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FORUM REVIEW ARTICLE

Signal Transducers and Activators of Transcription: STATs-Mediated Mitochondrial Neuroprotection

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Abstract

Cerebral ischemia is defined as little or no blood flow in cerebral circulation, characterized by low tissue oxygen and glucose levels, which promotes neuronal mitochondria dysfunction leading to cell death. A strategy to counteract cerebral ischemia-induced neuronal cell death is ischemic preconditioning (IPC). IPC results in neuroprotection, which is conferred by a mild ischemic challenge prior to a normally lethal ischemic insult. Although many IPC-induced mechanisms have been described, many cellular and subcellular mechanisms remain undefined. Some reports have suggested key signal transduction pathways of IPC, such as activation of protein kinase C epsilon, mitogen-activated protein kinase, and hypoxia-inducible factors, that are likely involved in IPC-induced mitochondria mediated-neuroprotection. Moreover, recent findings suggest that signal transducers and activators of transcription (STATs), a family of transcription factors involved in many cellular activities, may be intimately involved in IPC-induced ischemic tolerance. In this review, we explore current signal transduction pathways involved in IPC-induced mitochondria mediated-neuroprotection, STAT activation in the mitochondria as it relates to IPC, and functional significance of STATs in cerebral ischemia. *Antioxid. Redox Signal.* 14, 1853–1861.

Introduction

Cerebral ischemia is defined as little or no blood flow in cerebral circulation, characterized by low tissue oxygen and glucose levels, and by the accumulation of metabolic products (25). Due to high energy demands, the brain and the heart are most vulnerable during ischemia. Energy consumption is highest in the brain due to its innate physiological activities, and as a consequence, energy failure has severe consequences in the brain, such as loss of electrical activity, depletion of high energy intermediates (43), and loss of ion gradients (21), which results in the release of excitatory neurotransmitters (*i.e.,* glutamate) causing calcium excitotoxicity and irreversible pathologies (18). Global cerebral ischemia affects whole-brain vascular dynamics, promotes neuronal cell death in many brain regions including the hippocampus (12).

It is well accepted that reperfusion after cerebral ischemia causes increased ischemic injury characterized by two phases: rapid hyperemia (increased blood flow) and delayed hypoperfusion (decreased blood flow) (77). The hyperemia phase leads to ischemia-induced cell death to different areas of the brain (87) as well as decreased blood flow (hypoperfusion) (5) resulting in yet another possible ischemic/hypoxic condition. Upon reperfusion, hyperemia and subsequent hypoperfusion of cerebral blood vessels (25) leads to enhanced superoxide generation (87).

Of the complicated cellular processes that occur during and after cerebral ischemia, dysfunction of the mitochondria is well accepted to play a central role in ischemic injury (15). Mitochondria are not only affected during the ischemic insult where they are deprived of substrates and oxygen, but also in the post-ischemic state where changes in redox activity of the respiratory chain components occur as represented by hyperoxidation of electron carriers (59) facilitating enhanced reactive oxygen species (ROS) (50) generation; all have been linked to reperfusion following cerebral ischemia. Consequently, hyperoxidation may result in release of cytochrome *c* from the mitochondria initiating the apoptotic cascade (6). Additional evidence of mitochondrial dysfunction was described in studies obtained from isolated brain mitochondria exhibiting decreased state 3 respiratory rates of $\sim$ 70% nicotinamide adenine dinucleotide (NAD)-linked respiratory substrates (66). Moreover, nonsynaptosomal mitochondria were insensitive to ischemia, but became dysfunctional in the late reperfusion phase (4). Mitochondria from synaptic terminals were greatly affected by ischemia, but partially recovered during reperfusion. In addition, in a rat model of forebrain transient ischemia, the rate of oxygen consumption decreased in the CA1, CA3, and CA4 regions of the hippocampus in the late reperfusion phase (67). This study was performed in brain homogenates from different brain subregions (52).

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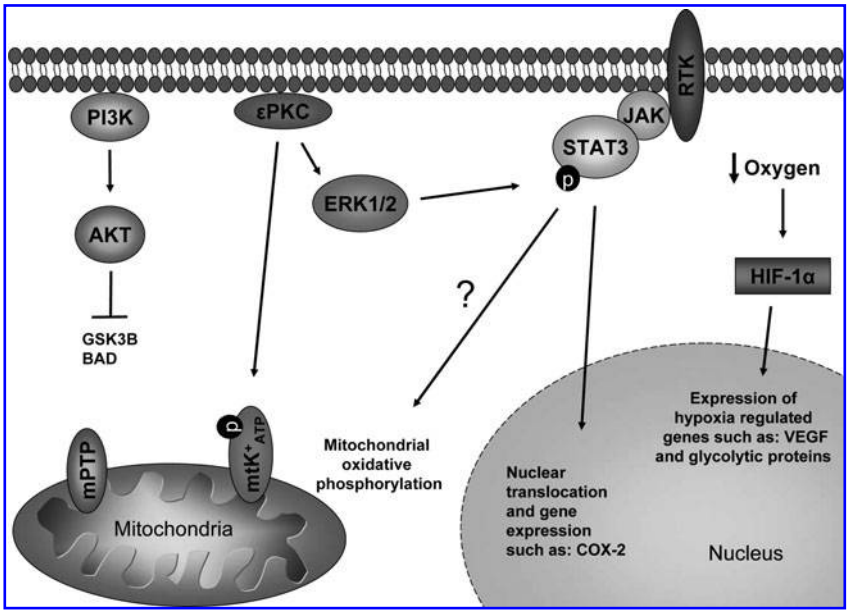

FIG. 1. Schematic diagram of the effector signaling pathways activated during ischemia preconditioning. Multiple signaling pathways are activated by ischemia preconditioning (IPC) that target different pathological features of the ischemic brain, leading to neuroprotection. Ischemia exposure allows for the accumulation of HIF-1α and the transcriptional activation of hypoxia regulated genes such as erythropoietin, inducible nitric oxide synthase, glycolytic proteins, and vascular endothelial growth factor (VEGF). Activation of the phosphoinositide 3 kinase (PI3K)-Akt pathway acts as a negative regulator of many pro-apoptotic proteins such as GSK3(and BAD; thereby maintaining the mitochondrial permeability transition pore (mPTP) in a closed configuration. Epsilon PKC (εPKC) phosphorylation is associated with the opening of the mitochondrial ATP sensitive potassium channels (mtK^+-ATP), which provides mitochondrial protection. Epsilon PKC activates the RAS–RAF–MEK–ERK1/2 signaling pathway, leading to STAT3 phosphorylation and nuclear translocation through receptor tyrosine kinase activation (RTK). In the nucleus, STAT3 enhances COX-2 expression, leading to neuroprotection. Recent research suggests that STATs may also play a role in mitochondrial bioenergetics, suggesting a possible role of mitochondrial localized STATs in IPC-mediated neuroprotection.

Many therapeutic approaches against cerebral ischemia emerged from understanding these pathways that lead to mitochondrial dysfunction. However, up to this point, not much success has been achieved. A different approach in the field of cerebral ischemia has emerged. It is now believed that by understanding endogenous metabolic adaptations that make sensitive organs like the heart and brain highly resistant to ischemia, we will be able to provide more effective therapies. One such adaptation is termed 'ischemic tolerance' or 'ischemic preconditioning'.

Ischemic Preconditioning

Many molecular and cellular signaling factors modulate neuronal homeostasis in the ischemic brain. Signaling molecules such as protein kinase B (Akt) and C are involved in neuroprotection by modulating apoptotic factors such as B cell lymphoma-2-associated death promoter (BAD), caspases, and p53 among others (3). Other factors such as mitogen-activated protein kinases (MAPKs), hypoxia-inducible factor 1α (HIF-1α), and signal transducers and activator of transcription (STATs) are also considered to be involved in mitochondria dysfunction (14). It is the influence of the mitochondria in the production of peroxide free radicals and enhanced levels of calcium that causes the activation of downstream effectors to induce cellular apoptosis/necrosis.

Resistance to these detrimental effects of neuronal cell death (acute or delayed) after ischemia has emerged from a widely accepted concept, named ischemic preconditioning (IPC), which is an innate neuroprotective mechanism whereby a sublethal ischemic insult protects against a subsequent lethal ischemic attack. First described in the heart by Murry and in brain slices by Schurr nearly 23 years ago (47, 64), IPC has been demonstrated in numerous tissues and species, including humans (78). IPC is characterized by an early or "classical" window of protection, which is sustained for several hours followed by a second window of protection 24–48 hours later, which can last for several days. The early window of protection is mediated by alteration in protein function whereas the delayed window of protection is mediated by changes in gene expression.

The therapeutic potential of IPC has led to numerous investigations into the subcellular mediators and effector pathways activated by the preconditioning stimuli. Some mediators of preconditioning include neuroactive cytokines (40), glutamate (17), γ-aminobutyric acid (13), adenosine (88), adenosine triphosphate (ATP)-sensitive potassium (K^+-ATP) channels (51), and hypoxia (41). Many effector signaling pathways have been demonstrated to induce ischemic tolerance. However, it is unlikely that one pathway alone is sufficient to induce a preconditioned response. Instead, ischemic tolerance is likely the result of a culmination of multiple signaling pathways acting in concert to target many of the pathophysiological mechanisms leading to ischemia-induced cell death.

Signaling Pathways Activated in Ischemic Preconditioning

The effector pathways activated by preconditioning typically result in the activation of protein kinase cascades such as protein kinases C (PKC), Akt, and the MAPK signaling cascade, including extracellular signal-regulated kinases (ERK), c-Jun N-terminal protein kinases (JNK), and p38 (Fig. 1). Akt is a serine/threonine kinase implicated in many cellular survival pathways. Akt exerts neuroprotection by phosphorylation and inactivation of many pro-apoptotic proteins including BAD, glycogen synthase kinase 3 beta (GSK3β), caspase 9, and apoptosis signal-regulating kinase 1. Akt is activated during ischemia-reperfusion in both preconditioned and nonconditioned animals. However, the duration of Akt

activation is significantly extended by preconditioning. In fact, Akt activation in preconditioned animals reduced apoptosis within the penumbral region reducing infarct expansion (48). In rat cerebellar granule neurons, hypoxic preconditioning increases Akt phosphorylation as well as the expression of vascular endothelial growth factor (VEGF) and its receptor VEGF receptor-2 (Flk-1), which is required for Akt phosphorylation. Inhibition of VEGF, Flk-1, or Akt was sufficient to prevent hypoxia preconditioning (80).

HIF-1α is a hypoxia-regulated transcription factor that controls the expression of many hypoxia associated genes. HIF-1α is rapidly degraded by the ubiquitin-proteasome pathway so that little to no HIF-1α protein is present under normal physiological oxygen concentrations. However, during hypoxia, HIF-1α protein degradation is halted, allowing for protein accumulation and nuclear translocation. In the nucleus, HIF-1α forms a heterodimer with HIF-1β, which allows for the binding of the activated transcription factor to promoter elements in hypoxia- regulated target genes. Some of the target genes regulated by HIF-1α include VEGF, erythropoietin, inducible nitric oxide synthase (iNOS), glucose transporter-1, a variety of glycolytic proteins, and other proteins that provide neuroprotection. Since HIF-1α plays a pivotal role in the cellular response to oxygen deprivation, it is not surprising that HIF-1α has been implicated in ischemic tolerance. For example, neuronal-specific inactivation of HIF-1α resulted in increased focal cerebral ischemia-induced cell death (73). Furthermore, expression of HIF-1α and its target genes have been demonstrated in numerous models of ischemia and hypoxic preconditioning (28, 55).

STATs are a family of transcription factors involved in many cellular activities. The transcriptional activity of STATs is regulated by phosphorylation-dependent dimerization that allows for DNA binding and recruitment of transcriptional coactivators. STAT-mediated ischemic tolerance in the heart and brain are well characterized. Our laboratory has demonstrated phosphorylation and nuclear translocation of STAT3 in response to preconditioning by oxygen and glucose deprivation (OGD) in mixed cortical/glial co-cultures (32) (Fig. 2). STAT3 was found to exert neuroprotection through the transcriptional upregulation of cyclooxygenase-2 (COX-2). Inhibition of STAT3 activity with the STAT3 inhibitory peptide (PpYLKTK) prevented COX-2 expression and neuroprotection (32). We have recently demonstrated that COX-2 expression during IPC is also regulated by nuclear factor kappa B (NF-κB). Similar to STAT3, NF-κB was found to translocate to the nucleus in response to preconditioning and was found to regulate COX-2 expression leading to neuroprotection (33).

The MAPK cascade is comprised of three protein kinases consisting of MAPK, MAPK kinase (MEK), and MAPK kinase kinase (MEKK) and results in the activation of ERK, p38, or JNK. There is increasing evidence that IPC regulates the activity of the MAPK family. For example, our laboratory has shown that preconditioning by OGD induces ERK1/2-dependent neuroprotection in cortical–glial co-cultures (32) (Fig. 2). Similarly, Choi *et al*. demonstrated ERK1/2 activation by IPC in the CA1 region of the rat hippocampus (10). A neuroprotective role for ERK1/2 in preconditioning has been demonstrated by numerous pharmacological studies using ERK1/2-specific inhibitors (20). In contrast to ERK1/2, JNK activation is associated with cellular apoptosis during cerebral ischemia (26). Interestingly, IPC can prevent JNK activation via ERK1/2 by mechanisms not fully understood (86).

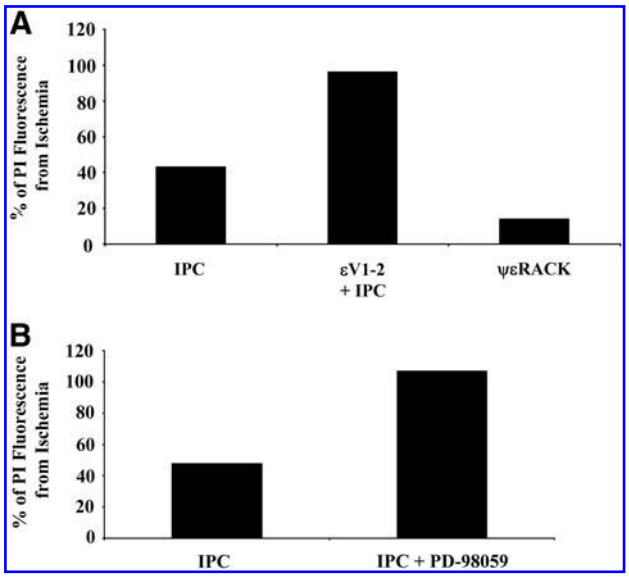

FIG. 2. Epsilon PKC and ERK1/2 are essential for IPC-mediated neuroprotection. **(A)** Cell death was determined by propidium iodide (PI) staining in organotypic slices exposed to 40 min of oxygen and glucose deprivation (ischemia) alone or 48 h after IPC (15 min of oxygen and glucose deprivation) (modified from Ref. 56). The neuroprotection provided by IPC is lost when slices were exposed to the εPKC antagonist, εV1-2. Similarly pharmacological preconditioning with the εPKC agonist, ψεRACK, increases cell survival during oxygen and glucose deprivation. **(B)** The role of ERK1/2 in the preconditioning response was determined by treating organotypic slices with the MEK1/2 inhibitor PD-98059 during IPC (modified from Ref. 38). Inhibition of ERK1/2 activation significantly increased cell death when compared to IPC vehicle-treated control groups. These results indicate that ERK1/2 is activated by IPC and contributes to ischemic tolerance.

The PKC family of serine/threonine kinases is comprised of 11 isoforms which are classified as either conventional, novel, or atypical, based upon their requirement for calcium and/or lipids for activation. Recent research in our laboratory and others has demonstrated a vital role for epsilon PKC (εPKC) in neuroprotection during IPC (46, 56). The neuroprotection initiated by IPC is lost in the presence of εPKC inhibitors and can be simulated with activators of εPKC (56) (Fig. 2). A vital role of εPKC in preconditioning is especially demonstrated in εPKC knockout mice, which failed to exhibit an IPC response (61). It is thought that ePKC serves as a central signaling protein in many preconditioning models.

Many of the effector pathways discussed above confers protection in the mitochondria. Zhang *et al.* demonstrated that IPC prevented mitochondrial swelling and preserved membrane integrity and metabolism during middle cerebral artery occlusion (MCAO) in rats (85). Our laboratory has demonstrated that preconditioning only preserves mitochondrial function in the delayed, but not the early window of protection (52). The mechanism by which these effector pathways protect the mitochondria are not fully understood, but is thought to involve inhibiting the opening of the mitochondrial permeability

transition pore (mPTP) via opening of ATP-sensitive potassium channels and by upregulating mitochondrial uncoupling proteins. Recently, it was shown that STAT3 serine phosphorylation induces mitochondrial translocation and enhanced mitochondrial oxidative phosphorylation (57). Therefore, STAT3 may provide ischemic tolerance by altering mitochondrial function. In the next sections, we will examine the role of STATs on mitochondria and cell death.

Overview of STATs

STATs are a family of transcription factors that modulates diverse biological activities throughout the body. STATs consist of seven family members (STAT1–4, STAT5a, STAT5b, and STAT6) (62) which can be activated by cytokines/growth factors, free radicals, neurotransmitters, and inflammatory mediators in the event of injury (1). STAT1, STAT3, and STAT5 have been shown to be activated in the event of cellular injury; therefore, these factors will be the focus of discussion (53, 74, 84). The mechanisms of STAT activation have been well characterized. Growth factor or cytokine receptors are present on cell surface membranes to serve as signaling molecules to the cell producing a variety of functions (*i.e.*, immune modulation, inflammation, cellular repair from injury). Janus kinase (JAK) (a tyrosine kinase), located in the cytosol, is closely linked to these growth factor/cytokine receptors. Upon ligand binding to its respective receptor, activated JAK kinases phosphorylate tyrosine residues on the cytosolic portion of the receptor complex. STATs, which are inactive in the cytosol, dock with the receptor-phosphorylated tyrosine residues, are then phosphorylated by JAKs, resulting in STAT activation. STAT activation can also be derived from other receptor tyrosine kinase receptors and Src family of kinases (63). Upon activation, STATs translocate to the nucleus to induce gene transcription resulting in cell survival or cell degeneration pathways (71) (summarized in Fig. 3). In this review, we will discuss the beneficial role of STAT3, STAT5, and STAT6 as anti-apoptotic transcription factors as it relates to cerebral ischemia, while STAT1 promotes pro-apoptotic events thought to be detrimental to the brain post-ischemia.

The Role of STATs on the Mitochondria

A major mechanism by which IPC confers neuroprotection is through the modification of mitochondrial properties. Previous studies have shown that while the JAK/STAT pathways are involved in mediating ischemia/reperfusion injury and apoptosis (45), this pathway is also involved in IPC-mediated mitochondrial protection. In studies of mice hearts, IPC induced nuclear translocation and activation of STAT1 and STAT3 (81), which have been shown to have opposing roles in cell survival. STAT1 activation leads to pro-apoptotic signaling production of ROS (8), and loss of the mitochondrial membrane potential (39). STAT1, along with STAT6 signaling, are involved in the upregulation of adenine nucleotide translocator 3 (27), a mitochondrial protein that exchanges mitochondrial ATP for cytosolic adenosine diphosphate and is linked to apoptosis (44). In contrast, STAT3 inhibits the activity and transcription of STAT1 (24) and opposes STAT1-mediated apoptosis (71). Furthermore, STAT3 regulates mitochondrial function in a neuroprotective manner (60) and is required for the protective mechanisms of IPC (68).

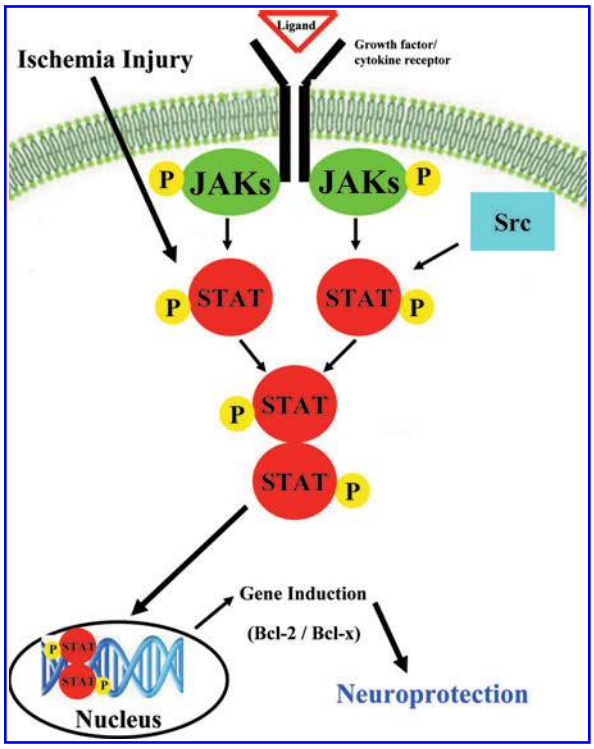

FIG. 3. Schematic diagram of general STAT activation pathway leading to neuroprotection.

STAT3 modulation of mitochondrial function and metabolism may explain its requirement for IPC-mediated protection (68). When STAT3 is knocked-out or downregulated, impairments in complexes of the electron transport chain are observed (summarized in Fig. 4). For example, lower rates of oxygen consumption in complexes I and II of heart mitochondria were detected in $STAT3^{-/-}$ mice (79). Ras-transformed STAT3-deficient mouse embryonic fibroblasts exhibited decreased complex II and V activity and lowered cellular ATP concentrations (16). Deletion of STAT3 in astrocytes led to similar results, but also caused increased ROS production, enhanced depolarization of the mitochondrial membrane potential, and led to reductions in mitochondrial mass. STAT3 appears to transcriptionally upregulate the activity of manganese superoxide dismutase (MnSOD) (29), an antioxidant that removes free radicals and deletion of STAT3 leads to increased production of ROS (60). Reconstitution of STAT3 in deficient cells reverses some of the mitochondrial impairments on complex activity and respiration that can be mediated by its deletion or downregulation (54, 79). The pervasive mitochondrial dysfunction that results from loss of STAT3 may partially explain the significance of STAT3-mediated neuroprotection during IPC (Fig. 4).

Recent studies have shown the presence of STAT3 in the mitochondria in a number of tissues including the heart, liver, brain, and kidney (16, 79). Immunoprecipitates of complex I from liver mitochondrial extracts were found to contain STAT3, which suggests a direct interaction of STAT3 with specific proteins on complex I (79). Furthermore, Wegrzyn *et al.* also found that mitochondria isolated from STAT3 deficient pro-B cells had reduced maximal state 3 oxidation rates, which suggests mitochondria-localized STAT3 plays a major role in modulating mitochondrial respiration. Therefore, STAT3 may

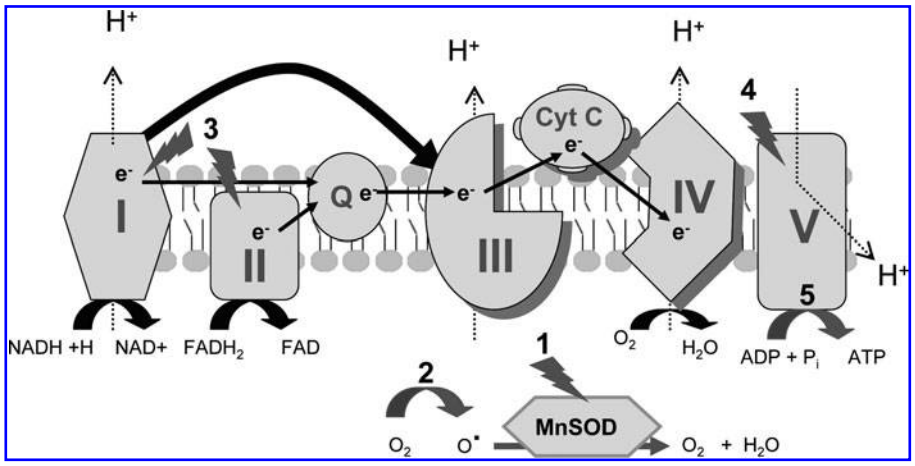

FIG. 4. STAT3 inhibition leads to mitochondrial dysfunction in the electron transport chain. Inhibition of STAT3 downregulates expression of free radical scavenger MnSOD[1] (29), increases levels of ROS[2] (60), decreases complex I & II oxygen consumption rates[3] (79), decreases activity of complex V[4] (16), and reduces cellular ATP levels[5] (60).

have the ability to regulate mitochondrial function independent of its already well-defined role as a transcription factor. However, the functional role of STAT3 as a mitochondrial-mediator and transcription factor as it relates to IPC remains unclear.

STATs and Apoptosis

STAT1 is activated by cytokines, growth factors, and hormones (74). STAT1 has been shown to play a dedicated role in interferon-γ (35) and physiological responses by inducing cyclin-dependent kinase inhibitor ($p21^{WAF1}$) to promote cell growth arrest (7). STAT1 activation is prevalent in neurons in the cortex and striatum following ischemic injury (53, 74). It is expressed normally in the adult rat brain and is induced after focal ischemia in the ipsilateral cortex up to 15 days post-ischemia (53). Several reports have suggested that STAT1 regulates apoptosis in cardiomyocytes and fibroblasts up-regulating pro-apoptotic factors such as caspases (8). In the heart, STAT1 decreases anti-apoptotic gene expression of B-cell lymphoma-2 (Bcl-2) and B-cell lymphoma-2-associated X protein (Bcl-x) in ischemia/reperfusion injury (71). Only a few reports have suggested the involvement of STAT1 in cerebral ischemia-induced cell death. In MCAO mice, STAT1 phosphorylation and nuclear translocation is enhanced, promoting apoptosis and cell death by enhanced Akt phosphorylation and caspase-3 activation (8, 74). Likewise, $STAT1^{-/-}$ mice are more resistant to ischemic brain injury (74), suggesting a neurodegenerative role for STAT1 during cerebral ischemia. In contrast, others reported that upregulation of STAT1 may be anti-apoptotic in other instances. For example, in human glioblastoma patients, STAT-1 expression was present via immunohistochemistry suggesting other downstream mediators regulating apoptosis (22). Pathological diseases such as infections or prion diseases also led to activation of STATs (70). In cerebellar granule neurons exposed to Clostridium difficile toxin B, upregulation of the JAK/STAT1 pathway revealed that it is pro-apoptotic in nature (42). Nevertheless, this paradigm may be beneficial in regulating cancer cells, although STAT1's involvement in neuroprotection after cerebral ischemia may be detrimental to critical neuronal function in the brain.

The role of STAT3 has also been well defined in the cortex, striatum, and hippocampus (CA1 region). STAT3 activation was found in numerous cell types in the brain including neurons, astrocytes, endothelial cells, microglia, and monocytes/macrophages (9, 31, 34, 72), impacting neuronal development (23), neuroprotection after ischemic injury (72), and regeneration after nerve injury (65). Major cellular functions such as cell proliferation, survival, and development are also regulated by STAT3 (11). Contrary to STAT1, in the MCAO model of transient focal ischemia, phosphorylated-STAT3 was observed to be co-localized with Bcl-2 (36) and not with cleaved caspase-3 (82), suggesting STAT3 is important in neuronal survival (Fig. 5). STAT3 activation has also been found in glia, which may provide indirect support to neuronal survival (69). For example, the presence of hypoxic preconditioning in cultured cortical neurons induced neuroprotection mediated by the STAT3 signaling pathway (76). Similarly, activation of STAT3-induced superoxide dismutase 2 gene expression resulted in neuroprotection (30).

Unlike STAT1, STAT3 and STAT5 induced Bcl-2 and Bcl-x gene expression resulting in anti-apoptotic events in the cell (71, 84). The opposing actions of STAT1 (pro-apoptotic) and

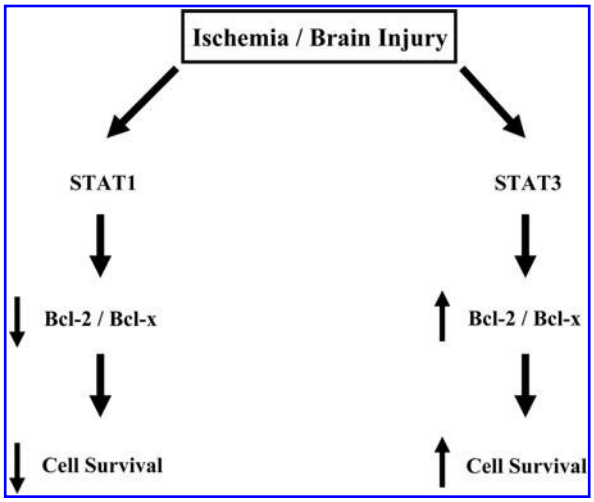

FIG. 5. Opposing effects of STAT1 and STAT3 during ischemia. Upon activation of STAT1 or STAT3 by ischemia or brain injury, Bcl-2/Bcl-x gene expression is decreased in the presence of STAT1 but enhanced in STAT3 activation. This results in decreased cell survival (pro-apoptosis) by STAT1 activation, while cell survival is enhanced via activation of STAT3 (anti-apoptosis).

STAT3 (anti-apoptotic) provide a balance for cellular homeostasis. Pathologically, upregulation of STAT3 after cerebral ischemia may prove beneficial by providing some degree of neuroprotection, while in cancer cells, STAT3 activation has been found to be enhanced for increased tumor growth (19). In contrast to the neuroprotection observed after cerebral ischemia and tumor cells, STAT3 mediated beta-amyloid-induced neuronal cell death in the cortex and hippocampus of mice (75). These results suggested that STAT3 activation is pro-apoptotic contrary to other reports. Thus, the general anti-apoptotic properties of STAT3 must be interpreted with caution. The role of STAT3 as an anti- or pro-apoptotic signaling pathway may depend on cell type and pathological condition and warrants further investigation.

STATs and IPC

The role of STATs and IPC has predominately been demonstrated in the heart but not in the brain, except for Kim *et al*, (32). For example, STAT3 activation via JAK was cardioprotective in the infarcted-reperfused heart by inducing expression of Bcl-2 or Bcl-x (49). STAT3 was overexpressed in transgenic hearts of mice, providing protection from oxidative stress via doxorubicin-induced cardiomyopathy (37). Other reports have suggested different STATs (STAT5A) are involved in preconditioning of the heart via Src kinases and JAK signaling pathways (83).

STAT activation and function as it relates to IPC have not been well defined. In fact, current literature focuses predominately on the heart. IPC enhances STAT3 expression in astrocytes in the hippocampus (34). We demonstrated that in mixed cortical neurons/astrocyte cultures, the IPC signaling cascade involves STAT3 activation mediating ischemic tolerance *in vitro* (32) (Fig. 6). In addition, 6 hours post-OGD, JAK-STAT signaling was detected in adult rat hippocampal slices (2) concurrent with our previous findings (32).

We hypothesize that more subtypes of STATs are involved in IPC-induced tolerance that will confer neuroprotection in the brain after stroke, cardiac arrest, or general cerebral ischemic events that can occur in the body. Besides neuroprotection, little is known regarding STATs, as it relates to cerebral blood flow (CBF) in the presence of CBF-related deficits (stroke, cerebral ischemia, etc). Since STATs also affect brain parenchyma, it is plausible that STATs can affect vascular-associated cells, providing not only neuroprotection, but proper CBF in the presence of pathology (58).

Conclusion

STATs modulate diverse biological activities throughout the body. A variety of signal transduction pathways that are activated by IPC, such as MAPK and εPKC, have been demonstrated to activate STAT3 and lead to ischemic tolerance. Moreover, STAT activation affects not only signal transduction mechanisms, but also mitochondrial bioenergetics. STAT1 activity depolarizes mitochondrial membrane, leads to the production of ROS, and is linked to apoptosis. STAT3 regulates mitochondria in a neuroprotective manner by preserving efficiency of electron transport chain complexes and maintaining cellular ATP levels. STAT3-mediated neuroprotection during IPC is well characterized in cardiac models, but few reports have described this phenomenon in the brain. STAT3 activation enhances Bcl-2 and Bcl-x gene expression, resulting in anti-apoptotic events in the cell, while STAT1 decreases these genes promoting pro-apoptotic situations. The opposing affects between STAT1 and STAT3 and in particular, the role of mitochondrial localized STATs needs further clarification in the ischemic preconditioned brain. Therefore, defining the mechanisms of STAT activation via IPC can prove very beneficial in providing a new dimension of neuroprotection in the brain against ischemic challenges.

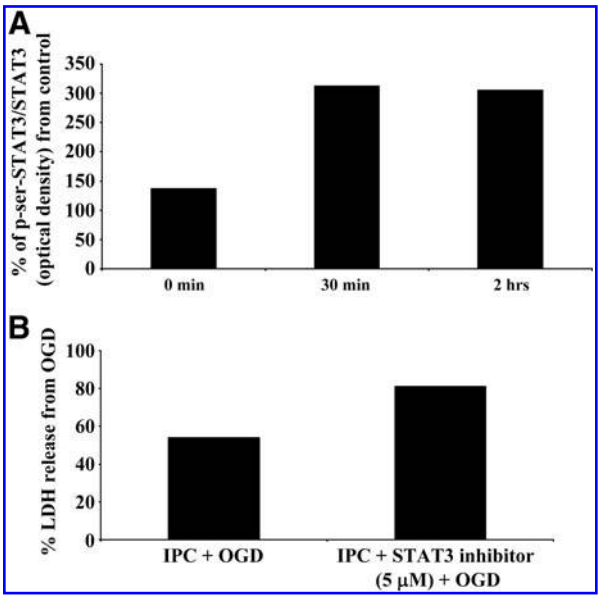

FIG. 6. STAT3 activation is required for IPC-mediated neuroprotection. STAT3 serine 727 phosphorylation was determined in cells lysed immediately after 1 h of PC and at 15 min, 30 min, and 2 h of reperfusion after 1 h of PC **(A)**. These results suggest that STAT3 is activated by IPC. **(B)** Histogram representing cell death measured by LDH release at 48 h of reperfusion after oxygen and glucose deprivation (OGD) (4 h) injury. Inhibition of STAT3 activity with the STAT3 inhibitory peptide (PpYLKTK, 1 and 5 mol/L) blocked IPC neuroprotection. These results indicate that STAT3 is activated by IPC and is required for neuroprotection during ischemia (modified from Ref. 32).

Acknowledgments

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Abbreviations Used

Akt = protein kinase B
ATP = adenosine triphosphate
BAD = B cell lymphoma-2-associated death promoter
Bcl-2 = B-cell lymphoma-2
Bcl-x = B-cell lymphoma-2-associated X protein
CBF = cerebral blood flow
Cox-2 = cyclooxygenase-2
εPKC = epsilon PKC
ERK = extracellular signal-regulated kinases
Flk-1 = VEGF receptor-2
GSK3β = glycogen synthase kinase 3 beta
HIF-1α = hypoxia-inducible factor 1α
iNOS = inducible nitric oxide synthase
IPC = ischemic preconditioning
JAK = janus kinase
JNK = c-Jun N-terminal protein kinases
MAPKs = mitogen-activated protein kinases
MCAO = middle cerebral artery occlusion
MEK = MAPK kinase
MEKK = MAPK kinase kinase
MnSOD = manganese superoxide dismutase
mPTP = mitochondrial permeability transition pore
NAD = nicotinamide adenine dinucleotide
NF-κB = nuclear factor kappa B
OGD = oxygen and glucose deprivation
PKC = protein kinases C
ROS = reactive oxygen species
RTK = receptor tyrosine kinase
STATs = signal transducers and activators of transcription
VEGF = vascular endothelial growth factor

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