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A Review on Ischemia-Reperfusion Injury and Its Clinical Management

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Anusha Velpula*, Archana Jorige

Department of Pharmacology, RBVRR Women's College Of Pharmacy, Affiliated to Osmania University, Narayanaguda, Hyderabad, Telangana-500027 India.

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ABSTRACT

Ischemia-reperfusion injury is the tissue impairment triggered when blood supply revenues to tissue after a period of ischemia or deficiency 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 stress rather than restoration of normal function.[1] Reperfusion of ischemic tissue is frequently associated with microvascular injury, particularly due to increased permeability of capillaries and arteries that lead to a surge of diffusion and fluid filtration across the tissues. Reperfusion injury plays a key part in the biochemistry of hypoxic brain injury in the stroke. The diverse mechanisms are involved in the different organs, Ischemia-reperfusion injury are kidneys, heart, brain, liver, etc [2].

INTRODUCTION:

Ischemia-reperfusion injury is defined as the paradoxical exacerbation of cellular dysfunction to death ensuing the restoration of blood flow to ischemic tissues. Reperfusion injury is a multifactorial process that results in wide tissue destruction. In simple Ischemia is defined as hypoperfusion in tissues.[3] Ischemic reperfusion initiates a wide and multifaceted array of inflammatory responses that may both exacerbate local injury as well as induce impairment of remote organ function. Conditions beneath which ischemia-reperfusion injury is come across include the different forms of acute vascular occlusions (stroke, myocardial infarction, limb ischemia) with the particular reperfusion strategies (thrombolytic therapy, angioplasty, operative revascularization) but also monotonous surgical procedures (organ transplantation, free-tissue-transfer, cardiopulmonary bypass, vascular surgery) and major trauma/shock.[4]

ROLE OF CEREBROVASCULAR DISEASES BY ISCHEMIA-REPERFUSION INJURY:

Stroke, including ischemic stroke and hemorrhagic stroke, leads to death. Spontaneous reperfusion occurs after stroke in 50-70% of ischemic stroke patients. The reperfusion followed by ischemia determines substantial damage to cerebral tissue.[5]

The mechanisms involved are:

1. Oxidative stress:

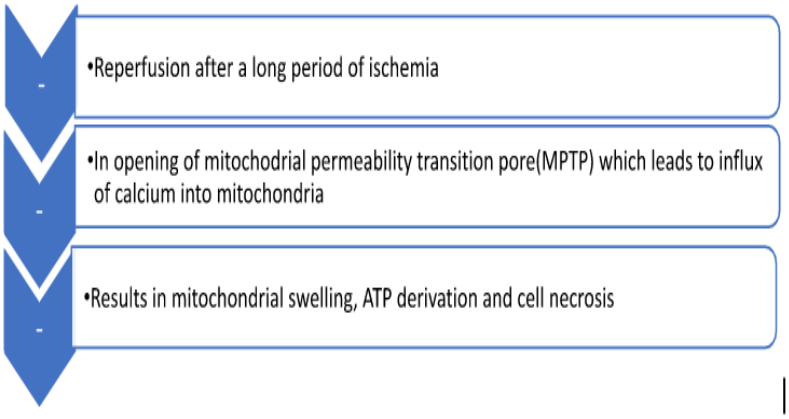
Reactive oxygen species mainly peroxides & free radicals such as superoxide anion devastate antioxidant capacity. Overprotection of ROS causes direct damage to all cellular components including proteins, DNA, RNA & lipids.[6]

Increased superoxide generation was detected *in-vivo* in a cerebral ischemia-reperfusion model using a cytochrome C-coated platinized carbon electrode the superoxide reduces stopped ferric cytochrome C, then re-oxidized by the electrode.[7]

A major spring of ROS Production after ischemia-reperfusion is mitochondria, has been established that ischemia-reperfusion persuades post-translational modification of oxidative phosphorylation proteins which increases mitochondria membrane potential (MPP), a condition that leads to excessive generation of ROS.[8] Another significant source of ROS Production is NADPH Oxidase, a component of the electron transport chain in the plasma membrane, with generates free radicals by transferring one electron to molecular oxygen.[9]

2. Mitochondrial mechanisms:

Mitochondria are multi-functional organelles that play role in pathophysiology & physiological conditions. Mitochondria along with ROS generators also progression apoptosis and necrosis. [10,11]



3. Leukocyte infiltration:

A process of leukocyte exodus directed by chemotactic signals, leukocytes rolling on the endothelium, leukocyte adhesion to the microvascular endothelial surface through receptor or ligands interaction, matrix metalloproteinase production for the cessation of Blood Brain Barrier (BBB), leukocyte eruption into brain tissue & release of cytokines to brain tissue triggering inflammation and response. [12,13]

4. Platelet mediated:

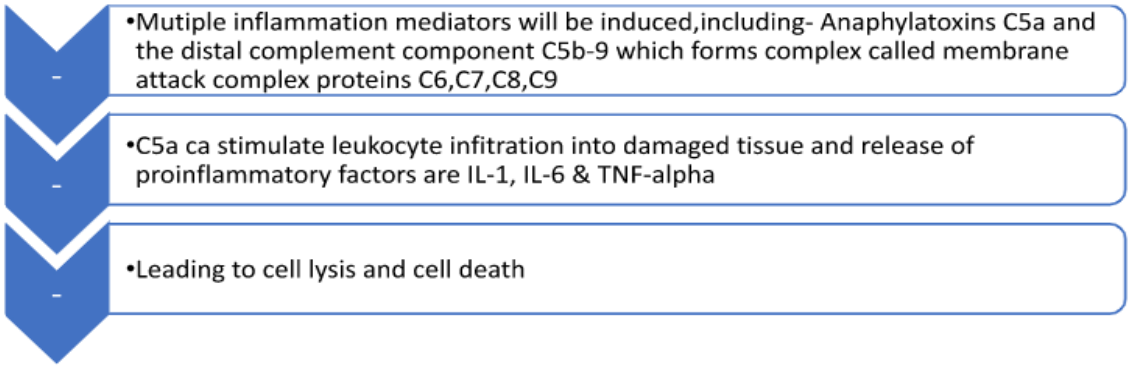
The platelets are activated by ischemia-reperfusion and amass in the vascular bed after reperfusion.[14] Upon activation, platelets generate oxygen radicals and release proinflammatory factors such as platelet-derived growth factor arachidonic acid metabolites, thromboxane A2, serotonin, and platelet factor.[15]

Platelet activation is also involved in leukocyte infiltration, as activated platelets twig to microvascular endothelial cells, causing a release of mediators ensuing in chemotaxis and migration of leukocytes exacerbating the inflammatory cascade.[16]

5. Complement mediated:

During reperfusion, the complement system can be triggered through diverse pathways, including the antibody-dependent classical pathway, substitute pathway, or lectin pathway involving MBL/MASP (Mannan-binding lectin/Mannan-binding lectin-associated serine

proteases).[17] These pathways are initiated by C1q,MBL/ficolin s/collectin-11, and C3b which leads to the activation and cleavage of C3 into C3a and Cb.[18]



6. Blood-brain barrier mediated:

The blood-brain barrier is a discriminating permeability barrier that separates blood circulation from the brain tissue. BBB is self-possessed of endothelial cells, pericytes, and astrocytes. [19]

Stages in BBB permeability changes after Ischemia-Reperfusion are:

1. Reactive hyperemia loss of cerebral autoregulation and improved BBB permeability.
2. Hypoperfusion caused by microvascular obstruction leads to inflammation response.
3. Upsurge in paracellular permeability occurs as a biphasic response.[20]

THERAPEUTICSTRATEGIES:

1. Antioxidant therapy:

Antioxidants such as iron chelating compounds such as catalase, superoxide dismutase, and vitamin E are able to avert stroke associated with cerebral Ischemia-Reperfusion Injury.[21]

EG: Iron chelating compound Deferoxamine was used to defend against ischemia-reperfusion injury in newborn piglets and continuous IV injection of recombinant superoxide dismutase for 5 days enhanced neurological functions.[22]

2. Inhibition of leukocyte infiltration:

The strategies include inhibition of leukocyte adhesion molecules synthesis, inflammation factor release, and receptor-mediated leucocyte adhesion to endothelial cells. Inhibitors of leukocyte adhesion molecule synthesis are glucocorticoids & D-Penicillamine. [23]

EG: 10,17S-Docosatriene shows potent inhibition for leukocyte infiltration and proinflammation gene induction and neuroprotective effect against ischemia-reperfusion injury. [24]

3. Inhibition of platelet aggregation:

Platelet is a bull's eye for therapeutics against ischemia-reperfusion injury. Platelet depletion using a filter can improve both pancreas [25] and liver [26] function after ischemia-reperfusion injury through reducing lipids peroxidation in the cell membrane and the rate of thromboxane A2 prostaglandin 12. Antiplatelet agents including Dipyridamole and Cilostazol will improve the myocardial function collective with statins after reperfusion injury.[27]

4. Complement therapy:

The inhibition of complement activation can shelter against ischemia-reperfusion injury. The inhibitor of C3 convertase the soluble complement receptor 1 reduced the myocardial infarct size and enhanced myocardial function in a rat model. The administration of a recombinant antibody against human C5 Pexelizumab diminished complement activation, and leukocyte activation was used for the post-operative transience of the patients.[28]

5. Post conditioning:

This treatment reduced infarct size by obstructive apoptosis and free radical generation. The effect of post conditioning might be sensitive and is within 30 minutes of reperfusion.

EG: Post conditioning after 90 minutes MCAO by releasing the femoral artery in the bilateral lower limbs for 3 cycles, each occlusion and release long-lasting for 10 minutes treatment which reduces brain infarct volume, brain edema, and BBB leakage.[29]

6. Intravenous Administration of Recombinant tissue Plasminogen activation is to date the only approved thrombolytic therapy for acute ischemic stroke treatment. It is safe within 24 hours after stroke onset. In the United States, stent retrievers have a beneficial treatment strategy.[30]

TABLE NO. 1: MECHANISMS INVOLVED AND TREATMENT CONDITIONING CARDIOVASCULARDISEASESCAUSEDBYISCHEMIA-REPERFUSION INJURY

MECHANISMS INVOLVED	TREATMENT CONDITION
Oxidative stress is caused by reactive oxygen species and free radicals.	Treated through the usage of antioxidants like catalase, and superoxide dismutase.
Mitochondria along with ROS generators process the cells for necrosis and apoptosis.	Treated by Mitochondrial permeability transition pore inhibitors like cyclosporin, and sanglifehrin A.
Leukocyte infiltration results in leukocyte extravasation into the brain and tissue triggering inflammation and response.	The condition is treated by the inhibition of leukocyte infiltration.
Platelet-mediated mechanisms through the release of proinflammatory factors.	Condition is dried by inhibiting the platelet aggregation by use of antiplatelet agents
Complement mediated mechanism is through diverse pathways like lectin, alternative pathway.	The inhibition of complement activation protects the ischemia-reperfusion injury by using an inhibitor of C3 convertase.
Calcium surplus and corresponding protection measures.	Verapamil, a voltage-dependent calcium channel blocker results in the inhibition of calcium accrual in hepatocytes.
Reduced ischemia-reperfusion injury caused by apoptosis.	Release of ATP through calcium to appeal phagocytic cells and inhibit ischemia-reperfusion injury cells by apoptosis.

The conditions caused by ischemia-reperfusion injury on the heart are myocardial infarction, and heart failure.

Mechanism:

The deficiency of oxygen and nutrients supply results in a series of biochemical and metabolic changes inside the myocardium. The absence of oxygen closes oxidative phosphorylation leading to mitochondrial membrane depolarization ATP depletion and inhibition of myocardial contractile function.[31]

The sudden reperfusion of actual ischemic myocardium in STEMI patients undergoing treatment can be escorted by ventricular arrhythmias. The reversible post-ischemic contractile dysfunction that occurs on reperfusion acute ischemic myocardium is stated as myocardial stunning. The major contributing factors include capillary damage with impaired vasodilation, external capillary compression by endothelial cell and cardiomyocyte distension, microembolization of friable material released from the atherosclerotic plaque, platelet microthrombi, the release of soluble vasomotor and thrombogenic substances and neutrophil plugging.

The main mediators of myocardial reperfusion injury are oxidative stress and intracellular calcium overload.[32]

THERAPEUTIC STRATEGIES:

The therapeutic strategies involved in treating myocardial infraction caused by ischemic reperfusion injury were-

The preconditioning stimulus starts in the remote organ to reach the target organ through their pathways. Intra mesenteric arterial adenosine administration induced cardio-protection, and this beneficial effect was congested by either pretreatment with hexamethonium or by an adenosine blocker.[33] The nitric oxide donors infused into the can increase intracellular nitric oxide bioavailability which is important to attain the preconditioning effect. As furthermore, clinical trials are on the procedure in milieu with the preconditioning and postconditioning studies to prevent myocardial infraction caused by Ischemic Reperfusion Injury.[34]

The modulators of the reperfusion injury rescue kinase prosurvival pathway such as adenosine, atrial natriuretic peptide, atorvastatin, erythropoietin, exenatide, and Delcasertib. Hyperbaric oxygen reduces Myocardial infarct size by lessening tissue edema, reducing the formation of lipid peroxide radicals, varying nitric oxide synthase expression ad inhibiting leukocyte adherence, and plugging in the microcirculation results in limited MI size. [35]

CONCLUSION:

Ischemia-reperfusion injury is a perilous challenge for physicians from a treatment standpoint. The major mechanisms of reperfusion injury include oxidative stress, leukocyte infiltration, platelet activation, complement activation, and BBB dysfunction leads to edema, stroke, and myocardial infiltration. Even though the detailed mechanisms associated with

ischemia-reperfusion injury remain to be fully elucidated, we believe an empathetic of the pathophysiology has the potential to provide a strong basis for the exploration of new therapeutic avenues.

Therapeutic studies are enduring targeting the mechanisms of ischemia-reperfusion injury.

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