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Ischemia-Reperfusion Damage

İskemi Reperfüzyon Hasarı

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Abstract

Ischemia-reperfusion damage is a complex pathological process that begins with tissue anoxia and continues with the production of free oxygen radicals, expanding with the inflammatory response. The literature suggests the importance of antioxidant and anti-inflammatory treatment to treat ischemia-reperfusion-related tissue damage.

Key Words: Ischemia, reperfusion damage

Özet

İskemi-reperfüzyon hasarı, dokunun oksijensiz kalması ile başlayan, serbest oksijen radikallerinin üretimi ile devam eden ve inflamatuar yanıtla genişleyen karmaşık patolojik bir süreçtir. Bu literetür bilgileri, iskemi-reperfüzyon doku hasarında antioksidan ve antiinflammatuar tedavinin önemini göstermektedir.

Anahtar Kelimeler: İskemi, reperfüzyon hasarı

Ischemic Damage

Ischemia is defined as an asphyxiated tissue state as a result of reduced or absent blood flow. In tissue ischemia, a series of chemical events that may extend to cell function disorders and cellular necrosis occurs. Healthy cellular functions are maintained through aerobic metabolism, whereas anaerobic metabolism is observed in ischemic cells [1]. Adenosine triphosphate (ATP) produced in healthy (aerobic) tissues is lysed into adenosine monophosphate (AMP), adenosine, inosine and hypoxanthine. The resulting hypoxanthine is metabolized into xanthine and uric acid. As nicotinamide adenine dinucleotide (NAD) is used in the metabolism of hypoxanthine by KDH in aerobic tissues, toxic oxygen radicals are not formed [2]. The metabolism of hypoxanthine in ischemic tissues is different from that in aerobic metabolism. Hypoxanthine is metabolized by xanthine oxidase (XO) in ischemic tissues, but not by KDH because KDH is transformed into XO during ischemia [3]. As molecular oxygen (O_2) is used in the metabolism of hypoxanthine by XO, toxic oxygen radicals are produced as intermediate products. However, because O_2 is not found in sufficient amounts in ischemic tissues, the accumulated hypoxanthine cannot be transformed into xanthine until reperfusion occurs, and toxic oxygen radicals cannot be produced as intermediate products [4]. However, cellular energy reservoirs are exhausted during long-term ischemia [5]. This exhaustion of energy reservoirs results in the inhibition of low Na^+/K^+-ATP pumps found in the cell membrane. Low ATP pump activity prevents the transport of Na^+ and Ca^{+2} ions to the outside of the cell, and the intracellular concentrations of Na^+ and Ca^{+2} ions increase as a result [6]. The intracellular increase in Na^+ increases water uptake by the cell by passive diffusion, causing cell swelling. This swelling decreases with the accumulation of anaerobic metabolites [7]. The intracellular increase in the Ca^{+2} ion concentration leads to pathological events within the cells [8]. Therefore, the first intervention for ischemic tissue should be to induce blood flow (reperfusion) within the tissue.

Reperfusion Damage

Formed during ischemia with reoxygenization during reperfusion, XO leads to the formation of excessive amounts of free oxygen radicals while transforming the accumulated hypoxanthine into xanthine using O_2 [3, 9, 10]. These free oxygen radicals, known as reperfusion mediators, lead to the formation of toxic products such as aldehyde and malondialdehyde lipids by oxidizing cell membrane lipids [11]. Moreover, oxygen radicals induce DNA oxidative damage [12]. Following free radical reactions, alkaline changes in nucleic acids and chain breaks in DNA occur. If the acquired DNA alterations cannot be repaired, the DNA mutates. It is accepted that 8-hydroxyguanine (8-OHGua) is a mutagenic type of DNA [12, 13]. Parks DA and colleagues have shown

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that reperfusion damage is more hazardous than ischemic damage alone [14]. Polymorphonuclear leukocytes (PMNLs) play an important role in the pathophysiology of reperfusion damage; PMNLs contain NADPH oxidase, which has oxidant effects, elastase, and myeloperoxidase in their azurophilic granules [15]. Respiratory burst occurs as a result of free oxygen radical release due to the increase of xanthine oxidase in active PMNLs. In the beginning of reperfusion following ischemia, approximately 70% of the oxygen provided to the tissue is oxidized to superoxide by xanthine oxidase. Superoxide is typically transformed into hydrogen peroxide by spontaneous dismutation. Hydrogen peroxide is reduced to hypochloric acid and chloride ions by myeloperoxidase. Hypochloric acid is a strong oxidant, and it can easily react with many biological molecules. Proteolytic enzymes, such as apolactoferrin, which is released from granules upon the activation of PMNLs, plasminogen activator, which activates complement, elastase, collagenase and gelatinase, damage the vessel endothelium [16]. Ischemia-reperfusion damage is also caused by the activation of phospholipase A2 with the increase of intracellular calcium during ischemia. Phospholipase A2 increases arachidonic acid, which is a membrane phospholipid. During tissue ischemia-reperfusion, cyclooxygenase-2 (COX-2) [15] is activated, leading to the formation of pro-inflammatory prostaglandins and free oxygen radicals from arachidonic acid [17-19]. Recent studies have demonstrated that histopathologic indications of inflammation and high COX-2 activity are observed in ovarian tissue following ischemia-reperfusion [20]. Reperfusion damage is known to be more severe than the damage caused by ischemia alone. Ischemia-reperfusion damage can be observed in almost all types of tissues. An increase in oxidant parameters and a decrease in antioxidant parameters have been reported following ischemia-reperfusion damage to the brain, myocardium, lung, kidney, ovary and stomach [21]. As a result, ischemia-reperfusion damage is a complicated pathological process beginning with tissue asphyxiation, continuing with the production of free oxygen radicals and expanding with the inflammatory response. The information reported in the literature underlines the importance of antioxidant and anti-inflammatory treatment to treat tissue with ischemia-reperfusion damage.

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