Chapter 3

Mitochondrial Regulators of Synaptic Plasticity in the Ischemic Brain

Han-A Park and Elizabeth A. Jonas

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67126

Abstract

Synaptic plasticity is a process by which neurons adapt or alter the strength of information transfer, and it is known to play a role in memory formation, learning, and recovery after injury. In this chapter, we describe how ischemic insults alter neuronal intracellular mechanisms and signaling pathways, and we discuss how, after neuronal injury, synaptic plasticity is regulated prior to and during death or rehabilitation and recovery. In addition, recently described regulators of synaptic plasticity will be introduced.

Keywords: ischemia, mitochondrial metabolism, neuroprotection, Bcl-xL, ATP synthase

1. Cellular mechanisms after cerebral ischemia

Cerebral ischemia occurs as a result of a lack of, or insufficiency of, blood supply to the brain, which results in the failure to meet neuronal metabolic demands. Thrombotic or embolic stroke (focal), and cardiac arrest or cardiac surgery (global) are common causes of cerebral ischemia. The loss of oxygen and glucose flow to the brain eventually leads to neuronal energy deficits. These energy deficits result in the failure of adenosine triphosphate (ATP)-dependent ion pumps expressed on the neuronal plasma membrane, permitting an unregulated surge of ion influx into the neuronal cytoplasm [1–3]. Calcium influx induces the release of neurotransmitters from presynaptic neurons and activation of postsynaptic glutamate receptors such as N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [4–6]. Uncontrolled opening of postsynaptic receptors provokes failure of intracellular ion homeostasis, resulting in excessive postsynaptic entrance of calcium or sodium through NMDA- or AMPA-regulated channels; this initiates signaling pathways.

Calcium is a trigger for a number of important cell-signaling pathways. Increased levels of intracellular calcium activate phospholipase C, which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) and forms diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3) [1]. The hydrophobic DAG molecule is expressed on the cell membrane, and recruits protein kinase C (PKC) from the cytosol. PKC regulates synaptic function by phosphorylating ion channels [7–9] and glutamate receptors [10, 11], and enhancing neuronal outgrowth [12, 13]. On the other hand, hydrophilic IP_3 travels into the cytosol and binds with the IP_3 receptor expressed on the endoplasmic reticulum (ER). The ER membrane-embedded IP_3 receptor releases calcium from the ER to mitochondria, depolarizing mitochondrial inner membranes and further compromising ATP production.

Ischemic conditions also activate death receptors (e.g., Fas, tumor necrosis factor (TNF)αR, DR) that cause caspase activation and ultimately lead to neuronal apoptosis [14, 15]. Death receptor-ligand binding releases caspase 8, which directly cleaves either caspase 3 (which can activate downstream death-inducing enzyme pathways) or BH3 interacting-domain death agonist (Bid) to form truncated tBid [16, 17]. tBid translocates to the mitochondria and initiates activation of the pro-apoptotic proteins Bax and Bak. Oligomerization of Bax on the mitochondrial membrane causes cytochrome c release. Cytochrome c forms an apoptosome complex made up of cytochrome c, apoptotic protease-activating factor 1 (APAF 1), and caspase 9. Caspase 9 cleaves and activates effectors such as caspase 3 and caspase 6 which results in neuronal apoptosis. Numerous proteins are subjected to caspase-mediated cleavage [18] including regulators for synaptic function such as glutamate receptors [19, 20], synaptic adhesion molecules [21], ion channels [2], neuronal growth/pruning regulators [22, 23], and inflammatory cytokines [24, 25].

In addition, ischemic stimulation increases the permeability of the blood-brain barrier, and activates neuroinflammatory responses in the brain. Inflammatory infiltration such as the entrance of leukocytes (e.g. neutrophils, macrophages, and lymphocytes) activates microglia and astrocytes which then release inflammatory regulators, including cytokines (e.g. interleukin-1β (IL-1β), IL-6), tumor necrosis factor α, chemokines (e.g. chemokine C-C motif ligand 2 (CCL2), CXC-chemokine ligand 1 (CXCL1)), nitric oxide, reactive oxygen species (ROS), and growth factors [26–29]. Neuroinflammation is a dual-purpose response that can hasten neuronal death or facilitate repair depending on the circumstances. For example, TNF-α is one of the most well-studied pro-inflammatory cytokines increased by ischemic events; it is clearly responsible in large part for ischemia-induced brain injury [30]. However, TNF-α also enhances synaptic strength by increasing the expression of AMPA receptors [31] and through the regulation of the transcription factor, NFκB [32], increasing the expression of anti-apoptotic proteins (Bcl2, and Bcl-xL) and facilitating the production of neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) [33, 34] which play a role in neuroprotection [35]. Taken together, ischemia triggers a multifunctional and complex process in the brain that can lead to neuronal death or facilitate the defense system to rescue the brain against neurotoxic stimulation.

2. Synaptic plasticity in the ischemic brain

The process of early neuronal growth and neurite elongation is critical for synapse formation and neuronal network development. Projection of filopodia, where actin and microtubules

http://dx.doi.org/10.5772/67126

become polymerized and attach to substrates, anchors a growth cone and guides a peripheral domain within the thin outer edge of the growth cone known as the lamellipodium. After the lamellipodium contacts the substrate, the central domain of the growth cone, where actin is reorganized and microtubules predominate, moves toward its target [36–38]. These steps occur repeatedly during neurite sprouting and branching. When the tip of the axon reaches its target (either dendrite, soma, or another axon), it differentiates to become suitable for neurotransmission. Presynaptic terminals contain a high density of mitochondria, presynaptic vesicles, and endosomes to enhance communication within the synapse. The target of presynaptic contact is the postsynapse, which matures by the expression of neurotransmitter receptors. Neurexin-neuroligin, N-cadherin, ephrin, and synaptic cell-adhesion molecules play a role in the interaction between presynaptic and postsynaptic neurons [37, 39–42].

Neuronal development is far from static in the mature brain. Recent studies have found that neurons are capable of plasticity during the entire human lifespan [43–46]. Mature neurons have the ability to repair their synaptic network after neurotoxic insults. Stroke induces changes in numerous genes including the ones involved in axonal sprouting in both young and aged animals [47]. Alteration of neuronal connectivity and degradation of neurites are well described after ischemic stroke [47–49], and strategies to strengthen the synaptic network to regain neuronal function and enhance brain repair after episodes of brain injury have been reported [47, 50]. Our study demonstrates examples of the dynamic and adaptive changes that occur in neurites after glutamate neurotoxic challenge. Neurite branches initially become fragmented and damaged (**Figure 1A** and **D**), but then neurites regain structure (**Figure 1B**and **C**) over time, or undergo degradation if severely damaged; in some case collateral sprouting occurs to compensate for lost neurites and to regain synaptic connectivity with healthy neighboring cells (**Figure 1D–F**).

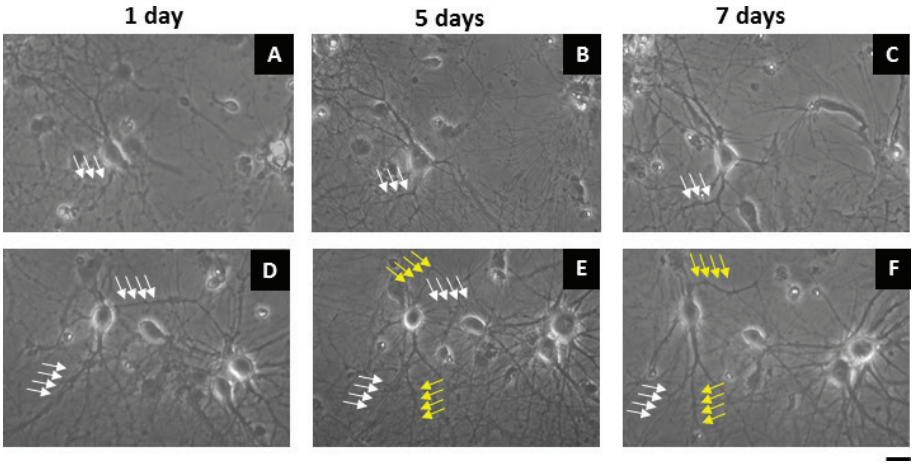

Figure 1. Adaptation of neurite sprouting and pruning after glutamate-induced neurotoxicity. Primary hippocampal neurons were treated with 20 μM glutamate and then imaged at days 1, 5 and 7 after introduction of the insult. Bar, 20 μm. (A) Damaged and fragmented neurite at 1 day after insult (white arrows). (B) Early recovery of injured neurite at day 5 (white arrows). (C) Thickening of recovering neurite at day 7 (white arrows). (D) Fragmented and damaged neurites at day 1 (white arrows) are cleared at day 5 (E, white arrows), but strengthening of collateral branches was found at day 7 (F, yellow arrows) to supplement synaptic networking.

Numerous studies have reported the modification of synaptic plasticity during or after ischemic events. Some studies describe synaptic modification as a part of death signaling; on the other hand, other studies suggest changes in synaptic function as a mechanism of protection or rehabilitation. Synaptic plasticity plays a role in the decision for the neuron to live or die. Synaptic transmission demands high levels of energy production [51]. Failure to control neurotransmitter release [6, 52], and abnormalities of synaptic transmitter release due to lack of energy supply after ischemic insult are well described previously [53]. Regulation of the postsynaptic receptor is critical to control synaptic plasticity [54, 55], and studies have reported that NMDAR or AMPAR are subject to alterations after ischemic events. Earlier studies have shown that brains of animals undergoing four vessel occlusion (4VO)-induced global ischemia show impaired voltage-dependent NMDAR responses, display NMDA-mediated hyperexcitability and loss of long-term potentiation (LTP), and manifest morphological changes of pyramidal neurons prior to the onset of delayed death in the CA1 region of hippocampus [56, 57]. Recent studies expand on these mechanisms and distinguish roles for individual ion channel subunits [58–61]. Studies have reported that ischemia is responsible for the alteration of AMPA receptor expression, especially the GluR2 subunit, transforming a non-calcium permeable into a calcium-permeable AMPA receptor, thereby further mediating calcium entry into CA1 neurons after global ischemia. Although this role contributes to delayed neuronal death in the globally ischemic rodent brain [62–65], these changes may also occur during normal events in synaptic plasticity [54, 66]. Despite the close relationship between ischemia-induced neuronal death and NMDA receptor activation, the application of NMDAR antagonists fails to prevent stroke-related brain injury in clinical trials [67] perhaps indicating involvement of NMDAR in neuronal survival. Indeed, functioning NMDARs are required for synaptogenesis, and the NMDAR plays a neuroprotective role against apoptotic stimulation and oxidative stress [61, 68–70]. In summary, synaptic changes that occur during ischemia may be protective or detrimental depending on the severity and temporal sequence of ischemic events.

2.1. Synaptic failure may lead to ischemic death

Structural damage including degradation of axons or dendrites, and loss of synaptic connectivity associated with synaptic dysfunction are described in various cerebral ischemic models [53, 71]. Animals undergoing ischemic surgery exhibit a reduction of the total neuronal population and an increased appearance of degenerating neurons and apoptotic cells [72–76]. Shy of frank cell demise, axonal morphological changes after brain ischemia have been reported within a variety of brain regions including cortex, striatum, and hippocampus. Degenerating axons exhibit swelling and the appearance of varicosities in both an acute and chronic manner; changes are observed over a period between 6 h and 4 weeks after ischemia reperfusion [49]. Cerebral ischemic insults also lead to cytoskeletal disruption in neurites such as a reduction in the amount of microtubule-associated protein (MAP2), an enhancement in neurofilament proteolysis and an alteration of tau in some neurons [77–79]. Ischemia causes an increase in intracellular calcium levels and ROS production [15] and triggers neuronal death by mechanisms such as enhancing mitochondrial permeability which can facilitate both apoptotic and necrotic death and neuritic degeneration [80]. Therefore,

http://dx.doi.org/10.5772/67126

ischemia is one of the major causes of structural and functional failure of both somata and neuronal processes during stroke.

2.2. Synaptic repair after ischemic events

Although ischemic stroke induces neuronal death that leads to functional disability, studies have reported evidence for synaptic plasticity contributing to recovery after stroke [81]. Rats undergoing neocortical ischemia had induction of the growth-associated protein 43 (GAP-43) which is enriched in the growth cone, promoting synaptogenesis and behavioral recovery [82, 83]. Axonal sprouting and plasticity in the intracortical circuitry was observed in post-ischemic brain regions [84, 85]. Plasticity was not limited to neurons but also occurred in other cells including reorganization of vascular structures. Enhancement of the dendritic network such as increased dendritic density has been reported in post-ischemic brain [86, 87]. Moreover, the brain is capable of generating new neurons. The subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus are reported to be the site of neurogenesis, exhibiting therapeutic potential for the treatment of brain diseases [88]. In particular, studies have shown that stroke increases neuronal progenitor cell populations in the brain [89, 90], and enhances cell proliferation in the SVZ [91] and in the ischemic penumbra of stroke patients [92]. These studies indicate that ischemia-induced signaling, even denervation itself, may act as a stimulus for the functional and structural recovery of synapses.

2.3. Preconditioning in synaptic potentiation

Despite the possibility of severe ischemia to trigger adaptive responses on its own, studies have also reported that non-noxious, lower levels of injury (preconditioning) may augment ischemic tolerance. Moderate levels of neurotoxic stimuli such as glutamate, ROS, or inflammation initiate survival mechanisms without impairing brain function. Thus, preconditioning builds a latent neuroprotective environment in the brain and provides for a reprogrammed defense response when the truly injurious stimulation occurs [93, 94].

Zukin's group has reported that ischemic preconditioning downregulates AMPA receptors, and blocks mitochondrial release of death molecules such as Smac and DIABLO without altering the pro-survival inhibitor of apoptosis (IAP) family, therefore attenuating ischemia-induced damage in rodent hippocampal neurons [95, 96]. Neuroprotective mechanisms of preconditioning are further evidenced as a change in dynamics of mitochondrial proteins. Preconditioning prevents translocation of the pro-apoptotic protein Bad, enhances the availability of the pro-survival protein Bcl-xL, blocks activation of caspase 3, decreases release of Smac, DIABLO, and cytochrome *c*, and prevents large conductance mitochondrial channel activity, eventually rescuing hippocampal neurons after ischemic insult [72]. In addition, mitochondrial Bcl2 protein family [97–99], redox regulators [100, 101], and transcription factors such as hypoxia-inducible factor (HIF) [102, 103], NFκB [104, 105], c-Fos [106], CREB [97, 105], Nrf2 [101, 107], and AP1 [108] are involved in gene regulation after preconditioning, further modifying neuronal functions such as neurotransmitter release, channel activity, and synaptic networking by regulating the expression of new proteins.

3. Regulators of mitochondrial function and synaptic plasticity

Ischemic insults damage the mitochondrial electron transport chain, decrease mitochondrial ATP production, impair ATP-dependent transporters, and allow intracellular calcium entrance that triggers opening of the mitochondrial permeability transition pore (mPTP) [80, 109, 110]. Ischemia also impairs electron transfer and causes ROS generation from mitochondrial proteins such as complex I and III [111]; ROS greatly contributes to mPT-mediated responses in the mitochondrial membrane [112]. On the other hand, ischemia alters proteins that resides in the mitochondria, and changes levels of transcription factors that target the promoter regions of mitochondrial and nuclear genes. Thus, mitochondria are an essential organelle in ischemia-mediated neuronal responses. There are several regulators that modify mitochondrial function and plasticity to either enhance synaptic recovery after injury or signal for synaptic decline prior to neuronal death. We describe these individually and then show how they work together to support synaptic function during stress.

3.1. Mitochondrial reactive oxygen species

Oxidative phosphorylation is the metabolic process that produces ATP, but it is also the main source of production of superoxide in the mitochondria that can be converted into hydrogen peroxide. Due to the high metabolic rate of neurons, ROS is highly produced in the brain. However, the brain is also more vulnerable than other organs to ROS-induced damage, because it is rich in polyunsaturated fatty acids, and lacking in catalase activity [113, 114]. Indeed, ROS is one of the main causes of mPTP opening, release of mitochondrial death molecules and cell death in ischemic brain [15]. Although numerous studies have reported that an ischemia-induced surge of ROS causes functional and structural injury to neurons, ROS plays multifunctional roles. Physiological levels of ROS regulate synaptic signaling. Approaches that block production or enhance clearance of superoxide using depletion of NADPH oxidase, or overexpression of superoxide dismutase (SOD), respectively, failed to allow for LTP in hippocampal slice [115–117]. Moreover, SOD-overexpressing mice demonstrate defective hippocampal memory formation as measured by water maze learning and fear conditioning [117, 118].

Nitric oxide synthase (NOS) is an enzyme that generates nitric oxide (NO) gas from arginine. NO is considered to be a ROS, due to its ability to generate highly reactive peroxynitrite [119]. Indeed, 4VO-induced global ischemia causes induction of NO in various regions of the brain including hippocampus, cortex, striatum, and cerebellum [120]. Excessive NO production is reported to be neurotoxic as it damages mitochondria, and exacerbates excitotoxicity [121–123]. However, NO is also required for synaptic transmission and synaptic plasticity [124, 125]. NADPH oxidase (NOX) is a cell membrane-bound enzymatic complex that generates superoxide from NADPH, and it also expresses in the mitochondria [126]. NOX contributes to ROS-induced neuroinflammation and apoptosis [127, 128]. Studies reported an upregulation of NOX mRNA and protein level in response to experimental stroke [129, 130]. Inhibition of NOX using the pharmacological inhibitor apocynin improved ischemia-induced brain damage and mortality [131, 132]. However, mice lacking NOX subunits had impaired long-term

http://dx.doi.org/10.5772/67126

potentiation and manifested hippocampus-mediated memory deficits, indicating that a physiological level of NOX and ROS may be required for synaptic plasticity and memory formation [114, 115].

3.2. Mitochondrial permeability transition pore (mPTP) and ATP synthase

Ischemia-induced death signaling opens a calcium-sensitive inner mitochondrial membrane pore called mPTP, causing permeabilization of the mitochondrial inner membrane [80, 109, 110]. Loss of mitochondrial inner membrane integrity leads to leakage of intermembrane molecules such as cytochrome *c*, Smac, and DIABLO into the cytoplasmic space, facilitates death-signaling cascades, and results in the impairment of mitochondrial outer membrane structure and cell death. Thus, mPTP is recognized as an important target for neuroprotection; inhibition of mPTP opening may delay or prevent mitochondrial-mediated cell death. Since the discovery of the calcium-induced mitochondrial membrane permeability transition (PT) [133, 134], several molecular participants in mPTP structure or formation have been reported. However, the identification of mPTP is still under investigation.

Cyclophilin D (Cyp D) is a peptidyl-prolyl *cis*/*trans* isomerase that is localized to the mitochondrial matrix. Cyp D has been considered as a main element of mPTP. However, recent studies have reported that depletion of Cyp D did not eliminate mPTP [135–137] indicating it may not be the critical component of pore opening. One target of Cyp D is a complex of proteins that includes the voltage-dependent anion channel (VDAC), localized to the mitochondrial outer membrane, and the adenine nucleotide translocase (ANT), an ADP/ATP translocator localized to the mitochondrial inner membrane. Therefore, this protein complex was widely studied for its possible role in forming mPTP [138]. Studies showed that mitochondrial swelling after stimulation facilitates the formation of VDAC and ANT complexes along with Cyp D binding, leading to opening of pores in the mitochondrial inner and outer membranes [139–143]. Studies have continuously reported new participants of Cyp D-ANT-VDAC complex: the mitochondrial phosphate carrier binds to Cyp D and ANT [144], spastic paraplegia 7 forms a heterooligomeric complex with VDAC [145], and hexokinase binds to VDAC [146, 147]. However, a recent study revealed that animals lacking VDAC genes did not show improvement of mPTP-mediated mitochondrial stress. They exhibited equivalent levels of cytochrome c release, caspase activation, and cell death compared to control animals [135]. In addition, mitochondria from mice lacking ANT also displayed mPT and cytochrome c release at similar rates compared to wild-type controls [148]. These studies indicate that further investigations are required to clarify the roles of VDAC and ANT in mPTP activation.

In contrast to the studies of VDAC and ANT, knockdown of the membrane-embedded portion (c-subunit) of the F_1F_0 ATP synthase does regulate the ability of mitochondria to undergo PT. Several recent studies have reported that F_1F_0 ATP synthase is an important candidate to form mPTP [149–157]. F_1F_0 ATP synthase is localized in the mitochondrial inner membrane (F_0 unit) and matrix (F_1 unit), and produces ATP by using the potential energy of the hydrogen ion gradient. F_1F_0 ATP synthase gained attention as a putative candidate for mPTP when it was found that it binds CypD [152] and when it was reported to regulate the efficiency of mitochondrial energy metabolism via controlling an inner mitochondrial membrane ion leak

[158]; the c-subunit of the ATP synthase was found to be required for mPTP [149]; the c-subunit of ATP synthase was revealed to form a voltage-sensitive channel, the opening of which is correlated with PT and neuronal death [155]. Bonora and Alavian also showed that shRNA-mediated c-subunit depletion protects neurons from PT-induced cell death, such as excitotoxic and oxidative stress. Together, the findings suggest that the c-subunit forms the pore component of mPTP [155]. Moreover, the depletion of c-subunit of F_1F_0 ATP synthase causes resistance to calcium-induced mPTP opening, while overexpression of c-subunit accelerates calcium-mediated responses, decreases mitochondrial potential, and promotes mitochondrial fragmentation [149, 155]. In addition to the role of the ATP synthase monomer, dimerization of F_1F_0 ATP synthase in mPTP has been correlated with the onset of mPT [151, 159–161].

3.3. B-cell lymphoma-extra large (Bcl-xL) and other Bcl2 family proteins regulate the synapse

Bcl-xL is a member of the Bcl-2 family of proteins. It is traditionally known for anti-apoptotic properties through its role to inhibit the activation/oligomerization of pro-apoptotic Bax and Bak on mitochondrial membranes [162, 163], and its ability to block mitochondria-mediated cytochrome c release and cell death [164]. However, recent studies have reported multifunctional roles of Bcl-xL in the brain. Bcl-xL facilitates reorganization and biogenesis of mitochondria by regulation of fission and fusion [165–167]. Inhibition of Bcl-xL decreases neuronal ATP levels but increases oxygen flux, indicating that Bcl-xL enhances the efficiency of mitochondrial metabolism by preventing the wasteful leak of H^+ ions through the inner membrane [158, 168]. Inefficient leakage of H^+ through a mitochondrial inner membrane pore prevents ATP production. These latter studies provided the first evidence for a functional role for Bcl-xL at the mitochondrial inner membrane and F_1F_0 ATP synthase. Bcl-xL interacts with α- and β-subunits [158, 169] of F_1F_0 ATP synthase in the mitochondrial matrix. These protein-protein interactions may cause conformational changes of the Bcl-xL-F_1F_0 ATP synthase complex, favoring closure of the c-subunit channel (putative mPTP), enhanced mitochondrial energy metabolism, and increased ATP production with minimal oxygen use (decreased inner membrane uncoupling).

It is therefore not surprising that Bcl-xL is an important player in energy-demanding processes such as neuronal outgrowth [74, 170] and synapse formation [167, 171]. Depletion of Bcl-xL in primary hippocampal neurons impairs neuronal branching and elongation [74]. Abnormalities of neurite sprouting caused by Bcl-xL depletion do not induce immediate cytotoxicity, but cause delayed neuronal death, presumably as more synapses fail. Despite their low propensity toward death in the absence of stress, neurons depleted of Bcl-xL are significantly vulnerable to hypoxic insult compared with control neurons, presumably due to failure of synaptic connections and impaired metabolism. In contrast to depletion, Bcl-xL overexpression increases levels of pre- and postsynaptic markers on axons and on the opposing dendrites and enhances the number of mitochondria and synaptic vesicles in the presynaptic bouton [167]. Bcl-xL also enhances synaptic vesicle recycling during presynaptic plasticity, by forming a complex of clathrin, Bcl-Xl, and Drp1 which is necessary for normal or enhanced endocytosis [171]. In addition, Bcl-xL is reported to have multiple binding partners besides those of traditional Bcl2 family proteins that regulate apoptotic pathways (**Table 1**); thus, additional functions of Bcl-xL in synaptic plasticity need to be further investigated.

Protein	Roles	References
Bcl2 family protein		
Bak	Regulates apoptosis	[163, 208]
Bax	Regulates apoptosis	[209–211]
Beclin 1	Prevents autophage	[212]
Bad	Regulates apoptosis and cell cycle	[213–215]
Bim	Regulates apoptosis	[216, 217]
Bid	Regulates apoptosis	[217]
PUMA	Regulates apoptosis	[209, 218]
Non-Bcl2 family proteins		
Apoptotic protease-activating factor 1 (Apaf-1)	Regulates caspase 9-mediated apoptosis	[219, 220]
Apoptosis regulatory protein Siva (Siva-1)	Sequestrates Bcl-xL and induces apoptosis	[221]
F_1F_0 ATP synthase	Regulates mitochondrial energy metabolism	[158, 169]
Aven	Stabilizes Bcl-xL and regulates caspase-dependent apoptosis	[222, 223]
Dynamin-related protein 1 (Drp1)	Regulates synaptic vesicle endocytosis	[165, 167, 171]
IP3 receptor	Regulates calcium signaling and apoptosis	[224, 225]
Phosphoglycerate mutase family 5 (PGAM5)	Enhances Keap1-dependent degradation	[226, 227]
PTEN-induced putative kinase 1 (PINK1)	Regulates phosphorylation of Bcl-xL to prevent its cleavage	[228]
Voltage-dependent anion channel (VDAC)	Regulates mitochondrial calcium, cytochrome c release, ATP release	[164, 229, 230]
Tumor protein p53	Regulates cytochrome c release and apoptosis	[231, 232]

Table 1. List of proteins that bind to Bcl-xL.

In contrast to its neuroprotective properties, Bcl-xL is also capable of decreasing synaptic strength [172, 173] and inducing neurotoxicity [73, 174]. Bcl-xL is subject to caspase-mediated fragmentation [174–176], and forms N-terminus truncated ΔN-Bcl-xL. The N-terminally localized BH4 region has been reported as the functional domain that carries out the anti-apoptotic role of Bcl-xL [177, 178], and cleavage of Bcl-xL to remove this domain gives pro-apoptotic characteristics to this molecule. ΔN-Bcl-xL is reported to induce large channel activity in the synaptic mitochondria [172], to cause decline of the amplitude of post synaptic potentials [173], and to increase cytochrome c release [179]. Studies show that transient global ischemia induces ΔN-Bcl-xL formation prior to delayed neuronal death in the CA1 region of hippocampus [72, 73]. The strategies to block ΔN-Bcl-xL formation such as administration of pharmacological inhibitors, or mutation of the caspase cleavage site protect rodent brains against ischemic injury [73, 172].

Bcl-2-associated x protein (Bax) is a pro-apoptotic member of the Bcl2 family containing BH1, BH2, and BH3 domains but lacking the BH4 domain found in many anti-apoptotic

family members. Bax forms channel activity in lipid bilayers [180], induces cytochrome c release [162, 181], and cooperates with mPTP candidates such as ANT and VDAC [138, 164]. Interestingly, although it is mostly known as a pro-apoptotic protein, it also has important functions in healthy synapses undergoing plasticity. Injection of Bax protein into the presynaptic terminal induces enhanced neurotransmitter release, similarly to effects of pro-survival Bcl-xL, indicating that Bax is capable of supporting normal synaptic plasticity in unstressed neurons [182]. In healthy hippocampal neurons, Bax is necessary for the formation of synaptic plasticity known as NMDA receptor-dependent LTD. Despite comparable expression of NMDA receptors in Bax knockout animals, these animals fail to demonstrate hippocampal LTD induction [183].

Bid is a pro-apoptotic BH3 only protein. Bid is normally expressed in the cytoplasm, but during cytotoxic stimulation, caspase cleaves Bid into truncated Bid (tBid) which activates other members of the pro-apoptotic Bcl2 family [184] or antagonizes anti-apoptotic Bcl2 proteins [17]. tBid contributes to the mobilization of cytochrome c by Bax and alters mitochondrial cristae independent of its function to activate Bax, and it opens mitochondrial intermembrane spaces [185]. Bid enhances mitochondrial membrane permeabilization, cooperates with mPT or Bax, and mediates large-channel conductances [186]. Studies show that Bid is an important activator in ischemia-induced brain injury [187, 188]. Cleavage of Bid was also found after middle cerebral artery occlusion (MCAO)-induced stroke in mouse. Bid knockout animals show decreased levels of cytochrome c release and infarct volume [187, 188].

3.4. Hypoxia-inducible factor 1 (HIF1-α)

HIF1-α is a transcriptional factor activated in response to hypoxia. In normoxic conditions, HIF1-α is generally degraded by prolyl hydroxylases (PHD)-mediated ubiquitination, but hypoxia inhibits PHD activity and leads to stabilization of HIF1-α which then is translocated to the nucleus and regulates gene expression. Although HIF1-α is not generally considered as a mitochondrial protein, HIF1-α is reported as an important player in mitochondrial function [189–191]. HIF1-α directly binds with the promoter region of Bcl-xL [192] and targets the expression of BNIP3, a BH3-only protein member of the Bcl2 family that mediates hypoxia-induced mitochondrial autophagy [193–195]. HIF1- α regulates a subunit of cytochrome c oxidase [196] which is an essential member in the mitochondrial electron transport chain. In addition, a recent study showed localization of HIF1-α to both the nucleus and mitochondria after hypoxia [197].

Since ischemia is closely related to hypoxic stimulation, there are studies reporting functions of HIF1-α in models of cerebral ischemia. HIF1-α is enhanced by MCAO-induced stroke in rodent brains, and co-regulated with death-signaling molecules such as caspases, inflammatory cytokines, and apoptotic molecules [198–202]. On the other hand, the neuroprotective role of HIF1-α has been studied by several groups during the past decade [203–205]. Impairment of dopaminergic differentiation and reduction of vascular endothelial growth factor are reported in a HIF-1α knockout model [206]. Tomita et al. reported that neuron-specific-HIF1-α knockout mice have reduced numbers of neurons and impaired spatial memory [207]. Therefore, understanding both physiological and pathological roles of HIF-1α and its targets is important to understand synaptic plasticity in cerebral ischemia.

http://dx.doi.org/10.5772/67126

4. Conclusion

Mitochondria are the center of intracellular energy production, and the executor of cellular fate. Ischemic injury triggers or is caused by mitochondria-mediated signaling pathways. We have discussed in this chapter the intracellular signals activated during and after episodes of ischemia, the alteration in the dynamics of structural components of the synapse, and how these elements play a role in attenuation of synaptic plasticity or recovery of synaptic responses. Since after ischemia, increased energy demands are inherent in the formation of new synapses and repair of the normal operation of existing synapses, we are particularly focused on mitochondrial components that regulate mPTP and neuronal energy metabolism. Although details of the structure of mPTP are still in question, it is clear that prevention of mPT and conservation of energy are critical in management of ischemia-induced damage in the brain. We have also highlighted non-canonical roles of mitochondrial Bcl2 family proteins in the synapse besides their known functions in apoptosis; these roles should be further studied to elucidate the crucial functions of mitochondria in synaptic plasticity.

Author details

Han-A Park and Elizabeth A. Jonas*

*Address all correspondence to: elizabeth.jonas@yale.edu

Department of Internal Medicine, Section of Endocrinology, Yale University, New Haven, CT, USA

References

[1] F. B. Meyer (1989) Calcium, neuronal hyperexcitability and ischemic injury. Brain Res Brain Res Rev 14:227–243.

[2] B. L. Schwab, D. Guerini, C. Didszun, D. Bano, E. Ferrando-May, E. Fava, J. Tam, D. Xu, S. Xanthoudakis, D. W. Nicholson, E. Carafoli and P. Nicotera (2002) Cleavage of plasma membrane calcium pumps by caspases: a link between apoptosis and necrosis. Cell death and differentiation 9:818–831.

[3] D. Bano, K. W. Young, C. J. Guerin, R. Lefeuvre, N. J. Rothwell, L. Naldini, R. Rizzuto, E. Carafoli and P. Nicotera (2005) Cleavage of the plasma membrane Na+/Ca2+ exchanger in excitotoxicity. Cell 120:275–285.

[4] D. W. Choi (1987) Ionic dependence of glutamate neurotoxicity. The Journal of neuroscience: the official journal of the Society for Neuroscience 7:369–379.

[5] K. Szydlowska and M. Tymianski (2010) Calcium, ischemia and excitotoxicity. Cell Calcium 47:122–129.

[6] Y. Nishizawa (2001) Glutamate release and neuronal damage in ischemia. Life Sci 69:369–381.

[7] Y. Zhang, J. S. Helm, A. Senatore, J. D. Spafford, L. K. Kaczmarek and E. A. Jonas (2008) PKC-induced intracellular trafficking of Ca(V)2 precedes its rapid recruitment to the plasma membrane. The Journal of neuroscience: the official journal of the Society for Neuroscience 28:2601–2612.

[8] C. M. Macica, C. A. von Hehn, L. Y. Wang, C. S. Ho, S. Yokoyama, R. H. Joho and L. K. Kaczmarek (2003) Modulation of the kv3.1b potassium channel isoform adjusts the fidelity of the firing pattern of auditory neurons. The Journal of neuroscience: the official journal of the Society for Neuroscience 23:1133–1141.

[9] Y. Chen, A. R. Cantrell, R. O. Messing, T. Scheuer and W. A. Catterall (2005) Specific modulation of Na+ channels in hippocampal neurons by protein kinase C epsilon. The Journal of neuroscience: the official journal of the Society for Neuroscience 25:507–513.

[10] T. A. Macek, H. Schaffhauser and P. J. Conn (1998) Protein kinase C and A3 adenosine receptor activation inhibit presynaptic metabotropic glutamate receptor (mGluR) function and uncouple mGluRs from GTP-binding proteins. The Journal of neuroscience: the official journal of the Society for Neuroscience 18:6138–6146.

[11] S. Kawabata, R. Tsutsumi, A. Kohara, T. Yamaguchi, S. Nakanishi and M. Okada (1996) Control of calcium oscillations by phosphorylation of metabotropic glutamate receptors. Nature 383:89–92.

[12] J. L. Bixby (1989) Protein kinase C is involved in laminin stimulation of neurite outgrowth. Neuron 3:287–297.

[13] R. Zeidman, U. Troller, A. Raghunath, S. Pahlman and C. Larsson (2002) Protein kinase Cepsilon actin-binding site is important for neurite outgrowth during neuronal differentiation. Mol Biol Cell 13:12–24.

[14] K. Matsushita, Y. Wu, J. Qiu, L. Lang-Lazdunski, L. Hirt, C. Waeber, B. T. Hyman, J. Yuan and M. A. Moskowitz (2000) Fas receptor and neuronal cell death after spinal cord ischemia. The Journal of neuroscience: the official journal of the Society for Neuroscience 20:6879–6887.

[15] B. R. Broughton, D. C. Reutens and C. G. Sobey (2009) Apoptotic mechanisms after cerebral ischemia. Stroke; a journal of cerebral circulation 40:e331–339.

[16] H. Li, H. Zhu, C. J. Xu and J. Yuan (1998) Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. Cell 94:491–501.

[17] X. Luo, I. Budihardjo, H. Zou, C. Slaughter and X. Wang (1998) Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. Cell 94:481–490.

[18] U. Fischer, R. U. Janicke and K. Schulze-Osthoff (2003) Many cuts to ruin: a comprehensive update of caspase substrates. Cell death and differentiation 10:76–100.

[19] S. L. Chan, W. S. Griffin and M. P. Mattson (1999) Evidence for caspase-mediated cleavage of AMPA receptor subunits in neuronal apoptosis and Alzheimer's disease. J Neurosci Res 57:315–323.

[20] G. W. Glazner, S. L. Chan, C. Lu and M. P. Mattson (2000) Caspase-mediated degradation of AMPA receptor subunits: a mechanism for preventing excitotoxic necrosis and ensuring apoptosis. The Journal of neuroscience: the official journal of the Society for Neuroscience 20:3641–3649.

[21] I. Hunter, D. McGregor and S. P. Robins (2001) Caspase-dependent cleavage of cadherins and catenins during osteoblast apoptosis. J Bone Miner Res 16:466–477.

[22] F. G. Gervais, D. Xu, G. S. Robertson, J. P. Vaillancourt, Y. Zhu, J. Huang, A. LeBlanc, D. Smith, M. Rigby, M. S. Shearman, E. E. Clarke, H. Zheng, L. H. Van Der Ploeg, S. C. Ruffolo, N. A. Thornberry, S. Xanthoudakis, R. J. Zamboni, S. Roy and D. W. Nicholson (1999) Involvement of caspases in proteolytic cleavage of Alzheimer's amyloid-beta precursor protein and amyloidogenic A beta peptide formation. Cell 97:395–406.

[23] A. Nikolaev, T. McLaughlin, D. D. O'Leary and M. Tessier-Lavigne (2009) APP binds DR6 to trigger axon pruning and neuron death via distinct caspases. Nature 457:981–989.

[24] L. Tong, G. A. Prieto, E. A. Kramar, E. D. Smith, D. H. Cribbs, G. Lynch and C. W. Cotman (2012) Brain-derived neurotrophic factor-dependent synaptic plasticity is suppressed by interleukin-1beta via p38 mitogen-activated protein kinase. The Journal of neuroscience: the official journal of the Society for Neuroscience 32:17714–17724.

[25] N. A. Thornberry, H. G. Bull, J. R. Calaycay, K. T. Chapman, A. D. Howard, M. J. Kostura, D. K. Miller, S. M. Molineaux, J. R. Weidner, J. Aunins and et al. (1992) A novel heterodimeric cysteine protease is required for interleukin-1 beta processing in monocytes. Nature 356:768–774.

[26] A. H. Jacobs, B. Tavitian and I. N. consortium (2012) Noninvasive molecular imaging of neuroinflammation. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism 32:1393–1415.

[27] M. V. Sofroniew (2015) Astrocyte barriers to neurotoxic inflammation. Nat Rev Neurosci 16:249–263.

[28] M. L. Block (2014) Neuroinflammation: modulating mighty microglia. Nat Chem Biol 10:988–989.

[29] D. N. Xanthos and J. Sandkuhler (2014) Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. Nat Rev Neurosci 15:43–53.

[30] T. Liu, R. K. Clark, P. C. McDonnell, P. R. Young, R. F. White, F. C. Barone and G. Z. Feuerstein (1994) Tumor necrosis factor-alpha expression in ischemic neurons. Stroke; a journal of cerebral circulation 25:1481–1488.

[31] E. C. Beattie, D. Stellwagen, W. Morishita, J. C. Bresnahan, B. K. Ha, M. Von Zastrow, M. S. Beattie and R. C. Malenka (2002) Control of synaptic strength by glial TNFalpha. Science 295:2282–2285.

[32] M. Tamatani, Y. H. Che, H. Matsuzaki, S. Ogawa, H. Okado, S. Miyake, T. Mizuno and M. Tohyama (1999) Tumor necrosis factor induces Bcl-2 and Bcl-x expression through NFkappaB activation in primary hippocampal neurons. The Journal of biological chemistry 274:8531–8538.

[33] R. N. Saha, X. Liu and K. Pahan (2006) Up-regulation of BDNF in astrocytes by TNF-alpha: a case for the neuroprotective role of cytokine. J Neuroimmune Pharmacol 1:212–222.

[34] Y. Takei and R. Laskey (2008) Tumor necrosis factor alpha regulates responses to nerve growth factor, promoting neural cell survival but suppressing differentiation of neuroblastoma cells. Mol Biol Cell 19:855–864.

[35] I. Figiel (2008) Pro-inflammatory cytokine TNF-alpha as a neuroprotective agent in the brain. Acta Neurobiol Exp (Wars) 68:526–534.

[36] D. M. Suter and P. Forscher (1998) An emerging link between cytoskeletal dynamics and cell adhesion molecules in growth cone guidance. Curr Opin Neurobiol 8:106–116.

[37] L. A. Lowery and D. Van Vactor (2009) The trip of the tip: understanding the growth cone machinery. Nature reviews. Molecular cell biology 10:332–343.

[38] K. Kalil and E. W. Dent (2014) Branch management: mechanisms of axon branching in the developing vertebrate CNS. Nat Rev Neurosci 15:7–18.

[39] A. M. Craig and Y. Kang (2007) Neurexin-neuroligin signaling in synapse development. Curr Opin Neurobiol 17:43–52.

[40] T. C. Sudhof (2008) Neuroligins and neurexins link synaptic function to cognitive disease. Nature 455:903–911.

[41] M. Takeichi (2007) The cadherin superfamily in neuronal connections and interactions. Nat Rev Neurosci 8:11–20.

[42] M. B. Dalva, A. C. McClelland and M. S. Kayser (2007) Cell adhesion molecules: signalling functions at the synapse. Nat Rev Neurosci 8:206–220.

[43] A. Nissant, C. Bardy, H. Katagiri, K. Murray and P. M. Lledo (2009) Adult neurogenesis promotes synaptic plasticity in the olfactory bulb. Nat Neurosci 12:728–730.

[44] P. M. Lledo, M. Alonso and M. S. Grubb (2006) Adult neurogenesis and functional plasticity in neuronal circuits. Nat Rev Neurosci 7:179–193.

[45] C. R. Bramham and E. Messaoudi (2005) BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog Neurobiol 76:99–125.

[46] A. Pascual-Leone, A. Amedi, F. Fregni and L. B. Merabet (2005) The plastic human brain cortex. Annu Rev Neurosci 28:377–401.

[47] S. Li, J. J. Overman, D. Katsman, S. V. Kozlov, C. J. Donnelly, J. L. Twiss, R. J. Giger, G. Coppola, D. H. Geschwind and S. T. Carmichael (2010) An age-related sprouting transcriptome provides molecular control of axonal sprouting after stroke. Nat Neurosci 13:1496–1504.

[48] J. D. Hinman, M. N. Rasband and S. T. Carmichael (2013) Remodeling of the axon initial segment after focal cortical and white matter stroke. Stroke; a journal of cerebral circulation 44:182–189.

[49] Q. Zhang, T. Gao, Y. Luo, X. Chen, G. Gao, X. Gao, Y. Zhou and J. Dai (2012) Transient focal cerebral ischemia/reperfusion induces early and chronic axonal changes in rats: its importance for the risk of Alzheimer's disease. In: PloS one 7:e33722.

[50] B. P. Liu, W. B. Cafferty, S. O. Budel and S. M. Strittmatter (2006) Extracellular regulators of axonal growth in the adult central nervous system. In: Philos Trans R Soc Lond B Biol Sci 361:1593–1610.

[51] J. J. Harris, R. Jolivet and D. Attwell (2012) Synaptic energy use and supply. Neuron 75:762–777.

[52] D. J. Rossi, T. Oshima and D. Attwell (2000) Glutamate release in severe brain ischaemia is mainly by reversed uptake. Nature 403:316–321.

[53] J. Hofmeijer and M. J. van Putten (2012) Ischemic cerebral damage: an appraisal of synaptic failure. Stroke; a journal of cerebral circulation 43:607–615.

[54] J. T. Isaac, M. C. Ashby and C. J. McBain (2007) The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. Neuron 54:859–871.

[55] S. Cull-Candy, L. Kelly and M. Farrant (2006) Regulation of Ca2+-permeable AMPA receptors: synaptic plasticity and beyond. Curr Opin Neurobiol 16:288–297.

[56] N. Hori and D. O. Carpenter (1994) Functional and morphological changes induced by transient in vivo ischemia. Exp Neurol 129:279–289.

[57] N. Hori, N. Doi, S. Miyahara, Y. Shinoda and D. O. Carpenter (1991) Appearance of NMDA receptors triggered by anoxia independent of voltage in vivo and in vitro. Exp Neurol 112:304–311.

[58] H. Y. Wu, E. Y. Yuen, Y. F. Lu, M. Matsushita, H. Matsui, Z. Yan and K. Tomizawa (2005) Regulation of N-methyl-D-aspartate receptors by calpain in cortical neurons. The Journal of biological chemistry 280:21588–21593.

[59] Y. Liu, T. P. Wong, M. Aarts, A. Rooyakkers, L. Liu, T. W. Lai, D. C. Wu, J. Lu, M. Tymianski, A. M. Craig and Y. T. Wang (2007) NMDA receptor subunits have differential roles in mediating excitotoxic neuronal death both in vitro and in vivo. The Journal of neuroscience: the official journal of the Society for Neuroscience 27:2846–2857.

[60] M. Chen, T. J. Lu, X. J. Chen, Y. Zhou, Q. Chen, X. Y. Feng, L. Xu, W. H. Duan and Z. Q. Xiong (2008) Differential roles of NMDA receptor subtypes in ischemic neuronal cell death and ischemic tolerance. Stroke; a journal of cerebral circulation 39:3042–3048.

[61] K. Yashiro and B. D. Philpot (2008) Regulation of NMDA receptor subunit expression and its implications for LTD, LTP, and metaplasticity. Neuropharmacology 55:1081–1094.

[62] J. A. Gorter, J. J. Petrozzino, E. M. Aronica, D. M. Rosenbaum, T. Opitz, M. V. Bennett, J. A. Connor and R. S. Zukin (1997) Global ischemia induces downregulation of Glur2 mRNA

and increases AMPA receptor-mediated Ca2+ influx in hippocampal CA1 neurons of gerbil. The Journal of neuroscience: the official journal of the Society for Neuroscience 17:6179–6188.

[63] P. L. Peng, X. Zhong, W. Tu, M. M. Soundarapandian, P. Molner, D. Zhu, L. Lau, S. Liu, F. Liu and Y. Lu (2006) ADAR2-dependent RNA editing of AMPA receptor subunit GluR2 determines vulnerability of neurons in forebrain ischemia. Neuron 49:719–733.

[64] S. Liu, L. Lau, J. Wei, D. Zhu, S. Zou, H. S. Sun, Y. Fu, F. Liu and Y. Lu (2004) Expression of Ca(2+)-permeable AMPA receptor channels primes cell death in transient forebrain ischemia. Neuron 43:43–55.

[65] T. Opitz, S. Y. Grooms, M. V. Bennett and R. S. Zukin (2000) Remodeling of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor subunit composition in hippocampal neurons after global ischemia. Proceedings of the National Academy of Sciences of the United States of America 97:13360–13365.

[66] D. L. Hunt and P. E. Castillo (2012) Synaptic plasticity of NMDA receptors: mechanisms and functional implications. Curr Opin Neurobiol 22:496–508.

[67] C. Ikonomidou and L. Turski (2002) Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury? Lancet Neurol 1:383–386.

[68] G. E. Hardingham (2009) Coupling of the NMDA receptor to neuroprotective and neurodestructive events. Biochem Soc Trans 37:1147–1160.

[69] S. Papadia, F. X. Soriano, F. Leveille, M. A. Martel, K. A. Dakin, H. H. Hansen, A. Kaindl, M. Sifringer, J. Fowler, V. Stefovska, G. McKenzie, M. Craigon, R. Corriveau, P. Ghazal, K. Horsburgh, B. A. Yankner, D. J. Wyllie, C. Ikonomidou and G. E. Hardingham (2008) Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. Nat Neurosci 11:476–487.

[70] M. Sheng, J. Cummings, L. A. Roldan, Y. N. Jan and L. Y. Jan (1994) Changing subunit composition of heteromeric NMDA receptors during development of rat cortex. Nature 368:144–147.

[71] J. T. Wang, Z. A. Medress and B. A. Barres (2012) Axon degeneration: molecular mechanisms of a self-destruction pathway. The Journal of cell biology 196:7–18.

[72] T. Miyawaki, T. Mashiko, D. Ofengeim, R. J. Flannery, K. M. Noh, S. Fujisawa, L. Bonanni, M. V. Bennett, R. S. Zukin and E. A. Jonas (2008) Ischemic preconditioning blocks BAD translocation, Bcl-xL cleavage, and large channel activity in mitochondria of postischemic hippocampal neurons. Proceedings of the National Academy of Sciences of the United States of America 105:4892–4897.

[73] D. Ofengeim, Y. B. Chen, T. Miyawaki, H. Li, S. Sacchetti, R. J. Flannery, K. N. Alavian, F. Pontarelli, B. A. Roelofs, J. A. Hickman, J. M. Hardwick, R. S. Zukin and E. A. Jonas (2012) N-terminally cleaved Bcl-xL mediates ischemia-induced neuronal death. In: Nat Neurosci, 2012/03/01 Edition 15:574–580.

[74] H. A. Park, P. Licznerski, K. N. Alavian, M. Shanabrough and E. A. Jonas (2015) Bcl-xL Is Necessary for Neurite Outgrowth in Hippocampal Neurons. Antioxidants & redox signaling 22:93–108.

[75] H. A. Park, N. Kubicki, S. Gnyawali, Y. C. Chan, S. Roy, S. Khanna and C. K. Sen (2011) Natural vitamin E alpha-tocotrienol protects against ischemic stroke by induction of multidrug resistance-associated protein 1. Stroke; a journal of cerebral circulation 42:2308–2314.

[76] W. A. Pulsinelli, J. B. Brierley and F. Plum (1982) Temporal profile of neuronal damage in a model of transient forebrain ischemia. Ann Neurol 11:491–498.

[77] D. F. Matesic and R. C. Lin (1994) Microtubule-associated protein 2 as an early indicator of ischemia-induced neurodegeneration in the gerbil forebrain. Journal of neurochemistry 63:1012–1020.

[78] K. Kitagawa, M. Matsumoto, M. Niinobe, K. Mikoshiba, R. Hata, H. Ueda, N. Handa, R. Fukunaga, Y. Isaka, K. Kimura and et al. (1989) Microtubule-associated protein 2 as a sensitive marker for cerebral ischemic damage–immunohistochemical investigation of dendritic damage. Neuroscience 31:401–411.

[79] J. Aronowski, K. H. Cho, R. Strong and J. C. Grotta (1999) Neurofilament proteolysis after focal ischemia; when do cells die after experimental stroke? Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism 19:652–660.

[80] C. P. Baines (2009) The mitochondrial permeability transition pore and ischemia-reperfusion injury. Basic Res Cardiol 104:181–188.

[81] T. H. Murphy and D. Corbett (2009) Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci 10:861–872.

[82] R. P. Stroemer, T. A. Kent and C. E. Hulsebosch (1995) Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. Stroke; a journal of cerebral circulation 26:2135–2144.

[83] R. P. Stroemer, T. A. Kent and C. E. Hulsebosch (1998) Enhanced neocortical neural sprouting, synaptogenesis, and behavioral recovery with D-amphetamine therapy after neocortical infarction in rats. Stroke; a journal of cerebral circulation 29:2381–2393; discussion 2393–2385.

[84] S. T. Carmichael (2003) Plasticity of cortical projections after stroke. Neuroscientist 9:64–75.

[85] S. T. Carmichael, L. Wei, C. M. Rovainen and T. A. Woolsey (2001) New patterns of intracortical projections after focal cortical stroke. Neurobiology of disease 8:910–922.

[86] C. E. Brown, P. Li, J. D. Boyd, K. R. Delaney and T. H. Murphy (2007) Extensive turnover of dendritic spines and vascular remodeling in cortical tissues recovering from stroke. The Journal of neuroscience: the official journal of the Society for Neuroscience 27:4101–4109.

[87] R. Mostany, T. G. Chowdhury, D. G. Johnston, S. A. Portonovo, S. T. Carmichael and C. Portera-Cailliau (2010) Local hemodynamics dictate long-term dendritic plasticity in peri-infarct cortex. The Journal of neuroscience: the official journal of the Society for Neuroscience 30:14116–14126.

[88] C. Zhao, W. Deng and F. H. Gage (2008) Mechanisms and functional implications of adult neurogenesis. Cell 132:645–660.

[89] J. Macas, C. Nern, K. H. Plate and S. Momma (2006) Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. The Journal of neuroscience: the official journal of the Society for Neuroscience 26:13114–13119.

[90] O. Lindvall and Z. Kokaia (2015) Neurogenesis following Stroke Affecting the Adult Brain. Cold Spring Harb Perspect Biol 7:1–19.

[91] J. Marti-Fabregas, M. Romaguera-Ros, U. Gomez-Pinedo, S. Martinez-Ramirez, E. Jimenez-Xarrie, R. Marin, J. L. Marti-Vilalta and J. M. Garcia-Verdugo (2010) Proliferation in the human ipsilateral subventricular zone after ischemic stroke. Neurology 74:357–365.

[92] K. Jin, X. Wang, L. Xie, X. O. Mao, W. Zhu, Y. Wang, J. Shen, Y. Mao, S. Banwait and D. A. Greenberg (2006) Evidence for stroke-induced neurogenesis in the human brain. Proceedings of the National Academy of Sciences of the United States of America 103:13198–13202.

[93] J. M. Gidday (2006) Cerebral preconditioning and ischaemic tolerance. Nat Rev Neurosci 7:437–448.

[94] U. Dirnagl, K. Becker and A. Meisel (2009) Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. Lancet Neurol 8:398–412.

[95] H. Tanaka, A. Calderone, T. Jover, S. Y. Grooms, H. Yokota, R. S. Zukin and M. V. Bennett (2002) Ischemic preconditioning acts upstream of GluR2 down-regulation to afford neuroprotection in the hippocampal CA1. Proceedings of the National Academy of Sciences of the United States of America 99:2362–2367.

[96] H. Tanaka, H. Yokota, T. Jover, I. Cappuccio, A. Calderone, M. Simionescu, M. V. Bennett and R. S. Zukin (2004) Ischemic preconditioning: neuronal survival in the face of caspase-3 activation. The Journal of neuroscience: the official journal of the Society for Neuroscience 24:2750–2759.

[97] R. Meller, M. Minami, J. A. Cameron, S. Impey, D. Chen, J. Q. Lan, D. C. Henshall and R. P. Simon (2005) CREB-mediated Bcl-2 protein expression after ischemic preconditioning. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism 25:234–246.

[98] C. Wu, H. Fujihara, J. Yao, S. Qi, H. Li, K. Shimoji and H. Baba (2003) Different expression patterns of Bcl-2, Bcl-xl, and Bax proteins after sublethal forebrain ischemia in C57Black/Crj6 mouse striatum. Stroke; a journal of cerebral circulation 34:1803–1808.

[99] L. Y. Wu, A. S. Ding, T. Zhao, Z. M. Ma, F. Z. Wang and M. Fan (2004) Involvement of increased stability of mitochondrial membrane potential and overexpression of Bcl-2 in enhanced anoxic tolerance induced by hypoxic preconditioning in cultured hypothalamic neurons. Brain Res 999:149–154.

[100] S. A. Stroev, T. S. Gluschenko, E. I. Tjulkova, G. Spyrou, E. A. Rybnikova, M. O. Samoilov and M. Pelto-Huikko (2004) Preconditioning enhances the expression of mitochondrial antioxidant thioredoxin-2 in the forebrain of rats exposed to severe hypobaric hypoxia. J Neurosci Res 78:563–569.

[101] K. F. Bell, J. H. Fowler, B. Al-Mubarak, K. Horsburgh and G. E. Hardingham (2011) Activation of Nrf2-regulated glutathione pathway genes by ischemic preconditioning. Oxid Med Cell Longev 2011:689524.

[102] M. Liu and N. J. Alkayed (2005) Hypoxic preconditioning and tolerance via hypoxia inducible factor (HIF) 1alpha-linked induction of P450 2C11 epoxygenase in astrocytes. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism 25:939–948.

[103] N. M. Jones and M. Bergeron (2001) Hypoxic preconditioning induces changes in HIF-1 target genes in neonatal rat brain. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism 21:1105–1114.

[104] A. Ravati, B. Ahlemeyer, A. Becker, S. Klumpp and J. Krieglstein (2001) Preconditioning-induced neuroprotection is mediated by reactive oxygen species and activation of the transcription factor nuclear factor-kappaB. Journal of neurochemistry 78:909–919.

[105] E. Rybnikova, T. Gluschenko, E. Tulkova, A. Churilova, O. Jaroshevich, K. Baranova and M. Samoilov (2008) Preconditioning induces prolonged expression of transcription factors pCREB and NF-kappa B in the neocortex of rats before and following severe hypobaric hypoxia. Journal of neurochemistry 106:1450–1458.

[106] E. Rybnikova, T. Glushchenko, E. Tyulkova, K. Baranova and M. Samoilov (2009) Mild hypobaric hypoxia preconditioning up-regulates expression of transcription factors c-Fos and NGFI-A in rat neocortex and hippocampus. Neurosci Res 65:360–366.

[107] K. F. Bell, B. Al-Mubarak, J. H. Fowler, P. S. Baxter, K. Gupta, T. Tsujita, S. Chowdhry, R. Patani, S. Chandran, K. Horsburgh, J. D. Hayes and G. E. Hardingham (2011) Mild oxidative stress activates Nrf2 in astrocytes, which contributes to neuroprotective ischemic preconditioning. Proceedings of the National Academy of Sciences of the United States of America 108:E1–2; author reply E3–4.

[108] K. Kapinya, R. Penzel, C. Sommer and M. Kiessling (2000) Temporary changes of the AP-1 transcription factor binding activity in the gerbil hippocampus after transient global ischemia, and ischemic tolerance induction. Brain Res 872:282–293.

[109] P. Bernardi and F. Di Lisa (2015) The mitochondrial permeability transition pore: molecular nature and role as a target in cardioprotection. Journal of molecular and cellular cardiology 78:100–106.

[110] E. A. Jonas (2009) Molecular participants in mitochondrial cell death channel formation during neuronal ischemia. Exp Neurol 218:203–212.

[111] K. M. Holmstrom and T. Finkel (2014) Cellular mechanisms and physiological consequences of redox-dependent signalling. Nature reviews. Molecular cell biology 15:411–421.

[112] A. J. Kowaltowski, R. F. Castilho and A. E. Vercesi (2001) Mitochondrial permeability transition and oxidative stress. FEBS Lett 495:12–15.

[113] B. Halliwell (1992) Reactive oxygen species and the central nervous system. Journal of neurochemistry 59:1609–1623.

[114] C. A. Massaad and E. Klann (2011) Reactive oxygen species in the regulation of synaptic plasticity and memory. Antioxidants & redox signaling 14:2013–2054.

[115] K. T. Kishida, C. A. Hoeffer, D. Hu, M. Pao, S. M. Holland and E. Klann (2006) Synaptic plasticity deficits and mild memory impairments in mouse models of chronic granulomatous disease. Mol Cell Biol 26:5908–5920.

[116] E. Klann (1998) Cell-permeable scavengers of superoxide prevent long-term potentiation in hippocampal area CA1. J Neurophysiol 80:452–457.

[117] E. Thiels, N. N. Urban, G. R. Gonzalez-Burgos, B. I. Kanterewicz, G. Barrionuevo, C. T. Chu, T. D. Oury and E. Klann (2000) Impairment of long-term potentiation and associative memory in mice that overexpress extracellular superoxide dismutase. The Journal of neuroscience: the official journal of the Society for Neuroscience 20:7631–7639.

[118] E. Gahtan, J. M. Auerbach, Y. Groner and M. Segal (1998) Reversible impairment of long-term potentiation in transgenic Cu/Zn-SOD mice. Eur J Neurosci 10:538–544.

[119] R. Radi, J. S. Beckman, K. M. Bush and B. A. Freeman (1991) Peroxynitrite oxidation of sulfhydryls. The cytotoxic potential of superoxide and nitric oxide. The Journal of biological chemistry 266:4244–4250.

[120] S. P. Olesen, A. Moller, P. I. Mordvintcev, R. Busse and A. Mulsch (1997) Regional measurements of NO formed in vivo during brain ischemia. Acta Neurol Scand 95:219–224.

[121] V. L. Dawson, T. M. Dawson, E. D. London, D. S. Bredt and S. H. Snyder (1991) Nitric oxide mediates glutamate neurotoxicity in primary cortical cultures. Proceedings of the National Academy of Sciences of the United States of America 88:6368–6371.

[122] J. P. Bolanos, A. Almeida and J. M. Medina (1998) Nitric oxide mediates brain mitochondrial damage during perinatal anoxia. Brain Res 787:117–122.

[123] J. P. Bolanos, S. Peuchen, S. J. Heales, J. M. Land and J. B. Clark (1994) Nitric oxide-mediated inhibition of the mitochondrial respiratory chain in cultured astrocytes. Journal of neurochemistry 63:910–916.

[124] E. M. Schuman and D. V. Madison (1991) A requirement for the intercellular messenger nitric oxide in long-term potentiation. Science 254:1503–1506.

[125] J. P. Bolanos and A. Almeida (1999) Roles of nitric oxide in brain hypoxia-ischemia. Biochimica et biophysica acta 1411:415–436.

[126] K. A. Graham, M. Kulawiec, K. M. Owens, X. Li, M. M. Desouki, D. Chandra and K. K. Singh (2010) NADPH oxidase 4 is an oncoprotein localized to mitochondria. Cancer Biol Ther 10:223–231.

[127] S. P. Tammariello, M. T. Quinn and S. Estus (2000) NADPH oxidase contributes directly to oxidative stress and apoptosis in nerve growth factor-deprived sympathetic neurons. The Journal of neuroscience: the official journal of the Society for Neuroscience 20:RC53.

[128] C. Cheret, A. Gervais, A. Lelli, C. Colin, L. Amar, P. Ravassard, J. Mallet, A. Cumano, K. H. Krause and M. Mallat (2008) Neurotoxic activation of microglia is promoted by a nox1-dependent NADPH oxidase. The Journal of neuroscience: the official journal of the Society for Neuroscience 28:12039–12051.

[129] P. Vallet, Y. Charnay, K. Steger, E. Ogier-Denis, E. Kovari, F. Herrmann, J. P. Michel and I. Szanto (2005) Neuronal expression of the NADPH oxidase NOX4, and its regulation in mouse experimental brain ischemia. Neuroscience 132:233–238.

[130] H. Li, Y. Wang, D. Feng, Y. Liu, M. Xu, A. Gao, F. Tian, L. Zhang, Y. Cui, Z. Wang and G. Chen (2014) Alterations in the time course of expression of the Nox family in the brain in a rat experimental cerebral ischemia and reperfusion model: effects of melatonin. J Pineal Res 57:110–119.

[131] X. N. Tang, B. Cairns, N. Cairns and M. A. Yenari (2008) Apocynin improves outcome in experimental stroke with a narrow dose range. Neuroscience 154:556–562.

[132] H. Chen, Y. S. Song and P. H. Chan (2009) Inhibition of NADPH oxidase is neuroprotective after ischemia-reperfusion. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism 29:1262–1272.

[133] R. A. Haworth and D. R. Hunter (1979) The Ca2+-induced membrane transition in mitochondria. II. Nature of the Ca2+ trigger site. Arch Biochem Biophys 195:460–467.

[134] D. R. Hunter and R. A. Haworth (1979) The Ca2+-induced membrane transition in mitochondria. I. The protective mechanisms. Arch Biochem Biophys 195:453–459.

[135] C. P. Baines, R. A. Kaiser, T. Sheiko, W. J. Craigen and J. D. Molkentin (2007) Voltage-dependent anion channels are dispensable for mitochondrial-dependent cell death. Nat Cell Biol 9:550–555.

[136] T. Nakagawa, S. Shimizu, T. Watanabe, O. Yamaguchi, K. Otsu, H. Yamagata, H. Inohara, T. Kubo and Y. Tsujimoto (2005) Cyclophilin D-dependent mitochondrial permeability transition regulates some necrotic but not apoptotic cell death. Nature 434:652–658.

[137] E. Basso, L. Fante, J. Fowlkes, V. Petronilli, M. A. Forte and P. Bernardi (2005) Properties of the permeability transition pore in mitochondria devoid of Cyclophilin D. The Journal of biological chemistry 280:18558–18561.

[138] C. Brenner, H. Cadiou, H. L. Vieira, N. Zamzami, I. Marzo, Z. Xie, B. Leber, D. Andrews, H. Duclohier, J. C. Reed and G. Kroemer (2000) Bcl-2 and Bax regulate the channel activity of the mitochondrial adenine nucleotide translocator. Oncogene 19:329–336.

[139] I. Szabo, V. De Pinto and M. Zoratti (1993) The mitochondrial permeability transition pore may comprise VDAC molecules. II. The electrophysiological properties of VDAC are compatible with those of the mitochondrial megachannel. FEBS Lett 330:206–210.

[140] I. Szabo and M. Zoratti (1993) The mitochondrial permeability transition pore may comprise VDAC molecules. I. Binary structure and voltage dependence of the pore. FEBS Lett 330:201–205.

[141] M. Crompton (1999) The mitochondrial permeability transition pore and its role in cell death. The Biochemical journal 341 (Pt 2):233–249.

[142] K. M. Debatin, D. Poncet and G. Kroemer (2002) Chemotherapy: targeting the mitochondrial cell death pathway. Oncogene 21:8786–8803.

[143] K. Woodfield, A. Ruck, D. Brdiczka and A. P. Halestrap (1998) Direct demonstration of a specific interaction between cyclophilin-D and the adenine nucleotide translocase confirms their role in the mitochondrial permeability transition. The Biochemical journal 336 (Pt 2):287–290.

[144] A. W. Leung, P. Varanyuwatana and A. P. Halestrap (2008) The mitochondrial phosphate carrier interacts with cyclophilin D and may play a key role in the permeability transition. In: The Journal of biological chemistry 283:26312–26323.

[145] S. Shanmughapriya, S. Rajan, N. E. Hoffman, A. M. Higgins, D. Tomar, N. Nemani, K. J. Hines, D. J. Smith, A. Eguchi, S. Vallem, F. Shaikh, M. Cheung, N. J. Leonard, R. S. Stolakis, M. P. Wolfers, J. Ibetti, J. K. Chuprun, N. R. Jog, S. R. Houser, W. J. Koch, J. W. Elrod and M. Madesh (2015) SPG7 Is an Essential and Conserved Component of the Mitochondrial Permeability Transition Pore. Mol Cell 60:47–62.

[146] H. Azoulay-Zohar, A. Israelson, S. Abu-Hamad and V. Shoshan-Barmatz (2004) In self-defence: hexokinase promotes voltage-dependent anion channel closure and prevents mitochondria-mediated apoptotic cell death. The Biochemical journal 377: 347–355.

[147] J. G. Pastorino and J. B. Hoek (2008) Regulation of hexokinase binding to VDAC. J Bioenerg Biomembr 40:171–182.

[148] J. E. Kokoszka, K. G. Waymire, S. E. Levy, J. E. Sligh, J. Cai, D. P. Jones, G. R. MacGregor and D. C. Wallace (2004) The ADP/ATP translocator is not essential for the mitochondrial permeability transition pore. Nature 427:461–465.

[149] M. Bonora, A. Bononi, E. De Marchi, C. Giorgi, M. Lebiedzinska, S. Marchi, S. Patergnani, A. Rimessi, J. M. Suski, A. Wojtala, M. R. Wieckowski, G. Kroemer, L. Galluzzi and P. Pinton (2013) Role of the c subunit of the FO ATP synthase in mitochondrial permeability transition. Cell Cycle 12:674–683.

[150] M. Bonora, M. R. Wieckowski, C. Chinopoulos, O. Kepp, G. Kroemer, L. Galluzzi and P. Pinton (2015) Molecular mechanisms of cell death: central implication of ATP synthase in mitochondrial permeability transition. Oncogene 34:1475–1486.

[151] V. Giorgio, S. von Stockum, M. Antoniel, A. Fabbro, F. Fogolari, M. Forte, G. D. Glick, V. Petronilli, M. Zoratti, I. Szabo, G. Lippe and P. Bernardi (2013) Dimers of mitochondrial ATP synthase form the permeability transition pore. Proceedings of the National Academy of Sciences of the United States of America 110:5887–5892.

[152] V. Giorgio, E. Bisetto, M. E. Soriano, F. Dabbeni-Sala, E. Basso, V. Petronilli, M. A. Forte, P. Bernardi and G. Lippe (2009) Cyclophilin D modulates mitochondrial F0F1-ATP synthase by interacting with the lateral stalk of the complex. The Journal of biological chemistry 284:33982–33988.

[153] T. S. Azarashvili, J. Tyynela, I. V. Odinokova, P. A. Grigorjev, M. Baumann, Y. V. Evtodienko and N. E. Saris (2002) Phosphorylation of a peptide related to subunit c of the F0F1-ATPase/ATP synthase and relationship to permeability transition pore opening in mitochondria. J Bioenerg Biomembr 34:279–284.

[154] T. Azarashvili, I. Odinokova, A. Bakunts, V. Ternovsky, O. Krestinina, J. Tyynela and N. E. Saris (2014) Potential role of subunit c of F0F1-ATPase and subunit c of storage body in the mitochondrial permeability transition. Effect of the phosphorylation status of subunit c on pore opening. Cell Calcium 55:69–77.

[155] K. N. Alavian, G. Beutner, E. Lazrove, S. Sacchetti, H. A. Park, P. Licznerski, H. Li, P. Nabili, K. Hockensmith, M. Graham, G. A. Porter, Jr. and E. A. Jonas (2014) An uncoupling channel within the c-subunit ring of the F1FO ATP synthase is the mitochondrial permeability transition pore. Proceedings of the National Academy of Sciences of the United States of America 111:10580–10585.

[156] E. A. Jonas, G. A. Porter and K. N. Alavian (2014) Bcl-xL in neuroprotection and plasticity. Front Physiol 5:355.

[157] S. Couoh-Cardel, Y. C. Hsueh, S. Wilkens and L. Movileanu (2016) Yeast V-ATPase Proteolipid Ring Acts as a Large-conductance Transmembrane Protein Pore. Sci Rep 6:24774.

[158] K. N. Alavian, H. Li, L. Collis, L. Bonanni, L. Zeng, S. Sacchetti, E. Lazrove, P. Nabili, B. Flaherty, M. Graham, Y. Chen, S. M. Messerli, M. A. Mariggio, C. Rahner, E. McNay, G. C. Shore, P. J. Smith, J. M. Hardwick and E. A. Jonas (2011) Bcl-xL regulates metabolic efficiency of neurons through interaction with the mitochondrial F1FO ATP synthase. Nat Cell Biol 13:1224–1233.

[159] F. Minauro-Sanmiguel, S. Wilkens and J. J. Garcia (2005) Structure of dimeric mitochondrial ATP synthase: novel F0 bridging features and the structural basis of mitochondrial cristae biogenesis. Proceedings of the National Academy of Sciences of the United States of America 102:12356–12358.

[160] B. Daum, A. Walter, A. Horst, H. D. Osiewacz and W. Kuhlbrandt (2013) Age-dependent dissociation of ATP synthase dimers and loss of inner-membrane cristae in mitochondria. Proceedings of the National Academy of Sciences of the United States of America 110:15301–15306.

[161] P. Bernardi (2013) The mitochondrial permeability transition pore: a mystery solved? Front Physiol 4:95.

[162] J. M. Jurgensmeier, Z. Xie, Q. Deveraux, L. Ellerby, D. Bredesen and J. C. Reed (1998) Bax directly induces release of cytochrome c from isolated mitochondria. In: Proceedings of the National Academy of Sciences of the United States of America 95:4997–5002.

[163] M. Sattler, H. Liang, D. Nettesheim, R. P. Meadows, J. E. Harlan, M. Eberstadt, H. S. Yoon, S. B. Shuker, B. S. Chang, A. J. Minn, C. B. Thompson and S. W. Fesik (1997) Structure of Bcl-xL-Bak peptide complex: recognition between regulators of apoptosis. Science 275:983–986.

[164] S. Shimizu, M. Narita and Y. Tsujimoto (1999) Bcl-2 family proteins regulate the release of apoptogenic cytochrome c by the mitochondrial channel VDAC. Nature 399:483–487.

[165] S. B. Berman, Y. B. Chen, B. Qi, J. M. McCaffery, E. B. Rucker, 3rd, S. Goebbels, K. A. Nave, B. A. Arnold, E. A. Jonas, F. J. Pineda and J. M. Hardwick (2009) Bcl-x L increases mitochondrial fission, fusion, and biomass in neurons. The Journal of cell biology 184:707–719.

[166] P. Delivani, C. Adrain, R. C. Taylor, P. J. Duriez and S. J. Martin (2006) Role for CED-9 and Egl-1 as regulators of mitochondrial fission and fusion dynamics. Mol Cell 21:761–773.

[167] H. Li, Y. Chen, A. F. Jones, R. H. Sanger, L. P. Collis, R. Flannery, E. C. McNay, T. Yu, R. Schwarzenbacher, B. Bossy, E. Bossy-Wetzel, M. V. Bennett, M. Pypaert, J. A. Hickman, P. J. Smith, J. M. Hardwick and E. A. Jonas (2008) Bcl-xL induces Drp1-dependent synapse formation in cultured hippocampal neurons. Proceedings of the National Academy of Sciences of the United States of America 105:2169–2174.

[168] Y. B. Chen, M. A. Aon, Y. T. Hsu, L. Soane, X. Teng, J. M. McCaffery, W. C. Cheng, B. Qi, H. Li, K. N. Alavian, M. Dayhoff-Brannigan, S. Zou, F. J. Pineda, B. O'Rourke, Y. H. Ko, P. L. Pedersen, L. K. Kaczmarek, E. A. Jonas and J. M. Hardwick (2011) Bcl-xL regulates mitochondrial energetics by stabilizing the inner membrane potential. The Journal of cell biology 195:263–276.

[169] M. Veas-Perez de Tudela, M. Delgado-Esteban, C. Maestre, V. Bobo-Jimenez, D. Jimenez-Blasco, R. Vecino, J. P. Bolanos and A. Almeida (2015) Regulation of Bcl-xL-ATP Synthase Interaction by Mitochondrial Cyclin B1-Cyclin-Dependent Kinase-1 Determines Neuronal Survival. The Journal of neuroscience: the official journal of the Society for Neuroscience 35:9287–9301.

[170] A. Kretz, S. Kugler, C. Happold, M. Bahr and S. Isenmann (2004) Excess Bcl-XL increases the intrinsic growth potential of adult CNS neurons in vitro. Mol Cell Neurosci 26:63–74.

[171] H. Li, K. N. Alavian, E. Lazrove, N. Mehta, A. Jones, P. Zhang, P. Licznerski, M. Graham, T. Uo, J. Guo, C. Rahner, R. S. Duman, R. S. Morrison and E. A. Jonas (2013) A Bcl-xL-Drp1 complex regulates synaptic vesicle membrane dynamics during endocytosis. Nat Cell Biol 15:773–785.

[172] E. A. Jonas, J. A. Hickman, M. Chachar, B. M. Polster, T. A. Brandt, Y. Fannjiang, I. Ivanovska, G. Basanez, K. W. Kinnally, J. Zimmerberg, J. M. Hardwick and L. K. Kaczmarek (2004) Proapoptotic N-truncated BCL-xL protein activates endogenous mitochondrial channels in living synaptic terminals. Proceedings of the National Academy of Sciences of the United States of America 101:13590–13595.

[173] J. A. Hickman, J. M. Hardwick, L. K. Kaczmarek and E. A. Jonas (2008) Bcl-xL inhibitor ABT-737 reveals a dual role for Bcl-xL in synaptic transmission. J Neurophysiol 99:1515–1522.

[174] R. J. Clem, E. H. Cheng, C. L. Karp, D. G. Kirsch, K. Ueno, A. Takahashi, M. B. Kastan, D. E. Griffin, W. C. Earnshaw, M. A. Veliuona and J. M. Hardwick (1998) Modulation of cell death by Bcl-XL through caspase interaction. Proceedings of the National Academy of Sciences of the United States of America 95:554–559.

[175] N. S. Seng, J. Megyesi, A. Tarcsafalvi and P. M. Price (2016) Mimicking Cdk2 phosphorylation of Bcl-xL at Ser73 results in caspase activation and Bcl-xL cleavage. Cell Death Discov 2:1–6.

[176] N. Fujita, A. Nagahashi, K. Nagashima, S. Rokudai and T. Tsuruo (1998) Acceleration of apoptotic cell death after the cleavage of Bcl-XL protein by caspase-3-like proteases. Oncogene 17:1295–1304.

[177] R. Sugioka, S. Shimizu, T. Funatsu, H. Tamagawa, Y. Sawa, T. Kawakami and Y. Tsujimoto (2003) BH4-domain peptide from Bcl-xL exerts anti-apoptotic activity in vivo. Oncogene 22:8432–8440.

[178] M. Hirotani, Y. Zhang, N. Fujita, M. Naito and T. Tsuruo (1999) NH2-terminal BH4 domain of Bcl-2 is functional for heterodimerization with Bax and inhibition of apoptosis. The Journal of biological chemistry 274:20415–20420.

[179] G. Basanez, J. Zhang, B. N. Chau, G. I. Maksaev, V. A. Frolov, T. A. Brandt, J. Burch, J. M. Hardwick and J. Zimmerberg (2001) Pro-apoptotic cleavage products of Bcl-xL form cytochrome c-conducting pores in pure lipid membranes. The Journal of biological chemistry 276:31083–31091.

[180] B. Antonsson, F. Conti, A. Ciavatta, S. Montessuit, S. Lewis, I. Martinou, L. Bernasconi, A. Bernard, J. J. Mermod, G. Mazzei, K. Maundrell, F. Gambale, R. Sadoul and J. C. Martinou (1997) Inhibition of Bax channel-forming activity by Bcl-2. Science 277:370–372.

[181] M. Narita, S. Shimizu, T. Ito, T. Chittenden, R. J. Lutz, H. Matsuda and Y. Tsujimoto (1998) Bax interacts with the permeability transition pore to induce permeability transition and cytochrome c release in isolated mitochondria. Proceedings of the National Academy of Sciences of the United States of America 95:14681–14686.

[182] E. A. Jonas, J. M. Hardwick and L. K. Kaczmarek (2005) Actions of BAX on mitochondrial channel activity and on synaptic transmission. Antioxidants & redox signaling 7:1092–1100.

[183] S. Jiao and Z. Li (2011) Nonapoptotic function of BAD and BAX in long-term depression of synaptic transmission. Neuron 70:758–772.

[184] M. C. Wei, T. Lindsten, V. K. Mootha, S. Weiler, A. Gross, M. Ashiya, C. B. Thompson and S. J. Korsmeyer (2000) tBID, a membrane-targeted death ligand, oligomerizes BAK to release cytochrome c. Genes & development 14:2060–2071.

[185] L. Scorrano, M. Ashiya, K. Buttle, S. Weiler, S. A. Oakes, C. A. Mannella and S. J. Korsmeyer (2002) A distinct pathway remodels mitochondrial cristae and mobilizes cytochrome c during apoptosis. Dev Cell 2:55–67.

[186] N. Zamzami, C. El Hamel, C. Maisse, C. Brenner, C. Munoz-Pinedo, A. S. Belzacq, P. Costantini, H. Vieira, M. Loeffler, G. Molle and G. Kroemer (2000) Bid acts on the permeability transition pore complex to induce apoptosis. Oncogene 19:6342–6350.

[187] N. Plesnila, S. Zinkel, D. A. Le, S. Amin-Hanjani, Y. Wu, J. Qiu, A. Chiarugi, S. S. Thomas, D. S. Kohane, S. J. Korsmeyer and M. A. Moskowitz (2001) BID mediates neuronal cell death after oxygen/ glucose deprivation and focal cerebral ischemia. Proceedings of the National Academy of Sciences of the United States of America 98:15318–15323.

[188] X. M. Yin, Y. Luo, G. Cao, L. Bai, W. Pei, D. K. Kuharsky and J. Chen (2002) Bid-mediated mitochondrial pathway is critical to ischemic neuronal apoptosis and focal cerebral ischemia. The Journal of biological chemistry 277:42074–42081.

[189] G. L. Semenza (2011) Hypoxia-inducible factor 1: regulator of mitochondrial metabolism and mediator of ischemic preconditioning. Biochimica et biophysica acta 1813:1263–1268.

[190] M. C. Simon (2006) Mitochondrial reactive oxygen species are required for hypoxic HIF alpha stabilization. Adv Exp Med Biol 588:165–170.

[191] Y. Benita, H. Kikuchi, A. D. Smith, M. Q. Zhang, D. C. Chung and R. J. Xavier (2009) An integrative genomics approach identifies Hypoxia Inducible Factor-1 (HIF-1)-target genes that form the core response to hypoxia. Nucleic Acids Res 37:4587–4602.

[192] N. Chen, X. Chen, R. Huang, H. Zeng, J. Gong, W. Meng, Y. Lu, F. Zhao, L. Wang and Q. Zhou (2009) BCL-xL is a target gene regulated by hypoxia-inducible factor-1{alpha}. The Journal of biological chemistry 284:10004–10012.

[193] H. Zhang, M. Bosch-Marce, L. A. Shimoda, Y. S. Tan, J. H. Baek, J. B. Wesley, F. J. Gonzalez and G. L. Semenza (2008) Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia. The Journal of biological chemistry 283:10892–10903.

[194] G. Bellot, R. Garcia-Medina, P. Gounon, J. Chiche, D. Roux, J. Pouyssegur and N. M. Mazure (2009) Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains. Mol Cell Biol 29:2570–2581.

[195] K. Tracy, B. C. Dibling, B. T. Spike, J. R. Knabb, P. Schumacker and K. F. Macleod (2007) BNIP3 is an RB/E2F target gene required for hypoxia-induced autophagy. Mol Cell Biol 27:6229–6242.

[196] R. Fukuda, H. Zhang, J. W. Kim, L. Shimoda, C. V. Dang and G. L. Semenza (2007) HIF-1 regulates cytochrome oxidase subunits to optimize efficiency of respiration in hypoxic cells. Cell 129:111–122.

[197] T. Briston, J. Yang and M. Ashcroft (2011) HIF-1alpha localization with mitochondria: a new role for an old favorite? Cell Cycle 10:4170–4171.

[198] G. Hsiao, J. J. Lee, Y. C. Chen, J. H. Lin, M. Y. Shen, K. H. Lin, D. S. Chou and J. R. Sheu (2007) Neuroprotective effects of PMC, a potent alpha-tocopherol derivative, in brain ischemia-reperfusion: reduced neutrophil activation and anti-oxidant actions. Biochem Pharmacol 73:682–693.

[199] Y. Chang, C. Y. Hsieh, Z. A. Peng, T. L. Yen, G. Hsiao, D. S. Chou, C. M. Chen and J. R. Sheu (2009) Neuroprotective mechanisms of puerarin in middle cerebral artery occlusion-induced brain infarction in rats. J Biomed Sci 16:9.

[200] Y. Chang, G. Hsiao, S. H. Chen, Y. C. Chen, J. H. Lin, K. H. Lin, D. S. Chou and J. R. Sheu (2007) Tetramethylpyrazine suppresses HIF-1alpha, TNF-alpha, and activated caspase-3 expression in middle cerebral artery occlusion-induced brain ischemia in rats. Acta Pharmacol Sin 28:327–333.

[201] L. Chen, P. Feng, S. Li, D. Long, J. Cheng, Y. Lu and D. Zhou (2009) Effect of hypoxia-inducible factor-1alpha silencing on the sensitivity of human brain glioma cells to doxorubicin and etoposide. Neurochem Res 34:984–990.

[202] X. Zhang, K. Deguchi, T. Yamashita, Y. Ohta, J. Shang, F. Tian, N. Liu, V. L. Panin, Y. Ikeda, T. Matsuura and K. Abe (2010) Temporal and spatial differences of multiple protein expression in the ischemic penumbra after transient MCAO in rats. Brain Res 1343:143–152.

[203] T. Soucek, R. Cumming, R. Dargusch, P. Maher and D. Schubert (2003) The regulation of glucose metabolism by HIF-1 mediates a neuroprotective response to amyloid beta peptide. Neuron 39:43–56.

[204] M. A. Puchowicz, J. L. Zechel, J. Valerio, D. S. Emancipator, K. Xu, S. Pundik, J. C. LaManna and W. D. Lust (2008) Neuroprotection in diet-induced ketotic rat brain after focal ischemia. J Cereb Blood Flow Metab 28:1907–1916.

[205] O. Baranova, L. F. Miranda, P. Pichiule, I. Dragatsis, R. S. Johnson and J. C. Chavez (2007) Neuron-specific inactivation of the hypoxia inducible factor 1 alpha increases brain injury in a mouse model of transient focal cerebral ischemia. J Neurosci 27:6320–6332.

[206] J. Milosevic, M. Maisel, F. Wegner, J. Leuchtenberger, R. H. Wenger, M. Gerlach, A. Storch and J. Schwarz (2007) Lack of hypoxia-inducible factor-1 alpha impairs midbrain neural precursor cells involving vascular endothelial growth factor signaling. J Neurosci 27:412–421.

[207] S. Tomita, M. Ueno, M. Sakamoto, Y. Kitahama, M. Ueki, N. Maekawa, H. Sakamoto, M. Gassmann, R. Kageyama, N. Ueda, F. J. Gonzalez and Y. Takahama (2003) Defective brain development in mice lacking the Hif-1alpha gene in neural cells. Mol Cell Biol 23:6739–6749.

[208] S. N. Willis, L. Chen, G. Dewson, A. Wei, E. Naik, J. I. Fletcher, J. M. Adams and D. C. Huang (2005) Proapoptotic Bak is sequestered by Mcl-1 and Bcl-xL, but not Bcl-2, until displaced by BH3-only proteins. Genes & development 19:1294–1305.

[209] L. Ming, P. Wang, A. Bank, J. Yu and L. Zhang (2006) PUMA Dissociates Bax and Bcl-X(L) to induce apoptosis in colon cancer cells. The Journal of biological chemistry 281:16034–16042.

[210] J. Ding, B. H. Mooers, Z. Zhang, J. Kale, D. Falcone, J. McNichol, B. Huang, X. C. Zhang, C. Xing, D. W. Andrews and J. Lin (2014) After embedding in membranes antiapoptotic Bcl-XL protein binds both Bcl-2 homology region 3 and helix 1 of proapoptotic Bax protein to inhibit apoptotic mitochondrial permeabilization. The Journal of biological chemistry 289:11873–11896.

[211] S. Rajan, M. Choi, Q. T. Nguyen, H. Ye, W. Liu, H. T. Toh, C. Kang, N. Kamariah, C. Li, H. Huang, C. White, K. Baek, G. Gruber and H. S. Yoon (2015) Structural transition in Bcl-xL and its potential association with mitochondrial calcium ion transport. Sci Rep 5:10609.

[212] M. C. Maiuri, G. Le Toumelin, A. Criollo, J. C. Rain, F. Gautier, P. Juin, E. Tasdemir, G. Pierron, K. Troulinaki, N. Tavernarakis, J. A. Hickman, O. Geneste and G. Kroemer (2007) Functional and physical interaction between Bcl-X(L) and a BH3-like domain in Beclin-1. The EMBO journal 26:2527–2539.

[213] A. M. Petros, D. G. Nettesheim, Y. Wang, E. T. Olejniczak, R. P. Meadows, J. Mack, K. Swift, E. D. Matayoshi, H. Zhang, C. B. Thompson and S. W. Fesik (2000) Rationale for Bcl-xL/Bad peptide complex formation from structure, mutagenesis, and biophysical studies. Protein Sci 9:2528–2534.

[214] A. Chattopadhyay, C. W. Chiang and E. Yang (2001) BAD/BCL-[X(L)] heterodimerization leads to bypass of G0/G1 arrest. Oncogene 20:4507–4518.

[215] T. Moldoveanu, A. V. Follis, R. W. Kriwacki and D. R. Green (2014) Many players in BCL-2 family affairs. Trends Biochem Sci 39:101–111.

[216] X. Liu, S. Dai, Y. Zhu, P. Marrack and J. W. Kappler (2003) The structure of a Bcl-xL/Bim fragment complex: implications for Bim function. Immunity 19:341–352.

[217] S. Rajan, M. Choi, K. Baek and H. S. Yoon (2015) Bh3 induced conformational changes in Bcl-Xl revealed by crystal structure and comparative analysis. Proteins 83:1262–1272.

[218] A. V. Follis, J. E. Chipuk, J. C. Fisher, M. K. Yun, C. R. Grace, A. Nourse, K. Baran, L. Ou, L. Min, S. W. White, D. R. Green and R. W. Kriwacki (2013) PUMA binding induces partial unfolding within BCL-xL to disrupt p53 binding and promote apoptosis. Nat Chem Biol 9:163–168.

[219] Y. Hu, M. A. Benedict, D. Wu, N. Inohara and G. Nunez (1998) Bcl-XL interacts with Apaf-1 and inhibits Apaf-1-dependent caspase-9 activation. Proceedings of the National Academy of Sciences of the United States of America 95:4386–4391.

[220] G. Pan, K. O'Rourke and V. M. Dixit (1998) Caspase-9, Bcl-XL, and Apaf-1 form a ternary complex. The Journal of biological chemistry 273:5841–5845.

[221] L. Xue, F. Chu, Y. Cheng, X. Sun, A. Borthakur, M. Ramarao, P. Pandey, M. Wu, S. F. Schlossman and K. V. Prasad (2002) Siva-1 binds to and inhibits BCL-X(L)-mediated protection against UV radiation-induced apoptosis. Proceedings of the National Academy of Sciences of the United States of America 99:6925–6930.

[222] B. N. Chau, E. H. Cheng, D. A. Kerr and J. M. Hardwick (2000) Aven, a novel inhibitor of caspase activation, binds Bcl-xL and Apaf-1. Mol Cell 6:31–40.

[223] O. Kutuk, S. G. Temel, S. Tolunay and H. Basaga (2010) Aven blocks DNA damage-induced apoptosis by stabilising Bcl-xL. Eur J Cancer 46:2494–2505.

[224] G. Monaco, E. Decrock, H. Akl, R. Ponsaerts, T. Vervliet, T. Luyten, M. De Maeyer, L. Missiaen, C. W. Distelhorst, H. De Smedt, J. B. Parys, L. Leybaert and G. Bultynck (2012) Selective regulation of IP3-receptor-mediated Ca2+ signaling and apoptosis by the BH4 domain of Bcl-2 versus Bcl-Xl. Cell death and differentiation 19:295–309.

[225] G. Monaco, M. Beckers, H. Ivanova, L. Missiaen, J. B. Parys, H. De Smedt and G. Bultynck (2012) Profiling of the Bcl-2/Bcl-X(L)-binding sites on type 1 IP(3) receptor. Biochemical and biophysical research communications 428:31–35.

[226] S. C. Lo and M. Hannink (2006) PGAM5, a Bcl-XL-interacting protein, is a novel substrate for the redox-regulated Keap1-dependent ubiquitin ligase complex. The Journal of biological chemistry 281:37893–37903.

[227] S. K. Niture and A. K. Jaiswal (2011) Inhibitor of Nrf2 (INrf2 or Keap1) protein degrades Bcl-xL via phosphoglycerate mutase 5 and controls cellular apoptosis. The Journal of biological chemistry 286:44542–44556.

[228] G. Arena, V. Gelmetti, L. Torosantucci, D. Vignone, G. Lamorte, P. De Rosa, E. Cilia, E. A. Jonas and E. M. Valente (2013) PINK1 protects against cell death induced by mitochondrial depolarization, by phosphorylating Bcl-xL and impairing its pro-apoptotic cleavage. Cell death and differentiation 20:920–930.

[229] H. Huang, X. Hu, C. O. Eno, G. Zhao, C. Li and C. White (2013) An interaction between Bcl-xL and the voltage-dependent anion channel (VDAC) promotes mitochondrial Ca2+ uptake. The Journal of biological chemistry 288:19870–19881.

[230] M. G. Vander Heiden, X. X. Li, E. Gottleib, R. B. Hill, C. B. Thompson and M. Colombini (2001) Bcl-xL promotes the open configuration of the voltage-dependent anion channel and metabolite passage through the outer mitochondrial membrane. The Journal of biological chemistry 276:19414–19419.

[231] A. V. Follis, F. Llambi, L. Ou, K. Baran, D. R. Green and R. W. Kriwacki (2014) The DNA-binding domain mediates both nuclear and cytosolic functions of p53. Nat Struct Mol Biol 21:535–543.

[232] H. Endo, H. Kamada, C. Nito, T. Nishi and P. H. Chan (2006) Mitochondrial translocation of p53 mediates release of cytochrome c and hippocampal CA1 neuronal death after transient global cerebral ischemia in rats. The Journal of neuroscience: the official journal of the Society for Neuroscience 26:7974–7983.

INTECH