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Reperfusion Injury - Treatments Methanalytic Study

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Abstract

Introduction: Reperfusion injury is a term used to describe the functional and structural changes that become apparent during re-establishment of flow after a period of ischemia. There are several mechanisms involved during the reflow.

Objectives: In view of the difficulties and importance of the issue, we decided to update on types of treatments proposed so far.

Methods: A research was carried out based on papers published in English and Portuguese literature from 1997 to 2014.

Conclusion: A series of procedures and new therapies were presented. However, we think that the ischemia reperfusion phenomenon still needs the elucidation of many aspects related to the complex reactions that occur following restoration of blood flow to previously ischemic tissues.

Introduction

Cerebrovascular diseases are currently the third leading cause of death and are still responsible for considerable morbidity rates. Among these, 85% to 90% occur by ischemic mechanism. Thus, it is important to systematically study the pathophysiology of the mechanisms involved in ischemic neuronal injury and its treatment in order to formulate strategies that can reduce both mortality and the various neurological sequelae resulting from such diseases. The investigation of the pathophysiology of the mechanisms involved in ischemic neuronal and endothelial injury becomes essential to design new therapeutic methods for the prevention and treatment of the diseases. Reperfusion injury is a term used to describe the functional and structural changes that become apparent during reestablishment of flow after a period of ischemia. Although restoration of blood flow to an ischemic organ is essential to prevent irreversible cell damage, reperfusion per se may aggravate ischemic cell damage [1-3].

Due to the difficulties and controversies regarding the treatments of this kind of lesion, we decided to elaborate an evaluation of the proposed treatments up to now.

Results

Despite advances in the study of the pathophysiology of Ischemia and Reperfusion (I/R), much still remains to be investigated. Understanding the mechanisms of injury is essential for introducing new therapies [4]. Classically, trying to prevent hyperperfusion phenomenon, in some more general procedures, a slight hemodilution and mild hypotension is maintained during the circulatory return phases, thus avoiding the deleterious effects of arterial reperfusion.

However, some other possibilities are here presented

Antioxidant: Interventions have been extensively investigated to prevent the action of ROS (Reactive Oxygen Species). Free radical scavengers, including alupurinol, superoxide dismutase, catalase, dimethyl sulfoxide, and others, have been used, showing to attenuate I/R lesions in various animal experiments [4].

Nitrite: Is an inert oxidative metabolite of Nitric Oxide (NO) found in circulation at micromolecular levels. Recent studies have shown that intravenous nitrite administration prior to reperfusion exerts significant therapeutic protection against myocardial and liver I/R injury [5]. In the vascular endothelium, Nitric Oxide Synthase (eNOS) converts L-arginine to L-citrulline to generate NO, which is widely recognized as a protective factor for vascular homeostasis [4].

Hyperbaric oxygen therapy (HBO): Has been investigated by some authors in the treatment of

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I/R injury. Although the clinical efficacy of HBO has been recognized in small clinical trials, the potential mechanism is still uncertain [4].

Hypothermia: Is commonly used to maintain amputated tissues prior to reimplantation. Local hypothermia has been shown to be protective when applied during the early phase of skeletal muscle reperfusion, suggesting a potential clinical strategy to minimize I/R injuries [6]. Prandini et al. [7] demonstrated that mild hypothermia showed protective properties when applied in ischemic rabbit brain. In other experiment, the authors demonstrated that hypothermia could have an important anti-inflammatory effect, reducing polymorphonuclear leukocytes infiltration in induced brain inflammation [8]. Recently, hydrogen sulfide has been studied by Henderson et al. [7]. These authors showed that pre-ischemic hydrogen sulfide release limits I/R injury to skeletal muscle. Research into the benefit of antioxidants over I/R injury has also resurfaced. Some studies have shown that vitamin E has a protective effect, preventing I/R injury to skeletal muscle [9].

Drugs acting on endothelium and vascular reactivity have been studied. Thus, cilostazol and pentoxifylline used and others, such as pravastatin and simvastatin, used to lower cholesterol, have been shown to attenuate skeletal muscle I/R lesions [10].

New Substances Gaining Highlights: A considerable amount of human and animal studies has shown the beneficial effects of antioxidant action on endothelial and neuroprotective function, which is particularly important in the prevention and treatment of ischemic diseases [11]. Among the antioxidants present in vegetables, the most active and often found are phenolic compounds such as flavonoids. The beneficial properties of these compounds can be attributed to their ability to inhibit lipoperoxidation by acting against free radical action [12]. Recent studies show that *pequi* (Caryocar brasiliense) has a high concentration of phenols and that both aqueous and ethanolic extracts of the bark demonstrate the ability to neutralize oxygen free radicals [13]. Caryocar brasiliense, popularly known as "*pequi*", is a typical fruit of the Brazilian cerrado known for its great importance in regional cuisine. In addition, *pequi* pulp oil is widely used in folk medicine as a tonic agent against asthma, influenza, cold and bronchopulmonary diseases [14]. These compounds are natural antioxidants that have the ability to reduce and/or prevent oxidative stress present in chronic and age-related diseases such as cardiovascular disease, carcinogenesis and neurodegeneration [15].

Recently, Miguel [16] found that *pequi* peel crude ethanolic extract at doses of 300 mg/kg and 600 mg/kg has potential neuroprotective activity after induction of transient global cerebral ischemia. Reduce and/or prevent oxidative stress present in chronic and associated diseases, such as cardiovascular disease, carcinogenesis and neurodegeneration.

Melatonin: A hormone derived from the pineal gland, as well as its metabolites, has been well described as a potent antioxidant agent against oxidative and nitrosative stress [17], as well as anti-inflammatory agents. In addition, melatonin has the ability to facilitate angiogenesis and wound healing [18]. The vast and ubiquitous distribution of melatonin receptors in the nervous system, including the brain and SC, indicates their role in providing neuroprotection.

Similar results were obtained by other researchers. These data indicate that the addition of any other potent antioxidant or inflammatory agent may act synergistically with melatonin to provide complete protection against SCI-IRI (motor dysfunction in post-medullary Ischemic Reperfusion Injury) [19].

A-Tocopherol: Is one of the most potent lipid-soluble biological antioxidants and ROS (Reactive Oxygen Species) scavengers in most body tissues, including neural tissue [17,19]. Interestingly, by acting by inhibiting lipid peroxidation and eliminating ROS, α-tocopherol supplementation significantly reduced spinal cord injury-induced motor disturbance [20].

Discussion

The return of circulation after a period of ischemia may have deleterious effects on the affected region. Restoration of blood flow can cause irreversibly damaged cell necrosis by the ischemic process as well as marked cellular edema and non-uniform restoration of flow to the entire tissue area. I/R occur in a wide range of organs including the heart, lung, kidney, gut, skeletal muscle and brain [21].

Several mechanisms are involved in the pathophysiology of injury secondary to ischemia and reperfusion. The main one is the formation of reactive oxygen species. Under physiological conditions, their toxic effects may be prevented by some endogenous antioxidant enzymes and also by other non-enzymatic antioxidants. However, when production becomes excessive, oxidative stress may have a deleterious effect on the function and structural integrity of biological tissues [22].

The interruption of blood flow, depending on the time, intensity, speed of installation, nature of the organ and the temperature to which the tissue is subjected, may determine the most varied degrees of cell damage. In the acute period, in a few minutes to hours, Oxygen (O2) depletion, Adenosine Triphosphate (ATP) and glucose energy depletion occur, inducing the cell to initiate anaerobic metabolism and thus lactate production, development of acidosis and activation of intracellular proteases [23]. Ischemia-reperfusion injury in the recent past has been classically related to two phenomena: the calcium paradox and the oxygen paradox [24].

The calcium paradox was initially observed after a period of perfusion of rat hearts with a solution that did not contain this ion. As the hearts were reperfused and calcium was restored, they lost their contractility, resulting in extensive myocardial injury. The mechanisms of calcium paradox are not well known, but after reperfusion there is a massive influx of calcium into the cell, probably by altering membrane permeability. Ca^{2+} elevation also activates a number of enzymes, with potentially deleterious effects such as lipases, phospholipases, proteases, ATPases and endonucleases. Activation of these enzymes alters cellular function, destabilizes the structure of the plasma membrane and cytoskeleton, increases lipolysis by free fatty acid metabolism, induces superoxide radical production during reperfusion, and ultimately leads to cell death. Any intervention that mitigates Ca2 increase [25]. When an interruption of blood flow occurs in a certain region, a number of metabolic processes are affected. Depletion of ATP reserves, lactate accumulation occurs, the cell becomes acidotic, intracellular proteases are activated, capillary permeability increases favoring tissue edema. The therapeutic goal of an ischemia is to reestablish reperfusion as soon as possible. Although the benefit of early reperfusion is unquestionable, reintroduction of oxygen into an ischemic medium initiates a complex stream of events leading to further tissue damage and intracellular calcium accumulation. + cytosolic reduces cell dysfunction and death. The reperfusion injury is proportional to the calcium-free perfusion time but is already evident after 3 min [26].

The oxygen paradox was verified when it was observed that reperfusion with oxygenated solution, after a period of myocardial hypoxia, resulted in significant injury greater than recovery, with contracture, calcium overload and cell necrosis re-oxygenation causes damage to the sarcolemma, basement membrane, mitochondrial disorganization and other tissue changes, indicating that oxygen reintroduction initiates a rapid and severe process of cell injury. Considerable information has been accumulated showing that this paradoxical effect of re-oxygenation is due to the actions of oxygen free radicals. Another component that contributes to cell damage is inflammation. In the ischemic zone, cell adhesion receptors are activated and neutrophils migrate through the blood vessel wall, invade the parenchyma and release cytotoxic inflammatory mediators, oxygen free radicals. Another component that contributes to the most important inflammatory mediators of these leukocytes are lysosomal enzymes, present in granules; the active metabolites derived from oxygen, and arachidonic acid metabolism products, including prostaglandins and leukotrienes These products easily promote endothelial and tissue injury and amplify the effects of the initial inflammatory stimulus [27]. In addition to neutrophils, microgliocytes and activated astrocytes are important producers of various proinflammatory cytokines and toxic metabolites. In contrast, astrocytes produce neuroprotective factors such as erythropoietin, Transforming Growth Factor beta (TGF-β) and metallothionine [28].

The brain is extremely sensitive to oxidative stress due to the presence of a large amount of unsaturated fatty acids, a large iron reserve, a high oxygen metabolism rate and a vulnerable and inefficient defense system against reactive oxygen-specific EROs. The main injuries caused by free radicals are cell cytoskeleton disruption, cell membrane fatty acid peroxidation, and alteration of ionic pumps. Inefficient against ROS: Reactive Oxygen Species [29]. Hemodilution is an increase in plasma volume relative to red blood cells, with a consequent reduction in the concentration of these blood cells in the blood circulation. Unlike hypervolemia, hemodilution consists of a slight decrease in red blood cell/plasma ratio, whereas in hypervolemia the use of large volumes of serum causes an intense decrease followed by hypertension. In the case of a reperfusion injury, hemodilution is beneficial as it dilutes ROS-rich blood, leaves the medium less concentrated and allows the perfusion to be maintained at low oxidant concentrations.

In addition to hemodilution, it is also empirically used hypotension to attenuate the oxygen pressure available to the perfused area, thus avoiding the formation of new reactive species and increased reperfusion injury.

It is noteworthy again that both hemodilution and hypotension techniques are used classically and empirically.

Conclusion

The ischemia-reperfusion phenomenon still needs the elucidation of many aspects related to the complex reactions that occur following restoration of blood flow to previously ischemic tissues.

A deeper understanding, coupled with new therapies still in development will surely solve some clinical difficulties that are frequently encountered.

Our purpose was to draw attention to new possibilities for prevention and treatment of this delicate condition.

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