Ischemic Cerebral Damage
An Appraisal of Synaptic Failure

Jeannette Hofmeijer, MD, PhD; Michel J.A.M. van Putten, MD, PhD

Abstract—In the human brain, ≈30% of the energy is spent on synaptic transmission. Disappearance of synaptic activity is the earliest consequence of cerebral ischemia. The changes of synaptic function are generally assumed to be reversible and persistent damage is associated with membrane failure and neuronal death. However, there is overwhelming experimental evidence of isolated, but persistent, synaptic failure resulting from mild or moderate cerebral ischemia. Early failure results from presynaptic damage with impaired transmitter release. Proposed mechanisms include dysfunction of adenosine triphosphate-dependent calcium channels and a disturbed docking of glutamate-containing vesicles resulting from impaired phosphorylation. We review energy distribution among neuronal functions, focusing on energy usage of synaptic transmission. We summarize the effect of ischemia on neurotransmission and the evidence of long-lasting synaptic failure as a cause of persistent symptoms in patients with cerebral ischemia. Finally, we discuss the implications of synaptic failure in the diagnosis of cerebral ischemia, including the limited sensitivity of diffusion-weighted MRI in those cases in which damage is presumably limited to the synapses. (Stroke. 2012;43:607-615.)

Key Words: brain metabolism ▪ cerebral ischemia ▪ synaptic failure

The human brain is metabolically expensive. Although it represents only 2% of the body weight, it accounts for 20% of oxygen consumption and 25% of glucose utilization.1,2 Cerebral ischemia is a pathological condition in which blood flow to the brain is insufficient to meet these metabolic demands, causing a loss of neuronal function and viability. Ischemia may be focal if a brain artery is occluded or global, for example, after cardiac arrest.

In the 1950s, the concept of perfusion thresholds was introduced.3 It was shown that functional activity became impaired with moderately reduced perfusion (14–35 mL/100 g/min), along with electroencephalographic and evoked potential disturbances, whereas loss of ion gradients across the plasma membrane and subsequent cell swelling occur at lower perfusion levels ≈4.8 to 8.4 mL/100 g/min (Figure 1).3–5 In focal brain ischemia, the brain tissue that is perfused in the flow range between these 2 levels is now called the penumbra.6 The penumbra is considered structurally intact and viable, but functionally silent. The dysfunction is, in principle, reversible by restoration of blood flow. However, if oxygen and glucose are not resupplied in time, irreversible damage occurs.

Knowledge on the distribution of energy usage among different neuronal activities may contribute to understanding the successive loss of cell function and cell damage in cerebral ischemia. In the human brain, ≈30% of the energy is spent on synaptic transmission.7 Disappearance of synaptic activity is the earliest consequence of cerebral ischemia8 and failure of synaptic transmission has been proposed to account for electric silence in the penumbra.3,6,8–10 The changes of synaptic function are generally assumed to be reversible. It is even hypothesized that suppression of functional synaptic activity is a compensatory mechanism to balance oxygen supply and consumption in favor of maintaining resting potentials and preserving the neurons’ structural integrity.11 However, the observation that adenosine triphosphate (ATP) concentrations decline first in synaptic as compared to other slice regions, even before the occurrence of changes in synaptic activity,12 suggests failure as a result of energy exhaustion rather than energy saving.

Here, we review energy distribution among neuronal functions, focusing on energy usage of synaptic transmission. We summarize the effect of ischemia on neurotransmission and the evidence of long-lasting synaptic failure as a cause of persistent symptoms in patients with cerebral ischemia. Finally, we discuss the possible implications of synaptic failure in the diagnosis of cerebral ischemia.

Metabolic Demands in the Brain
Approximately 25% of the brain’s energy expenditure comprises basic cellular activities, such as protein synthesis, intracellular transport, and mitochondrial proton leakage.13,14 The remaining 75% is required for signaling processes. These

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From the Department of Neurology, Rijnstate Hospital, Arnhem, The Netherlands; Department of Clinical Neurophysiology, Medisch Spectrum Twente and Clinical Neurophysiology at MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands.
Correspondence to Jeannette Hofmeijer, neurologist, Department of Neurology, Rijnstate Hospital, Wagnerlaan 55, 6815 AD Arnhem, The Netherlands. E-mail jhofmeijer@rijnstate.nl
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may be further subdivided in maintaining a “communicable resting state” and “active signaling.” The “communicable resting state” depends on a transmembrane resting potential resulting from ion gradients across the semipermeable neuronal membranes. Ion gradients require proper functioning of various energy-dependent ion pumps.15,16 “Active signaling” comprises synaptic neurotransmission, action potential generation, and propagation. In rodents, active signaling accounts for \( \frac{87}{110} \) of energy consumption, half for synaptic processes and half for propagation of action potentials.13 In humans, the density of neurons is 3-fold to 10-fold lower than in rodents with an unchanged density of synapses, implying a 3-fold to 10-fold higher number of synapses per neuron.17 The expected share of synaptic consumption relative to other energy-dependent processes therefore is probably also higher.

Glucose is the main substrate for cerebral energy production.18–21 After transport across the blood–brain barrier and cell membrane, glucose is converted into pyruvate via the anaerobic glycolytic pathway in the cytosol. This results in the production of 2 mol ATP per mol of glucose. Pyruvate is subsequently transported into the mitochondria and converted into acetyl-CoA to enter the tricarboxylic acid cycle. In subsequent steps of the tricarboxylic acid cycle, oxidative phosphorylation produces an additional 30 mol ATP per mol of glucose.22 Thus, the energetic value of mitochondrial oxidative phosphorylation is obvious. A high density of mitochondria has been found around the synaptic cleft.23,24 Besides the fact that critical steps in the metabolism of the neurotransmitters glutamate and GABA are located in the mitochondrial tricarboxylic acid cycle,25 this high concentration of mitochondria probably reflects high energy consumption.

Most observations on synaptic transmission concern glutamatergic neurotransmission and are extrapolated because excitatory neurons outnumber inhibitory neurons with a factor of 9 to 1, and 90% of the synaptic transmission is glutamatergic.18,26 Energy needed for glutamatergic signaling comprises: (1) presynaptic ion fluxes and release of glutamate; (2) postsynaptic actions of glutamate; and (3) glutamate recycling (Figure 2). Calculations on the energy needs of these components were calculated and published by Attwell and Laughlin in 2001.13 The 3 steps can be summarized as follows.

First, the presynaptic action potential triggers calcium influx by the opening of voltage-dependent calcium channels, resulting in a strong increase in the intracellular calcium concentration. This is quickly followed by active extrusion of calcium by the \( 3\text{Na}^+/\text{Ca}^{2+}/\text{H}^+ \) exchanger, requiring \( \approx 12000 \) ATP per vesicle released.27 Vesicle release and recycling are not completely understood. Phosphorylation of synaptic proteins, called synapsins, plays a regulating role. Under resting conditions, synapsins bind synaptic vesicles to the cytoskeleton. Phosphorylation is induced by the increase in intracellular calcium and results in the undocking of vesicles from the reserve pool, allowing them to move to the membrane and release their neurotransmitter.28,29 The complete process of vesicle release and recycling needs \( \approx 1000 \) ATP per vesicle,17 in which membrane fusion costs \( \approx 400 \) ATP per vesicle.30
The total presynaptic energy consumption, therefore, is 13,000 ATP/vesicle.

Second, postsynaptic actions of glutamate comprise the induction of ion fluxes with Na\(^+\) influx through non-N-methyl-D-aspartate (NMDA) receptor channels, and Na\(^+\) and Ca\(^{2+}\) influx through NMDA receptor channels. Calcium is actively extruded by 3Na\(^+\)/Ca\(^{2+}\)+ and sodium by 3Na\(^+\)/2K\(^+\) exchange, at a mean cost of \(\approx 67,000\) and 70,000 ATP molecules per vesicle of glutamate, respectively. Furthermore, glutamate metabotropic receptors can actively activate phospholipase C to generate triphosphoinositol (a second messenger, also called IP3, which releases calcium influx from intracellular stores), alter cAMP production (which modulates neuronal excitability), or modulate calcium channels. The energy costs of all these processes have been estimated at 3000 ATP per released vesicle of glutamate.

Third, the released glutamate is taken-up mainly into astrocytes, driven by the cotransport of Na\(^+\) and H\(^+\) and the countertransport of K\(^+\). The Na\(^+\), K\(^+\), and H\(^+\) are actively pumped back by Na\(^+\)/K\(^+\) and Na\(^+\)/H\(^+\) pumps, respectively.\(^{31}\) The glutamate taken-up is partly converted into glutamine.\(^{32}\) Glutamine leaves glia and enters neurons passively, driven by the glutamine concentration gradient.\(^{33}\) Finally, glutamate is repackaged into vesicles powered by vesicular H\(^+\)-ATPase.\(^{34}\) For recycling of 1 vesicle of glutamate, the sum of these processes has been calculated to cost \(\approx 11 \times 10^3\) ATP.\(^{13,17}\) In sum, the total energy consumption associated with the release of a single vesicle of glutamate is 164,000 ATP. Postsynaptic actions of glutamate consume the largest portion (85%). Presynaptic ion fluxes, glutamate excretion, and vesicle recycling consume a share of 8%, whereas glutamate recycling uses only 7%.\(^{13}\)

For mouse pyramidal cells, the total cost of synaptic signaling by a single pyramidal cell has been estimated, assuming 8000 output synapses, a mean firing rate of 4 Hz, and a vesicle release probability of 0.25. This results in 2000 vesicles of glutamate per action potential, giving an estimated total synaptic cost of \(3.28 \times 10^8\) ATP/neuron/action potential.\(^{17}\)

### Synaptic Failure in Ischemia

In the 1960s, depression of excitatory synaptic transmission in hypoxic circumstances was shown in different regions of the brain.\(^{8,35,36}\) Thereafter, changes in synaptic responses after variable periods of hypoxia or ischemia have been shown frequently in vitro\(^{37,38,39,40}\) and in vivo,\(^{41,42,43}\) and several causes of presynaptic and postsynaptic ischemic failure have been postulated.

#### Evidence of Presynaptic Failure

Most evidence upholds the assumption that early hypoxic synaptic failure is primarily a result of presynaptic malfunction and associated with impaired transmitter release. This suggestion is based on a variety of observations of decreased postsynaptic potentials evoked by stimulation of afferent fibers in the presence of intact responses to exogenous glutamate or other postsynaptic receptor agonists\(^{44–47}\) or intact spontaneous miniature excitatory postsynaptic potentials in vitro.\(^{48}\) In several studies, this transmission defect could be demonstrated up to 4 weeks after the ischemic insult and was considered permanent.\(^{48–51}\)

Sun et al\(^{131}\) studied the effect of brief hypoxia on the rat hippocampus in vitro as well as in vivo. Two minutes of hypoxia caused a synaptic arrest with elimination of excitatory postsynaptic potentials in vitro. During the synaptic arrest, no depolarization was measured, indicating that the arrest could not result from membrane depolarization. Furthermore, local application of L-glutamate caused a postsynaptic response, indicating that the arrest was caused by failure of the presynaptic neuron. Moreover, they found long-lasting posthypoxic impaired learning and memory in rats according to a water maze test, without evidence of cellular damage on histological examination, consistent with a transmission defect without structural neuronal damage.\(^{43}\)

Bolay et al\(^{41}\) found a restored axonal conduction, but a lasting impairment of cortical synaptic transmission by means of intracortically evoked potentials in the rat motor cortex after transient focal ischemia in vivo. In a later study, they showed a long-lasting defect of synaptic transmission in the penumbral region after transient middle cerebral artery occlusion in rats. An intact response of postsynaptic neurons to glutamate as well as a preserved function of pyramidal cells to generate action potentials matched their hypothesis of presynaptic failure. They searched for the exact site of the presynaptic defect by examining phosphorylation of synapsin-1 by means of an antibody detecting the phospho-form of this protein. They found decreased phosphosynapsin immunoreactivity, suggesting a permanent ischemia-induced phosphorylation defect.\(^{42}\)

Evidence of failure of presynaptic calcium channels as a cause of presynaptic hypoxic failure dates from the 1980s and 1990s and has been demonstrated by voltage clamp experiments\(^{52–54}\) and measurements of extracellular in intracellular calcium concentrations in vitro.\(^{55–57}\) Elevated intracellular Ca\(^{2+}\) levels result from hypoxia-induced inflow from outside and release from internal stores. Elevation of intracellular Ca\(^{2+}\) inactivates voltage-gated calcium channels, thus hampering transmitter release.\(^{58,59}\) Moreover, decay of the calcium gradient between intracellular and extracellular space as a result of calcium inflow probably diminishes calcium currents that initiate transmitter release.\(^{52}\)

Other, provisionally unproven, mechanisms of presynaptic failure include failure of action potential propagation from the (myelinated) axon to the (unmyelinated) terminal branches and focal depolarization of presynaptic buttons. Depletion of available neurotransmitter is unlikely the cause of failure, because adding glutamine to hypoxic hippocampal slices does not alleviate the synaptic block.\(^{40}\)

Selective structural damage of presynaptic components as a result of transient focal ischemia has been shown in a few studies and comprises isolated loss of synaptic buttons\(^{60,61}\) and a decreased density of presynaptic projections.\(^{62}\) Elevated levels of proteins involved in synaptogenesis, such as growth-associated protein\(^{63,64}\) or synaptophysin,\(^{65}\) and an increase in the density of dendritic spines within hours to days after brief ischemia\(^{62,66,67}\) suggest efforts to normalize these structural changes. However, complete functional recovery is mostly not achieved.\(^{58}\)
Evidence of Postsynaptic Failure
In early studies, a decrease of postsynaptic excitability has been attributed to anoxic depolarization of the postsynaptic membrane.51-59 Later, a decreased membrane function was ascribed to a slight focal postsynaptic hyperpolarization occurring just before the massive hypoxic depolarization,50,71 resulting from an enhanced K+ conductance.52,71 As in presynaptic failure, an increased intracellular calcium concentration resulting from inflow from outside and release from internal stores probably plays a key role, either as the initial event or as the final common path.52

The postsynaptic density is a protein-dense region attached to the postsynaptic membrane. Hundreds of different proteins have been identified here with different functions in the cascade of signal transmission, including the postsynaptic receptors themselves and many signaling molecules.72 Detrimental effects of transient focal ischemia on specific subcomponents of the postsynaptic density have been found by several authors in rat hippocampal slices. The demonstrated defects strongly depended on the a priori hypothesis and the resulting research method. Deleterious effects on both morphological appearance73 and protein interactions have been shown.74-78

The effect of ischemia on the NMDA receptor is dual. Mild ischemia causes overactivation associated with unregulated calcium inflow and consequent delayed neuronal death, whereas severe ischemia causes inactivation with transmission failure.79 Synaptic failure as a result of NMDA receptor inactivation has been shown repeatedly in vitro80-84 and in vivo,79 and it has been associated with increased phosphorylation of the receptor.81,82 However, coexisting damage of presynaptic functions and neuronal damage were not unequivocally refuted in any of the studies examining postsynaptic effects. Moreover, overactivation of the postsynaptic neuron, which is considered an early sign in mild ischemia, is probably partly caused by increased levels of excitatory amino acids (mainly glutamate) in the synaptic cleft80,83,84 because of a coexisting presynaptic effect.

Structural degeneration or isolated focal swelling of postsynaptic dendrite spines without neuronal or axonal damage have been identified in vivo as characteristic early features of cerebral ischemia.73-76,85-88 In cortical neurons that survived global ischemia, a reduction in dendrite complexity and loss of dendritic spines was observed.89 Similar changes can be seen after brain cell injury as a result of excessive glutamatergic stimulation, one of the pathways linking ischemia and neuronal injury.90,85

Effects on Synaptic Plasticity
Under physiological conditions, synaptic strength is not fixed, but can be modulated. Long-term potentiation (LTP) is a form of synaptic plasticity to increase synaptic strength. It leads to an increased postsynaptic cell’s sensitivity to signals received from the presynaptic cell and is usually achieved by means of synchronous stimulation. LTP contributes to increased strength of NMDA receptor-dependent signal transmission. The NMDA receptor is a nonspecific cation channel, which is blocked by Mg2+ at physiological levels. It only opens if the presynaptic neuron emits glutamate to bind to the receptor and simultaneously the postsynaptic neuron is depolarized to remove Mg2+ from the channel. Once achieved, this leads to a long-lasting increased synaptic strength. Memory is thought to be encoded by modification of synaptic strength, and LTP is thought to be one of the mechanisms underlying the process of learning.91,92 In hippocampal neurons, LTP of synaptic transmission can be induced by high-frequency stimulation of Schaffer collaterals or perforant fibers and leads to a sustained increase of excitatory postsynaptic potentials amplitude.

Opposite effects of hypoxia on LTP in the hippocampus have been described. Diminishment of high-frequency stimulation-induced LTP has been shown in rat hippocampal slices and comes together with membrane failure.93 Anoxia-induced LTP leads to a persistent enhancement of glutamatergic excitatory postsynaptic potentials amplitude, without a change of the resting potential of the postsynaptic membrane.94-97 The increased excitatation is selectively related to NMDA receptor responses and results from a reduction of the ability of Mg2+ to induce a voltage-dependent blockade of the response.96,98 However, the exact mechanism is not understood.99 It has been hypothesized that structural modifications of synapses over the course of minutes or hours after mild ischemia may play a role, such as enlargement of existing spines and filopodia.100,101 Anoxia induced LTP also has been called pathological plasticity102 because the resulting hyperexcitability is associated with delayed neuronal cell death, resulting from increased calcium uptake.103,104 Increased excitability as a result of LTP has been associated with poststroke epileptic seizures.105,106

Selective Vulnerability
Hippocampal pyramidal and cerebellar Purkinje cells are relatively sensitive for oxygen or glucose deprivation, followed by pyramidal cells of the neocortex.107 The exact cause of this high sensitivity remains unclear. However, both pyramidal cells and Purkinje cells are large and have substantial connectivity, which may play a role. In the hippocampus, astrocytes are relatively sensitive for oxygen and glucose deprivation as well.108 Furthermore, synaptic disinhibition fails before synaptic excitation. This does not result from selective failure of GABAergic transmission: inhibitory synapses are probably even more resistant to hypoxia than excitatory synapses.109,110 The inhibition is caused by failure of the excitatory input to inhibitory interneurons, leading to silencing of inhibitory interneurons.110 This may contribute to excitotoxicity with delayed cell death. Also, it may lead to abnormal excitatory synchronicity after cerebral ischemia, manifesting as electroencephalographic status epilepticus in posthypoxic encephalopathy after cardiac arrest.111

Imaging of Ischemic Damage in Clinical Practice
Brain imaging in ischemia may focus on structural changes, perfusion abnormalities, or both. Diffusion-weighted MRI (DWI) is the most sensitive commonly available technique measuring tissue damage in acute cerebral ischemia.112-116 DWI provides signal contrast based on differences of random (Brownian) motion of water molecules or diffusion capacity.114 If the diffusion capacity is restricted, then signal
intensity increases. Diffusion restriction can be visible within minutes after the onset of cerebral ischemia. It is thought to reflect intracellular (cytotoxic) edema, resulting from failure of energy-dependent transmembrane Na+/K+ pumps. Signal changes on T2-weighted and fluid-attenuated inversion recovery MRI are based on prolonged T2 relaxation and reflect interstitial edema. These usually become visible 3 to 8 hours after the onset of focal ischemia. 

Many of the initial case series reported nearly 100% sensitivity for DWI in the acute stage of focal cerebral ischemia. Meanwhile, several cases of DWI-negative stroke have been reported. The sensitivity of DWI for the diagnosis of ischemic stroke is now estimated to be 80% to 90%. False-negative MRI results are usually attributed to infarct size in relation to spatial resolution. However, different observations of permanent ischemic neurological disturbances without DWI changes suggest functional damage with intact structural neural integrity. In particular, in global cerebral ischemia severe and extensive ischemic damage may occur in the absence of DWI abnormalities. Although the amount of brain tissue with reduced ADC values is inversely related to clinical outcome in comatose patients after cardiac arrest, lack of any relevant lesions on DWI or T2-weighted MRI in the acute, subacute, and chronic period have been found repeatedly. This absence of DWI abnormalities did not exclude severe functional deficits. In a recent prospective cohort study in patients with global cerebral ischemia after cardiac arrest, 3 out of 15 patients with poor neurological outcome had no DWI abnormalities at all after 2, 7, and 14 hours, respectively. Another patient with severe global ischemic brain injury affirmed by autopsy findings, no DWI abnormalities were found 6 hours after the onset of ischemia. Similar findings have been reported in patients with focal ischemia. In a recent prospective study in 246 patients with a clinical diagnosis of ischemic lacunar or minor cortical stroke, 60 patients did not show the infarct on MRI performed at 4 to 27 days after the insult. The mechanism of functional failure remains unclear in these patients. We propose that synaptic dysfunction may play an important role. This is supported by electroencephalography findings. In patients with postanoxic encephalopathy after cardiac arrest, a variety of electroencephalography changes can be observed that reflect diffuse synaptic disturbances. Moreover, bilateral absence of somatosensory-evoked potentials reflect thalamocortical gliomalatosities at all after 2, 7, and 14 hours, respectively. In a recent prospective cohort study in patients with heart failure, cognitive impairment occurs with an odds ratio of 1.6, as compared with subjects without heart failure, and is attributed to chronic hypoperfusion. Energy depletion is associated with decreased brain size, and in patients with cardiac failure medial temporal lobe atrophy, but not T2 white matter hyperintensities, it is associated with hypotension and impaired cognitive function. Furthermore, in a large prospective study in patients with chronic obstructive pulmonary disease, hypoxemia was the only parameter associated with the occurrence of cognitive failure after multivariable regression analysis and treatment with supplemental oxygen decreased the risk matching functional damage without structural lesions. 

An increased understanding of the pathophysiology of synaptic failure could serve the development of clinical applicable diagnostics to visualize transmission failure. Molecular imaging, for example, by means of nuclear imaging techniques directed toward proteins associated with neurotransmission, such as postsynaptic receptors, may increase possibilities to qualify events in the ischemic cascade. MRI-based molecular imaging of synaptic processes would need augmentation of the intrinsic low sensitivity. However, the combination of anatomic and functional information could contribute to the estimation of the severity of ischemic changes and prognosis with regard to standing deficit. Specific magnetic resonance spectroscopy techniques already allow quantitative studies of cerebral energy metabolism and neurotransmission. Knowledge of ischemic synaptic failure may gain even wider application, if it could contribute to the implementation of particular treatments. Specific defects of neurotransmission have been associated with secondary damage through uncontrolled transmitter release. Targeted neuroprotective therapy could prevent secondary damage in adequately selected patients. Patient selection for potentially dangerous treatments, such as aggressive recanalization therapy or neuroprotective cooling, could be guided by knowledge of the mechanisms and reversibility of synaptic failure. Patients with cognitive disturbances resulting from transmission failure attributable to chronic ischemia/hypoxemia could benefit from treatment to enhance cerebral perfusion or blood oxygenation.

In the past decennia, there has been much interest in neuroprotection after ischemic stroke. Various agents have been tested to antagonize injurious biochemical and molecular events, such as calcium channel blockers, glutamate antagonists, and GABA agonists. There has been a remarkable discrepancy between the results of experimental studies and clinical trials. Many studies in animal models showed that protection of ischemic brain by specific neuroprotective
agents is achievable. However, none of the agents has proven
effect in patients with brain infarction in clinical trials. Proposed explanations include methodological flaws of pre-
clinical studies, disparities between animals models and
clinical trials, and publication bias favoring positive animal studies. Another important explanation may be an insuffi-
ciently accurate translation of preclinical findings into clinical
trials. Here, the functional profile of the component
undergoing development in relation to the pathophysiology of
the disease should be the focus of interest. For example, it is
surprising that the neuroprotective effect of glutamate recep-
tor antagonists has been tested extensively in patients with
brain infarction but not in patients with global ischemia
resulting from cardiac arrest. Based on the current know-
eledge, the possibility of effect is probably larger in the latter
patient group. Glutamate-induced excitotoxicity is only rele-
vant in mild to moderate ischemia and persistent neurological
deficit without structural changes on MRI is more common in
this patient group.

Finally, a better understanding of ischemic synaptic dam-
age could contribute to prognostication and treatment of
patients during rehabilitation. Increasing knowledge of syn-
aptic damage and plasticity could possibly contribute to the
development of treatments to facilitate rehabilitation of pa-
tients with ischemic cerebral damage.

Further experimental research on the role of ischemic
synaptic failure should focus on the share of presynaptic and
postsynaptic disturbances and the mechanism of the pre-
sumed impairment of transmitter release. Furthermore, experi-
ments may focus on selective vulnerability, the degree of
reversibility, and the mechanisms that eventually lead to
irreversible transmission failure. In the clinic, diagnostic
studies with continuous electroencephalography monitoring
of synaptic failure may prove value in prognostication of
postanoxic encephalopathy after cardiac arrest. The notion of isolated ischemic synaptic failure in patients with-
out DWI changes could be supported by information on
absent evoked potentials in patients without DWI changes.
Therapeutic studies could consist of studies on the effect of
oxygen therapy on cognition and synaptic functioning in patients with chronic hypoxemia.

Conclusions
In conclusion, synaptic failure is a key process in ischemia-
duced cerebral damage, even in the absence of neuronal
death. Increased insight in ischemia-induced synaptic failure
may contribute to improved diagnosis and treatment of
patients with focal or global cerebral ischemia.

Disclosures
None.

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