition and the same myristoyl moiety as YT-003, these effects are unlikely to be attributable to the fatty acid conjugate alone. Several possibilities merit consideration. The scrambled peptide may itself be biologically active, for example, by interacting with RACK1 or another scaffolding protein in a manner that favors rather than prevents assembly of the NOX-2 complex. Alternatively, a myristoylated peptide at this concentration may perturb membrane organization or act as a nonspecific substrate, altering PKC-dependent phosphorylation. The dissociation between increased superoxide release and depressed contractile recovery on the one hand, and unchanged infarct size on the other, may indicate a predominantly functional rather than necrotic effect within the 50-min reperfusion window examined. Although these observations were not a primary focus of the present study and were not investigated mechanistically, they indicate that the scrambled peptide should not be assumed to be inert in this system. Future studies should determine

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whether its effects arise from sequence-specific interactions with RACK1, altered membrane organization, or engagement of other pathways involved in MIR injury.

To our knowledge, this is the first study to directly compare PKCβII activation and inhibition across identical experimental models of MIR injury. Collectively, the present findings suggest that selective PKCβII inhibition at the onset of reperfusion was more protective than the specific activator tested under these conditions. They also support further investigation into PKCβII inhibition as a therapeutic strategy to limit MIR injury. Because these observations derive exclusively from isolated cells and ex vivo perfused hearts, they do not by themselves establish clinical translatability.

YT-003 in Other I/R Models

Ischemia–reperfusion (I/R) injury is not limited to the heart but rather represents a common pathological feature across multiple organ systems. PKCβII inhibition improved survival in a mouse lung I/R model and reduced gut damage and oxidative stress in a mouse intestinal I/R model [50,55]. In a rat kidney transplant model, PKCβII inhibition improved transplant function and reduced tubular epithelial apoptosis [56]. YT-003 has demonstrated efficacy in a renal I/R model, where treatment significantly reduced serum creatinine levels and preserved glomerular filtration rate following ischemic injury [57].

Study Limitations

Several limitations should be acknowledged. Superoxide release from PMNs was measured over a short time window, whereas leukocyte infiltration persists for hours after reperfusion. Therefore, the long-term effects of PKCβII inhibition on PMN function remain unknown. The HUVEC hypoxia–reoxygenation model employed prolonged exposure periods that may not fully reflect the temporal and physiological complexity of in vivo MIR injury. HUVECs are of venous and non-cardiac origin and differ from coronary microvascular endothelial cells in receptor expression, shear-stress environment, redox handling, and PKC isoform profile; the protective effect reported here therefore requires confirmation in cardiac microvascular endothelial cells before it can be attributed to the coronary endothelium. Pharmacokinetic and tissue distribution data for YT-003 are currently lacking, limiting interpretation of drug exposure, tissue penetration, and optimal dosing strategies. In addition, the ex vivo Langendorff perfusion rat heart model uses acute global ischemia, which differs from the regional ischemia produced by coronary artery occlusion in human myocardial infarction. This model also lacks the hormonal, neuronal, or immunological inputs that the rest of the body normally provides. The crystalloid-perfused preparation is also acellular, so circulating leukocytes and platelets are absent, and the contribution of PMN-derived superoxide inferred from our isolated-cell experiments could not be tested directly in the intact heart. Perfusion at constant pressure removes coronary autoregulatory control, and the 50-min reperfusion period permits assessment only of early functional recovery and early infarct development rather than of established infarction or remodeling. Only male rats were studied, precluding assessment of potential sex-dependent responses. Long-term post-MI outcomes were not evaluated, limiting the ability to evaluate chronic functional outcomes and cardiac complications. Finally, our evaluation of PKCβII was limited to ex vivo and cellular models; therefore, further in vivo studies are needed to confirm its therapeutic potential.

Future Directions

Building on our prior work with peptide-based PKC inhibitors, we are continuing to develop next-generation PKCβII inhibitors with enhanced intracellular delivery and therapeutic potency. This study demonstrated that conjugating our PKCβII inhibitor to myristic acid improved its suppression of PMN ROS production. Earlier studies have demonstrated that conjugation of PKC-targeting peptides to the trans-activator of transcription (Tat) peptide improved intracellular delivery and enhanced efficacy in ischemia–reperfusion models, including cardiac transplantation and renal ischemia–reperfusion injury [58-61]. The Tat sequence (YGKKKRRQRRR), a positively charged amino acid motif, facilitates cellular entry through electrostatic interactions with negatively charged membrane components, thereby enhancing drug delivery to intracellular targets.

Building on these findings, our laboratory subsequently evaluated whether additional lipid conjugation could further improve peptide delivery and biological activity. Our previous studies demonstrated that dual conjugation of PKC-targeting peptides with myristic acid (Myr) and Tat significantly improved intracellular uptake and cardioprotective efficacy compared with single-conjugated peptides [58,61]. As a result, we developed a formulation of our PKCβII inhibitor, YT-004, that is conjugated to both myristic acid and Tat. In ex vivo rat hearts, YT-004 significantly reduced infarct size at femtomolar concentrations, while in vivo porcine myocardial ischemia–reperfusion models showed cardioprotection at doses as low as 20 ng/kg, corresponding to approximately 100 pM circulating drug levels [62,63]. These findings suggest that dual-conjugated PKCβII inhibitors may achieve potent biological effects at substantially lower concentrations than earlier-generation compounds.

Future studies will evaluate YT-004 across in vitro, ex vivo, and in vivo systems to further define its therapeutic efficacy and translational potential. Planned investigations include testing YT-004 in a clinically relevant porcine myocardial ischemia–reperfusion model involving regional ischemia followed by reperfusion and extended post-injury follow-up to assess chronic recovery. Longitudinal assessment will include left ventricular ejection fraction, hemodynamic performance, and circulating biomarkers of myocardial injury, with infarct size and post-injury remodeling quantified at study completion. Additional studies will characterize pharmacokinetics, tissue distribution, and dosing parameters to optimize therapeutic exposure and determine

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the durability of treatment effects.

Conclusion

Selective inhibition of PKCβII with YT-003 significantly reduced superoxide release, improved endothelial cell survival, decreased myocardial infarct size, and preserved left ventricular functional recovery following myocardial ischemia–reperfusion injury. In contrast, the specific PKCβII activator tested did not produce measurable protective effects in any of the experimental models examined. Together, these findings support a contributory role for PKCβII in MIR injury in these models and identify PKCβII inhibition as a candidate therapeutic strategy that requires confirmation in clinically relevant in vivo models before its therapeutic potential can be defined.

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