A Review on Pathogenesis of Cerebral Ischemia

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ABSTRACT

Current knowledge regarding the pathophysiology of cerebral ischemia and brain trauma indicates that similar mechanisms contribute to loss of cellular integrity and tissue destruction. Mechanisms of cell damage include excitotoxicity, oxidative stress, free radical production, apoptosis and inflammation. Genetic and gender factors have also been shown to be important mediators of patho mechanisms present in both injury settings. However, the fact that these injuries arise from different types of primary insults leads to diverse cellular vulnerability patterns as well as a spectrum of injury processes. Severe cerebral ischemic insults lead to metabolic stress, ionic perturbations, and a complex cascade of biochemical and molecular events ultimately causing neuronal death. Similarities in the pathogenesis of these cerebral injuries may indicate that therapeutic strategies protective following ischemia may also be beneficial after trauma. This review summarizes and contrasts injury mechanisms which leads to ischemia and trauma.

Keywords: Ischemic cascade, Excitotoxicity, Excitatory amino-acid transporters, Mitochondria.

INTRODUCTION

SCHEMATIC CASCADE

A cascade is a series of events in which one event triggers the next, in a linear fashion. Thus "ischemic cascade" is actually a misnomer, since in it events are not always linear, in some cases they are circular, and sometimes one event can cause or be caused by multiple events. In addition, cells receiving different amounts of blood may go through different chemical processes. Despite these facts, the ischemic cascade can be generally characterized as follows:

1. Lack of oxygen causes the neuron's normal process for making ATP for energy to fail.
2. The cell switches to anaerobic metabolism producing lactic acid.
3. ATP-reliant ion transport pumps fail, causing the cell to become depolarized, allowing, ions including calcium (Ca**+), to flow into the cell.
4. The ion pumps can no longer transport calcium out of the cell, and intracellular calcium levels get too high.
5. The presence of calcium triggers the release of the excitatory amino acid neurotransmitter Glutamate.
6. Glutamate stimulates AMPA receptors and Ca**+-permeable NMDA receptors, which open to allow more calcium into cells.
7. Excess calcium entry overexcites cells and causes the generation of harmful chemicals like free radicals, reactive oxygen species and calcium-dependent enzymes such as calpain, endonucleases, ATPase, and phospholipases, in a process called Excitotoxicity.
8. As the cell's membrane is broken down by phospholipases, it becomes more permeable, and more ions and harmful chemicals flow into the cell.
9. Mitochondria break down, releasing toxins and apoptic factors into the cell.
10. The caspase - dependent apoptosis cascade is initiated, causing cells to "commit suicide."
11. If the cell dies through necrosis, it releases glutamate and toxic chemicals into the environment around it. Toxins poison nearby neurons, and glutamate can over excite them.
12. If and when the brain is reperfused, a number of factors lead to reperfusion injury.
13. An inflammatory response is mounted, and phagocytic cells engulf damaged but still viable tissue.
14. Harmful chemicals damage the blood brain barrier. Cerebral edema (swelling of the brain) occurs due to leakage of large molecules like albumins from blood vessels through the damaged blood brain barrier. These large molecules pull water into the brain tissue after them by osmosis. This "vasogenic edema" causes compression of and damage to brain tissue.

1. HYPOXIA

Cerebral hypoxia is a form of hypoxia (reduced supply of oxygen) specifically involving the brain when the brain is completely deprived of oxygen. There are four categories of cerebral hypoxia; in order of severity they are:

1. Diffuse cerebral hypoxia (DCH): A mild to moderate impairment of brain function due to low oxygen levels in the blood.
2. Focal cerebral ischemia: Is a stroke occurring in a localized area that can either be acute (sudden onset) and/or transient (of short duration). This may be due to aneurysm, thrombus, embolus. Hypoxic/anoxic injuries (HAI).

3. Massive cerebral infarction: Is a "stroke", caused by complete oxygen deprivation due to an interference in cerebral blood flow which affects multiple areas of the brain.


Cerebral hypoxia can also be classified by the cause of the reduced brain oxygen:

- **Hypoxic hypoxia:** Limited oxygen in the environment causes reduced brain function.
- **Hypemic hypoxia:** Reduced brain function is caused by inadequate oxygen in the blood despite adequate environmental oxygen.
- **Ischemic hypoxia:** Reduced brain oxygen is caused by inadequate blood flow to the brain.
- **Histotoxic hypoxia:** Oxygen is present in brain tissue but cannot be metabolized by the brain tissue.

Causes: Severe asthma and various sorts of anemia can cause some degree of diffuse cerebral hypoxia. Other causes include work in nitrogen rich environments, ascent from deep water dive, flying at high altitudes in an unpressurized cabin, and intense exercise at high altitudes prior to acclimatization, choking, drowning, strangulation, smoke inhalation, drug over doses, crushing of the trachea, status asthmaticus, and shock. It is also recreationally self-induced in the fainting game and in erotic asphyxiation. Transient Ischemic Attack (TIA): TIA is defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. The symptoms of a TIA can resolve within a few minutes unlike a stroke. TIAs and strokes present with the same symptoms such as contralateral paralysis (opposite side of body from affected brain hemisphere), or sudden weakness or numbness. A TIA may cause sudden dimming or loss of vision, asphyxia slurred speech and mental confusion. The symptoms of a TIA typically resolve within 24 hours unlike a stroke. Brain injury may still occur in a TIA lasting only a few minutes. Having a TIA is a risk factor for eventually having a stroke. Silent stroke is a stroke which does not have any outward symptoms, and the patient is typically unaware they have suffered a stroke. Despite not causing identifiable symptoms a silent stroke still causes damage to the brain, and places the patient at increased risk for a major stroke in the future. Silent strokes typically cause lesions which are detected via the use of neuro imaging such as fMRI. The risk of silent stroke increases with age but may also affect younger adults. Women appear to be at increased risk for silent stroke, with hypertension and current cigarette smoking being predisposing factors. The two main mechanisms are hypoxic and anoxic, Brain injury as a result of oxygen deprivation either due to hypoxic or anoxic mechanisms are generally termed hypoxic/anoxic injuries (HAI).

2. ACIDOSIS

Acidosis is said to occur when arterial pH falls. In mammals, the normal pH of arterial blood lies between 7.35 and 7.50 depending on the species. Changes in the pH of arterial blood (and therefore the extracellular fluid) outside this range result in irreversible cell damage. Although glucose is usually assumed to be the main energy source for living tissues, there are some indications that it is lactate, and not, glucose that is preferentially metabolized by neurons in the brain of several mammal species. According to the lactate-shunting hypothesis, glial cells are responsible for transforming glucose into lactate, and for providing lactate to the neurons. Because of this local metabolic activity of glial cells, the extra cellular fluid immediately surrounding neurons strongly differs in composition from the blood cerebro spinal fluid, being much richer with lactate, as it was found in studies. The role of lactate is being utilized by the brain even more preferentially over glucose. It was also hypothesized that lactate may exert a strong action over GABAergic networks in the developing brain, making them more inhibitory, acting either through better support of metabolites or alterations in base intracellular pH levels or both. The energy metabolism features in brain slices of mice and showed that beta-hydroxybutyrate, lactate and pyruvate acted as oxidative energy substrates causing an increase in the NAD(P)H oxidation phase, that glucose was insufficient as an energy carrier during intense synaptic activity and finally, that lactate can be an efficient energy substrate capable of sustaining and enhancing brain aerobic energy metabolism in vitro. Also provides novel data on biphasic NAD(P)H fluorescence transients, an important physiological response to neural activation that has been reproduced in many studies and that is believed to originate predominantly from activity-induced concentration changes to the cellular NADH pools.

3. REPERFUSION INJURY

It is the tissue damage caused when blood supply returns to the tissue after a period of ischemia or lack of oxygen. The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than restoration of normal function. The inflammatory response is partially responsible for the damage of reperfusion injury. White blood cells carried to the area by the newly returning blood, release a host of inflammatory factor such as interleukins as well as free radicals in response to tissue damage. The restored blood flow reintroduces oxygen within cells that damages
cellular proteins, DNA and the plasma membrane. Damage to the cell’s membrane may in turn cause the release of more free radicals. Such reactive species may also act indirectly in redox signaling to turn on apoptosis when white blood cells may also bind to the endothelium of small capillaries, obstructing them and leading to more ischemia.  

4. XANTHINE OXIDASE

In prolonged ischemia (60 minutes or more), hypoxanthine is formed as breakdown product of ATP metabolism. The enzyme hypoxanthine dehydrogenase acts in reverse, that is as a xanthine oxidase as a result of the higher availability of oxygen. This oxidation results in molecular oxygen being converted into highly reactive superoxide and hydroxyl radicals. Xanthine oxidase also produces uric acid, which may act as both a pro oxidant and as a scavenger of reactive species such as peroxy nitrite. Excessive nitric oxide produced during reperfusion reacts with superoxide to produce the potent reactive species peroxy nitrite. Such radicals and reactive oxygen species attack cell membrane lipids, proteins, and glycosaminoglycans, causing further damage. They may also initiate specific biological processes by redox nitrite. Reperfusion can cause hyperkalaemia.

5. GLUTAMATE

Glutamate is the most abundant excitatory neurotransmitter in the vertebrate nervous system. At chemical synapsis glutamate is stored in vesicles nerve impulses trigger release of glutamate from the presynaptic cell. In the opposing post-synaptic cell, glutamate receptors, such as the NMDA receptors, bind glutamate and are activated. Because of its role in synaptic plasticity, glutamate is involved in cognitive functions like learning and memory in the brain. The form of plasticity known as long term potentiation takes place at glutamatergic synapses in the hippocampus, neocortex, and other parts of the brain. Glutamate works not only as a point-to-point transmitter but also through spill-over synaptic crosstalk between synapses in which summation of glutamate released from a neighboring synapse creates extra synaptic signaling/volume transmission. Glutamate transporters are found in neuronal and glial membranes. They rapidly remove glutamate from the extracellular space. In brain injury or disease, they can work in reverse, and excess glutamate can accumulate outside cells. This process causes calcium ions to enter cells via NMDA receptors channels, leading to neuronal damage and eventual cell death, and is called excitotoxicity. The mechanisms of cell death includes: Damage to mitochondria from excessively high intracellular calcium. Glu/Ca-mediated promotion of transcription factors for pro-apoptotic genes, or down regulation of transcription factors for anti-apoptotic genes. Excitotoxicity due to excessive glutamate release and impaired uptake occurs as part of the ischemic cascade and is associated with stroke and diseases like amyotrophic lateral sclerosis, lathyrisn, and some forms of mental retardation, and Alzheimer’s disease. In contrast, decreased glutamate release is observed under conditions of classical phenyl ketonuria leading to developmental disruption of glutamate receptors expression.

6. EXCITATORY AMINO-ACID TRANSPORTERS (EAATs)

It is also known as glutamate transporters, belong to the family of transporters. Glutamate is the principal excitatory neurotransmitter in the vertebrate brain. EAATs serve to terminate the excitatory signal by removal (uptake) of glutamate from the neuronal synapse into neuralgia and neurons. The EAATs are membrane-bound secondary transporters that superficially resemble ion channels. These transporters play the important role of regulating concentrations of glutamate in the extra cellular space by transporting it along with other ions across cellular membranes. After glutamate is released as the result of an action potential, glutamate transporters quickly remove it from the extracellular space to keep its levels low, thereby terminating the synaptic transmission. Without the activity of glutamate transporters, glutamate would build up and kill cells in a process called excitotoxicity, in which excessive amounts of glutamate acts as a toxin to neurons by triggering a number of biochemical cascades. The activity of glutamate transporters also allows glutamate to be recycled for repeated release. Over activity of glutamate transporters may result in inadequate synaptic glutamate and may be involved in schizophrenia and other mental illnesses. During injury processes such as ischemia and traumatic brain injury, the action of glutamate transporters may fail, leading to toxic buildup of glutamate. In fact, their activity may also actually be reversed due to inadequate amounts of adenosine triphosphate to power ATPase pumps, resulting in the loss of the electro chemical ion gradient. Since the direction of glutamate transport depends on the ion gradient, these transporters release glutamate instead of removing it, which results in neurotoxicity due to over activation of glutamate receptors. Loss of the Na+-dependent glutamate transporter EAAT2 is suspected to be associated with neuro degenerative diseases such as Alzheimer’s disease, Huntington’s disease, and ALS-parkinsonism dementia complex. Also degeneration of motor neurons in the disease amyotrophic lateral sclerosis has been linked to loss of EAAT2 from patients’ brains and spinal cords.

7. MITOCHONDRIA

Mitochondria produce more than 90% of our cellular energy by ox-phos. Energy production is the result of two closely coordinated metabolic processes — the tricarboxylic acid (TCA) cycle, also known as the Krebs or citric acid cycle, and the electron transport chain (ETC). The TCA cycle converts carbohydrates and fats into some ATP, but its major job is producing the coenzymes NADH and FADH, which are then used to enter the ETC. NADH and FADH carry electrons to the ETC, which is
embedded in the inner mitochondrial membrane and
consists of series of five enzyme complexes, designated I–V. Electrons donated from NADH and FADH flow through
the ETC complexes, passing down an electrochemical
gradient to be delivered to diatomic oxygen (O2) via a
chain of respiratory proton (H+) pumps 45. Complexes I–IV
involve ubiquinone (Coenzyme Q10, which is embedded
in the inner mitochondrial membrane and consists of a
series of five enzyme complexes, designated I–V. Complexes I–IV involve ubiquinone. Complex II is
succinate dehydrogenase (SDH), complex III is the bcl
complex, complex IV is cytochrome c oxidase (COX), and
complex V is ATP synthase 44. Complexes I–IV contain
flavins, which contain riboflavin, iron-sulfur clusters,
copper centers, or iron containing heme moieties. Ubiquinone shuttle electrons from complexes I and II to
to complex III. Cytochrome c, an iron-containing heme
protein with a binuclear center of a copper ion,46 transfers electrons from complex III to IV. During this
process, protons are pumped through the inner
mitochondrial membrane the inter membrane space to
establish a proton motive force, which is used by complex
V to phosphorylate adenosine diphosphate (ADP) by ATP
synthase, thereby creating ATP. Proper functioning of the
TCA cycle and ETC requires all the nutrients involved
in the production of enzymes and all the cofactors needed
to activate the enzymes.

Mechanisms includes damage to mitochondria is caused
primarily by reactive oxygen species (ROS) generated by
the mitochondria themselves 47,48. It is currently believed
that the majority of ROS are generated by complexes I
and III 49 likely due to the release of electrons by NADH
and FADH into the ETC. Mitochondria consume
approximately 85% of the oxygen utilized by the cell
during its production of ATP.50 During normal oxphos, 0.4–
4.0% of all oxygen consumed is converted in mitochondria
to the superoxide (O2 –) radical50–52. Superoxide is
transformed to hydrogen peroxide (H2O2) by the
detoxification enzymes manganese superoxide dismutase
(MnSOD) or copper/zinc superoxide dismutase (Cu/Zn
SOD)53 and then to water by glutathione peroxidase (GPX)
or peroxideroxidin III (PRX III)54. However, when these
enzymes cannot convert ROS such as the superoxide
radical to H2O fast enough, oxidative damage occurs and
accumulates in the mitochondria 55,56. Glutathione in GPX
is one of the body’s major antioxidants. Additionally, nitric
oxide (NO) is produced within the mitochondria by
mitochondrial nitric oxide synthase (mtNOS) 57 and also
freely diffuses into the mitochondria from the cytosol58
NO reacts with O2 – to produce another radical,
peroxynitrite (ONOO–) 58. Complex I is especially
susceptible to nitric oxide (NO) damage, and animals
administered natural and synthetic complex I antagonists
have undergone death of neurons 59–61. Complex I
dysfunction has been associated with Leber hereditary
optic neuropathy, Parkinson’s disease, and other
neurodegenerative conditions 52,63. Together, these two
radicals as well as others can do great damage to
mitochondria and other cellular within the mitochondria,
elements that are particularly vulnerable to free radicals
include lipids, proteins, oxidative phosphorylation
enzymes, and (mtDNA)64,65. Direct damage to
mitochondrial proteins decreases their affinity for
substrates or coenzymes and, thereby, decreases their
function 66. Compounding the problem, once a
mitochondria is damaged, mitochondrial function can be
further compromised by increasing the cellular
requirements for energy repair processes 67.
Mitochondrial dysfunction can result in a feed forward
process, whereby mitochondrial damage causes
additional damage.

8. INFLAMMATORY MEDIATORS

Inflammatory mediators such as tumor necrosis factor
alpha (TNF-α) have been associated in vitro with
mitochondrial TNF-α results in mitochondrial dysfunction
by reducing complex III dysfunction and increased ROS
generation 68. Medical research has found that iron
deficiency anemia is a major factor. Low iron status
decreases mitochondrial activity by causing a loss of
complex IV and increasing oxidative stress 68. Toxic
metals, especially mercury, generate many of their
deleterious effects through the formation of free radicals,
resulting in DNA damage, lipid peroxidation, depletion of
protein sulfhydryls (e.g. glutathione) These reactive
radicals include a wide-range of chemical species,
including oxygen-, carbon-, and sulfur radicals originating
from the superoxide radical, hydrogen peroxide, lipid
peroxides, and also from chelates of amino acids,
peptides, and proteins complexed with the toxic met One
major mechanism for metals toxicity appears to be direct
and indirect damage to mitochondria via depletion of
 glutathione, an endogenous thiol-containing (SH-) antioxidant which results in excessive free radical
generation and mitochondrial damage 69.

CONCLUSION

Ischemic cascade which follows the chain reaction in
which it mainly starts with the hypoxic conditions it
switches to anaerobic respiration followed by acidosis
condition which activates glutamate AMPA, NMDA. This
leads to generation of free radicals causes excitotoxicity,
necrosis. Xanthine oxidase which produces super oxide,
hydroxyl radicals and uric acid which triggers to peroxi
nitrile. These radicals react with oxygen species attack
the membrane lipids, proteins causes further damage.
Overall the formation of free radicals mainly causes the severe
ischemia, so the herbal plants which are having anti
oxidant activity shows much effectively to treat ischemia.

REFERENCES

flow, 24, 2004, 133-150.
itochondrial dysfunction and a determinant of her on ketone bodies nor on ter T, Bregestovski P "Neuronal activity in vitro

- mitochondrial dysfunction and association/American Stroke Association Stroke. 19. 2003

- Needham, A Comparative and Environmental Physiology. 2003

- pyruvate".

- Pellerin L, Bouzier millenium".

- evidence for lactate as a neuronal en

- Acidosis and Alkalosis. 2004


- 17 .Nedeham, A Comparative and Environmental Physiology. Acidosis and Alkalis. 2004


- Russuvuori E, Kiriikitin I, Pandya N, Kaila K. "Spontaneous network events driven by depolarizing GABA action in neonatal hippocampal slices are not attributable to deficient mitochondrial energy metabolism". J. Neurosci. 30 (46),2010, 15638–42.


- Zilberter, Yuri; Bregestovski, Piotr; Mukhtarov, Marat; Ivanov, Anton. "Lactate Effectively Covers Energy Demands during Neuronal Network Activity in Neonatal Hippocampal Slices". Frontiers in Neuroenergetics. 3: (2), 2011


