The Role of Protein Kinase C in Cerebral Ischemic and Reperfusion Injury

Rachel Bright, PhD; Daria Mochly-Rosen, PhD

Background and Purpose—Stroke is a leading cause of disability and death in the United States, yet limited therapeutic options exist. The need for novel neuroprotective agents has spurred efforts to understand the intracellular signaling pathways that mediate cellular response to stroke. Protein kinase C (PKC) plays a central role in mediating ischemic and reperfusion damage in multiple tissues, including the brain. However, because of conflicting reports, it remains unclear whether PKC is involved in cell survival signaling, or mediates detrimental processes.

Summary of Review—This review will examine the role of PKC activity in stroke. In particular, we will focus on more recent insights into the PKC isozyme-specific responses in neuronal preconditioning and in ischemia and reperfusion-induced stress.

Conclusion—Examination of PKC isozyme activities during stroke demonstrates the clinical promise of PKC isozyme-specific modulators for the treatment of cerebral ischemia. (Stroke. 2005;36:2781-2790.)

Key Words: cerebral infarction ■ cerebral ischemia ■ neuroprotection

Stroke is the third leading cause of death in the United States, with >700,000 new incidents occurring each year.1 Yet, we can claim only a modest understanding of the complex network of cellular processes that regulates cerebral injury. Although multiple agents have demonstrated efficacy in reducing stroke injury in preclinical studies, the only currently approved drug for stroke patients is a thrombolytic, tissue plasminogen activator. However, the narrow therapeutic window (3 hours after stroke onset) and associated risks, including hemorrhage,2 translate to limited therapeutic use; <2% of stroke patients in the United States receive tissue plasminogen activator.3 The great need for a new generation of agents that confer neuroprotection against ischemic/reperfusion injury and extend the therapeutic window is clear.

Molecular Mechanisms of Cerebral Ischemic and Reperfusion Injury

Multiple cellular processes are rapidly activated in response to ischemic/reperfusion-induced stress. The ischemic core, a region of tissue that is immediately distal to an occluded artery, undergoes rapid, anoxic cell death within minutes of ischemia onset. Irreversible processes including mitochondrial collapse, rapid energy depletion, and ion pump failure result in large increases in intracellular calcium, extracellular potassium, and edematous cell swelling, characteristic of necrotic cell death.4,5 However, in the ischemic penumbra, or “shadow” surrounding the core, metabolism and intracellular signaling cascades are maintained partly by hypoperfusion from a diminished collateral blood supply.6 The penumbra is considered “at-risk” tissue, affected by multiple stresses including regional glutamate and potassium diffusion and peri-infarct depolarizations emanating from the ischemic core.7,8 Importantly, the effects of reperfusion, the return of blood flow into an ischemic area after arterial recanalization, may contribute significantly to stroke damage.5,9

It is now recognized that ischemia and reperfusion initiate different intracellular responses.5 During reperfusion, the inability of impaired mitochondria to use oxygen in electron transport results in reduction in cellular ATP levels, production of reactive oxygen species (ROS), expression and activation of proapoptotic signaling intermediates, and initiation of inflammatory processes.4,10 Reversing or halting some of these processes can reduce damage,11–13 suggesting that delivering neuroprotectants, even at reperfusion, may lead to improved neurological outcome.

Salvage of “at-risk” tissue depends on reversing or arresting detrimental intracellular processes that control propagation of the infarct beyond the necrotic core. In tissue with residual energy levels, such as the ischemic penumbra, rapid changes occur in the activity of many different signaling paths, involving diverse protein kinase families. Alterations in the expression or activity of calcium/calmodulin-dependent protein kinase II, mitogen-activated protein kinase (MAPK) family members c-Jun N-terminal kinase and extracellular signal-regulated kinase (ERK), protein kinase B (Akt), and protein kinase C (PKC) suggest that multiple kinases participate in the response of the tissue to ischemia and reperfusion.14–18 The role of PKCs in...
mediating stroke injury has received particular attention. PKC activity has been seen in ischemic injury in multiple tissues, including heart, liver, and kidney, suggesting it is involved in a conserved ischemic response pathway. However, whether PKC mediates or is simply activated during ischemic injury is controversial because of mixed reports on PKC expression and activity, and thus is the focus of this review.

The PKC Family
The PKC family of serine/threonine kinases consists of 10 different isozymes. In the brain and spinal cord, PKCα, PKCβ1, PKCβ2, PKCγ, PKCε, PKCδ, PKCζ, PKCθ, and PKACζ mRNA and protein are present and demonstrate unique tissue, cellular, and subcellular localizations. However, the relative levels of PKC isozyme expression in different anatomic brain regions have not yet been examined in detail, and alterations in the expression and levels of these isozymes under conditions of cerebral ischemic stress have not been systematically examined. Importantly, individual PKC isozymes mediate different and sometimes opposing functions after activation by the same stimulus. However, the use of nonspecific pharmacological tools conceals the role of individual PKC isozymes, contributing to

### Table 1. PKC Pharmacological Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>PKC Isozyme Specificity</th>
<th>Nonspecific Targets</th>
<th>Activity (EC50/IC50)</th>
<th>Mechanism/Target Site</th>
<th>Cerebral Ischemia References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMA (phorbol 12-myristate 13-acetate)</td>
<td>α, β1, β2, γ, δ, ε, θ PKC</td>
<td>Multiple DAG-binding proteins</td>
<td>1–100 nmol/L</td>
<td>Mimic DAG</td>
<td>Reshef et al, 1997, Maiese et al, 1993</td>
</tr>
<tr>
<td>ωRACK</td>
<td>α, β1, β2, γPKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
<td>Wang et al, 2004</td>
</tr>
<tr>
<td>ωRACK</td>
<td>εPKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
<td>Di-Capua et al, 2003, Raval et al, 2003</td>
</tr>
<tr>
<td><strong>Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisindolylmaleimide I</td>
<td>all</td>
<td>JNK</td>
<td>10 nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gö 6976</td>
<td>α, β1, β2, γPKC</td>
<td>MAPK family</td>
<td>8 nmol/L</td>
<td>Substrate binding site</td>
<td>Hamabe et al, 2005, Cheung et al, 2003</td>
</tr>
<tr>
<td>Ro 31-8220</td>
<td>all</td>
<td>JNK1</td>
<td>10 nmol/L</td>
<td></td>
<td>Tauskela et al, 1999, Raval et al, 2003</td>
</tr>
<tr>
<td>LY333531</td>
<td>βPKC</td>
<td>5 nmol/L</td>
<td>Substrate binding site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chelerythrine</td>
<td>all</td>
<td>cyclic nucleotide phosphodiesterases</td>
<td>660 nmol/L</td>
<td>Catalytic domain: ATP binding site, phosphate acceptor site</td>
<td></td>
</tr>
<tr>
<td>αC2-4</td>
<td>αPKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β1V5-3</td>
<td>β1PKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
<td>Wang et al, 2004</td>
</tr>
<tr>
<td>β2V5-3</td>
<td>β2PKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>βC2-4</td>
<td>α, βPKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
<td>Koponen et al, 2003</td>
</tr>
<tr>
<td>γV5-3</td>
<td>γPKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
<td>Wang et al, 2004</td>
</tr>
<tr>
<td>δV1-1</td>
<td>δPKC</td>
<td>&gt;5 nmol/L</td>
<td>Translocation†</td>
<td></td>
<td>Bright et al, 2004, Raval et al, 2005</td>
</tr>
<tr>
<td>εV1-2</td>
<td>εPKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
<td>Di-Capua et al, 2003, Raval et al, 2003</td>
</tr>
<tr>
<td>γV1-1</td>
<td>γPKC</td>
<td>NA</td>
<td>Translocation†</td>
<td></td>
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*CaM kinase III indicates calcium/calmodulin–dependent kinase III; PKA, cAMP-dependent kinase; PKG, cGMP-dependent kinase; †translocation, subcellular translocation inhibitor or activator.
inconsistency in reports on PKC function. With the availability of isozyme-specific modulators, the unique roles of each PKC isozyme are becoming increasingly clear (note 1; Table 1).

PKC Activity in Stroke Models
When exposed to sublethal ischemic episode, the brain enacts endogenous neuroprotective mechanisms to induce tolerance, rendering it protected against a subsequent lethal transient ischemic attack. Two temporal waves of preconditioning have been described: a rapid induction phase, mediated in part through adenosine, ATP-sensitive potassium ($K_{ATP}$) channels, and low-level glutamate-induced calcium flux, and a delayed induction window, likely to rely on altered gene expression and protein synthesis.45 Multiple agents induce rapid tolerance in the brain, including exposure to low levels of N-methyl-d-aspartate (NMDA), NO, and adenosine.46 Ischemic tolerance induced by these endogenous preconditioning agents is dependent on PKC activation, suggesting that PKCs are key regulators of ischemic preconditioning in the brain.

A largely conflicting body of reports has emerged concerning the PKC response to ischemia (Table 2). Some studies demonstrate that total PKC levels and activity are increased at very early time points after ischemia in vivo and after oxygen and glucose deprivation (OGD) and excitotoxic damage in vitro. Inhibition of PKC using high concentrations of phorbol 12-myristate 13-acetate, or nonspecific PKC inhibitors such as H7, calphostin C, or staurosporine, protect cells against NO-, anoxic- or glutamate-induced excitotoxic damage in vitro and against ischemic damage in vivo. These data suggest that PKC is activated and plays a damaging role during stroke. However, a greater majority of studies report a rapid loss of total PKC activity and expression after ischemia, suggesting PKC is degraded.90–92 This loss of total PKC activity, also seen in vitro culture models of ischemic and excitotoxic cell death, correlates with neurodegenerative processes, implying that maintaining PKC activity may confer protection against excitotoxic damage. These apparently conflicting reports may stem from examination of varying animal models, brain regions, duration and intensities of ischemic/reperfusion insult, and may be compounded by the different, possibly opposing roles of individual PKC isoforms.

The mechanisms by which PKC is activated during stroke are likely to be multifactorial. Here, we focus on 3 specific PKC isoforms and examine their roles in widely studied processes: (1) adenosine-mediated upregulation of PKCs in the context of ischemic tolerance (preconditioning), and, in particular, the role of ePKC; (2) PKC response to glutamate-induced excitotoxicity during ischemia, focusing on the neuronal γPKC isoform; and (3) δPKC activation in delayed apoptotic processes during reperfusion. However, changes in PKC activity and expression in response to other ischemic/reperfusion processes have been reported, including inflammatory processes (as discussed with reference to δPKC below), cell necrosis, and alterations in microvascular tone and reactivity.

Ischemic Tolerance: Role for ePKC
The role of ePKC in ischemic injury has been subject to debate. Some reports demonstrate sustained activation of ePKC after OGD and, in response to kainic acid, a glutamate analog. Other reports suggest that ePKC is not activated in response to ischemia in an in vivo model of spreading depression by cortical KCl application or by ischemic preconditioning. ePKC mRNA increases slightly at 1 hour after reperfusion; however, more significant upregulations were observed in the transcription of other PKC isoforms. Importantly, many of these reports focus on the RNA, protein, and activity levels of ePKC during the reperfusion period. However, a potential role for ePKC may exist during ischemia or after less severe injuries.

Studies using PKC isozyme-selective modulators have demonstrated that ePKC is required for induction of ischemic tolerance; delivery of an ePKC inhibitor peptide abates NMDA-induced preconditioning in cell culture and isolated hippocampal slice models. Correspondingly, delivery of an ePKC-specific activator peptide reduces damage, as measured using lactate dehydrogenase (LDH) release, when delivered before OGD in pure neuronal and mixed neuronal/astrocyte cultures. Importantly, the protective effect of the ePKC activator was lost when delivered after OGD in these models. These data suggest that changes occur in ePKC activity over the time course of ischemic injury and begin to address the cell type-specific effects of ePKC.

The molecular basis of ePKC-induced protection is unclear. One mechanism (Figure 1) implicates adenosine and the mitochondrial $K^{+}_{ATP}$ ($mK^{+}_{ATP}$). Under metabolic stress such as ischemia, increases in adenosine levels (in addition to bradykinin and opioids) initiate a series of intracellular signaling events via G-protein–coupled receptor signaling, leading to activation of phospholipases, production of diacylglycerol (DAG), calcium influx, and PKC activation.

Multiple studies have now demonstrated that adenosine administration protects neuronal cells against ischemic-type injury via PKC, and more recent work has identified a role for ePKC in particular. Treatment of primary neuronal cultures with N6-(R)-phenylisopropyladenosine, an A1 adenosine receptor agonist, causes extended activation of PKC (6 hours after treatment), whereas delivery of an ePKC-selective inhibitor peptide blocks adenosine-induced neuroprotection against this chemical ischemia. Adenosine-mediated ePKC signaling is mediated in part through ERK, a MAPK family member that has been implicated in antiapoptotic signaling. Interestingly, studies in cardiac mitochondria demonstrate that ePKC forms functional modules with MAPK family members to maintain mitochondrial function, including inhibiting deleterious Bcl-2 associated death domain protein (BAD; a Bcl-2 family member) activity. ePKC activity at the mitochondria may also contribute to regulation of $mK^{+}_{ATP}$ channels, important for preserving mitochondrial membrane potential, maintaining energy and reducing calcium influx during metabolic challenge. PKC is thought to mediate the activity of this channel through direct phosphorylation and regulation of its internalization. In particular, reports in cardiac ischemia models suggest ePKC mediates adenosine-induced preconditioning via $K^{+}_{ATP}$ function.
suggest that ePKC confers cerebral ischemic protection, in part by maintaining mitochondrial function via ERK activity and potentially by mediating adenosine-induced $mK^{+}_{ATP}$ channel function.

Ischemia and the Role of Neuronal γPKC

One of the central events that contributes to injury during and after ischemic stroke is the release of the excitatory amino acid glutamate. Extrasynaptic glutamate causes waves of
peri-infarct depolarization in surrounding cells and spreading neuronal death. In part, via NMDA receptors (NMDARs), glutamate induces an influx of calcium and sodium into the cell, leading to release of intracellular calcium stores, lipid peroxidation, and generation of free radicals. These events lead to rapid activation and increased expression of multiple PKC isozymes, as seen after glutamate, KCl or kainic acid application in vitro and in vivo. Correspondingly, PKC inhibition reduces NMDA-mediated neurotoxicity, suggesting that PKC isozymes may mediate excitatory amino acid–induced signaling.

γPKC is expressed exclusively in neurons of the brain and spinal cord. Therefore, this isozyme may play a central nervous system (CNS)–specific role in mediating response to ischemic injury. γPKC is activated rapidly during ischemia in various models, consistent with increases in intracellular calcium and phospholipid metabolism during ischemia, required for γPKC activation. The use of γPKC knockout mice suggest γPKC may play a detrimental role during cerebral ischemic injury; γPKC knockout mice have significantly smaller infarcts, as measured using histological techniques, compared with wild-type animals after permanent ischemia. However, in an in vitro model of OGD, inhibition of γPKC using a γPKC-selective peptide inhibitor had no effect on cell survival, as assayed by LDH release.

Multiple reports now suggest that PKC may be involved in a positive feedback loop to potentiate NMDAR activity, worsening calcium loading, mitochondrial dysfunction, and promoting cell death (Figure 2). Modulating NMDAR activity may be attributable to direct phosphorylation of NR1 receptor subunits by PKC, although recent evidence suggests PKC indirectly mediates NMDAR via regulation of associated scaffolding proteins or Src-family tyrosine kinase activity. In particular, γPKC may regulate this feedback; γPKC interacts with NMDAR subunits in vivo to regulate postsynaptic excitotoxin signaling. However, indirect evidence also indicates that β1PKC and β2PKC subspecies may also modulate NMDAR function.

After extended ischemic injury and reperfusion, changes in γPKC activity are less clear. Several reports demonstrate that γPKC becomes inactive and downregulated, whereas others report that γPKC is activated specifically during reperfusion. In fact, a contrasting role for γPKC has been suggested during reperfusion; γPKC knockout mice demonstrate worsened injury after a transient ischemia, suggesting γPKC may mediate beneficial signaling processes during reperfusion injury.

Together, these data suggest that γPKC may play a deleterious role during early ischemic injury or permanent ischemic injury, potentially activated by DAG formation and flux of intracellular calcium that occur during early ischemic signaling. During ischemia, γPKC may be involved in potentiating NMDAR function, leading to calcium overloading and cell death. However, after reperfusion, γPKC may play an opposite role: mediating protective signaling and reducing cell death. These data demonstrate that individual PKC isozymes may play differing or opposing roles at different stages of injury, underscoring the importance of studying Figure 1.

**Figure 1.** εPKC in cerebral preconditioning. Progression of molecular events leading to εPKC-mediated preconditioning. a, Preconditioning stimuli, including hypoxia, lead to a decrease in cellular ATP stores and the subsequent generation of adenosine, which is released extracellularly. Adenosine stimulates G-protein–coupled receptors, such as the A1/A3 adenosine receptors (ARs), to activate phospholipases (phospholipase C [PLC]) via G-proteins (G/α). Other preconditioning stimuli, including extracellular glutamate, stimulate NMDARs, leading to increased cytosolic calcium and PLC activation. b, PLC causes membrane damage, increasing DAG production, which activates PKC isozymes including εPKC. c, εPKC may induce opening of K( ATP) channels in the mitochondria (KATP), maintain ATP production and reduce generation of ROS, which, in turn, mediates PKC activation. εPKC leads to activation of ERK, an MAPK family member, which is involved in antiapoptotic signaling and cell survival.
PKC isoform function during different periods of cell death by examining transient and permanent ischemia models.

Other PKC isoforms are also likely to be involved in mediating the cellular response to ischemia in the brain. For example, δPKC mediates NMDA-induced injury in primary neuronal cultures; inhibition of δPKC reduces cellular damage, as monitored by LDH release.74 A more detailed understanding of the molecular mechanism by which δPKC elicits death in response to NMDA toxicity awaits further study.

**PKCδ in Reperfusion Injury: Apoptosis, Necrosis, and Inflammation**

With increasing evidence that cerebral reperfusion generates its own host of detrimental intracellular signaling cascades and contributes to expansion of the ischemic infarct, the concept that reperfusion injury is a potent mediator of cell death is now widely accepted. Understanding reperfusion-induced processes is of particular interest for therapeutic targeting in combination with established thrombolytic therapy or mechanical recanalization techniques.

Multiple lines of data suggest that PKC plays an important role in mediating cerebral reperfusion injury. In particular, δPKC has been implicated in mediating oxidative stress, apoptosis, and inflammation, hallmarks of reperfusion injury.89,90 Studies demonstrate that δPKC is specifically upregulated and rapidly activated in response to reperfusion-induced intracellular signaling; in transient focal and global ischemia models, δPKC mRNA is upregulated within 24 hours after ischemia, as seen in perifocal cortex and in CA1 neurons, respectively.51,91,92 Concomitantly, δPKC protein levels are increased in the perifocal region during reperfusion,92 suggesting a role for this enzyme in mediating delayed-injury processes. Studies in an in vivo transient ischemia model show δPKC is rapidly activated at the onset of reperfusion, although this activity is not sustained at 24 hours after ischemia.93

How δPKC mediates reperfusion injury, whether increasing activity of this enzyme promotes or reduces reperfusion injury, has only more recently been addressed. Studies using 2 very different approaches, pharmacological agents and knockout animals, indicate that δPKC plays a detrimental role after stroke in vivo. Delivery of the δPKC-specific inhibitor peptide δV1-1 significantly reduced ischemic injury when delivered over an extended time window of reperfusion after a 2-hour middle cerebral artery occlusion in vivo, as assessed by histological staining techniques, and in an in vitro hippocampal slice model subject to OGD, as assessed by propidium iodide staining of CA1 neurons. However, this protective effect was not seen when δV1-1 was delivered before ischemia, suggesting that δPKC specifically mediates reperfusion-induced cell death in parenchymal cells of the brain.93 A complementary study using δPKC knockout mice demonstrates that δPKC may contribute to damage by mediating inflammatory processes during reperfusion damage; δPKC knockout mice have smaller infarcts after transient focal ischemia compared with wild-type animals and demonstrate reduced neutrophil invasion into infarcted tissue. Further, wild-type animals that received bone marrow transplants from δPKC knockout donor mice also demonstrate reduced ischemic injury,47 suggesting that δPKC activity in neutrophils, rather than neuronal or glial cells, is critical in this response.

A rapidly growing body of reports suggests a specific role for δPKC in mediating apoptotic processes in a variety of cell types.89,94 Apoptosis occurs largely in a delayed fashion during cerebral reperfusion, correlating with the reported increases in δPKC activation and expression, as described above. Reduced energy levels, as seen in the ischemic penumbra as well as spreading waves of depolarization, induce the generation of
ROS such as hydroxyl radicals, superoxide, and singlet oxygen. δPKC is responsive to ROS and other apoptotic mediators including caspase activation. In the heart, δPKC translocates to the mitochondria in response to oxidative stress, where it mediates superoxide production, pyruvate dehydrogenase inhibition, reduced ATP generation, and increased free radical formation. Inhibition of δPKC translocation reduces mitochondrial dysfunction, including Bcl-2 family protein dimerization and release of apoptogenic factors, and increases the rate of ATP regeneration and correction of cellular acidosis. Parallel findings have been demonstrated in a cerebral ischemia models. After transient focal ischemia, delivery of a δPKC inhibitor peptide reduced apoptotic cell death, as seen by TUNEL staining, increased antiapoptotic Akt (protein kinase B) activity, and reduced BAD translocation out of the cell cytosolic fraction, indicating reduction of BAD deleterious activity. In a rat cardiac arrest model, δPKC is activated via caspase-3-mediated cleavage in hippocampal CA1 neurons, contributing to reperfusion-induced hippocampal injury (Figure 3). The role of δPKC in promoting reperfusion-induced apoptotic cell death suggests it is an important therapeutic target for extended time windows after stroke injury in patients.

**PKC in Stroke: Unanswered Questions and Potential Clinical Implications**

A promising body of work supports a role for δPKC isozymes in mediating stroke-induced damage, with unique functions in preconditioning, in ischemia, and in reperfusion-induced signaling. Parallel findings concerning the positive or negative role of these isozymes in multiple models of ischemic/reperfusion damage, including focal and global ischemia models, suggest that PKCs may play an important role in mediating damage in multiple anatomical territories of the brain and brain injury paradigms. However, this underscores the need for more detailed studies about the distribution and activity of individual PKC isozymes in response to different stages and intensities of injury, different brain regions, different cell types, and different subcellular localizations. Identifying the roles for PKC in mediating endothelial cell dysfunction, maintenance of microvascular permeability, and cerebral vasospasm will provide a more comprehensive understanding of PKC function in cerebral ischemic/reperfusion injury. Finally, elaborating our understanding of the specific signaling pathways in which PKC participates, including different downstream effectors in different phases of stroke injury, will be critical to developing PKC-based therapeutic strategies.

The use of PKC-isozyme selective tools has demonstrated the importance of PKC signaling in mediating cerebral ischemic/reperfusion injury. However, further studies on the role of PKC isozymes in CNS ischemia are needed. Work to date has been performed largely in rodent models without translation to other animal models including primates and often does not include dose-response or long-term behavioral outcome analysis. The Stroke Therapy Academic Industry Roundtable criteria for evaluating preclinical drugs is therefore not complete. However, current research strongly suggests that regulating individual PKC isozymes has thera-
A useful review on this subject was published while this paper was under review: Chou WH, Messing RO. Protein kinase C isoforms in stroke. Trends Cardiovasc Med. 2005;15:47–51.

References


Note 1: Experimental Approaches to Study PKC Activity

The majority of commonly used pharmacological tools to study PKC function are nonspecific, altering the function of non-PKC kinases, or are nonselective for individual PKC isoforms. Designing agents that target individual PKC isoforms has been particularly difficult because of the high degree of homology between individual PKC isoforms and broad substrate specificity.105,106 Commonly used pharmacological agents include the H7 and staurosporine family of PKC inhibitors (Table 1), and usually show no discriminatory activity on individual PKC isozymes. The effect and isozyme selectivity of individual PKCs by enabling their anchoring to the corresponding RACKs.109 The effect and isozyme selectivity of individual PKC isozymes following transient ischemia has been particularly difficult because of the high degree of homology between individual PKC isoforms and broad substrate specificity.105,106 Commonly used pharmacological agents include the H7 and staurosporine family of PKC inhibitors (Table 1), and usually show no discriminatory activity on individual PKC isozymes. 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