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Review Article

Protective Effects of MESNA Against Carotid Artery Ischemia-Reperfusion: A Hypothesis

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Abstract

Carotid artery ischemia-reperfusion injury is a critical disease whose prevalence is increasing worldwide. It causes intense oxidative stress resulting from the narrowing of the carotid artery due to the lack of oxygen or cholesterol. Although some surgical applications such as endarterectomy are used for its treatment, no effective pharmacological treatment has yet been found. Today, MESNA is administered intravenously to treat hemorrhagic cystitis, which is a known side effect of anticancer drugs such as cyclophosphamide and ifosfamide. According to studies, MESNA acts by first neutralizing free radicals and then eliminating the destructive effects of oxidative stress. In this regard, MESNA is proposed to have protective effects in both carotid artery ischemia-reperfusion injury and distant tissue damage.

Keywords: Ischemia; Reperfusion; MESNA; Oxidative stress

Introduction

The carotid arteries are some of the most important vessels of the body that supply adequate blood to the brain, face, and neck [1, 2]. The right and left carotid arteries split into the internal carotid artery (ICA), which supplies the brain, and the external carotid artery (ECA), which supplies the face and neck [3].

In the event of an arterial occlusion, such as an embolism, blood flow is interrupted, and tissue hypoxia occurs [4]. This condition, which initiates carotid artery ischemia-reperfusion, triggers the formation of free radicals. Free radicals are molecules or atoms that cause cell death and tissue damage. This pathological condition ultimately affects the brain, and over time, distant tissues and organs also begin to be damaged [5]. This leads to many predictable acute injuries to the heart and lungs [6, 7]. The oxidative stress that occurs during reperfusion also affects vital organs such as the brain, heart, and lungs [8]. The antioxidant and anti-inflammatory effects of MESNA may be useful in managing all these conditions [9-11].

Hypothesis

MESNA, which has been shown to protect the brain, heart, and lungs from the deleterious effects of ROS/RNS, oxidative stress, and caspase, may have protective effects against carotid artery ischemia-reperfusion.

Free radicals and ischemia-reperfusion

Free radicals are toxic by-products of aerobic metabolism that cause oxidative modifications and loss of function in tissues (Figure 1). These free radicals, namely reactive oxygen species

(ROS) and reactive nitrogen species (RNS), have powerful oxidation and nitrification activities in the human brain [12]. Increased production of ROS and RNS during cerebral ischemia-reperfusion, particularly with blood reflow, results in cell death through DNA damage, protein dysfunction, and lipid peroxidation [5].

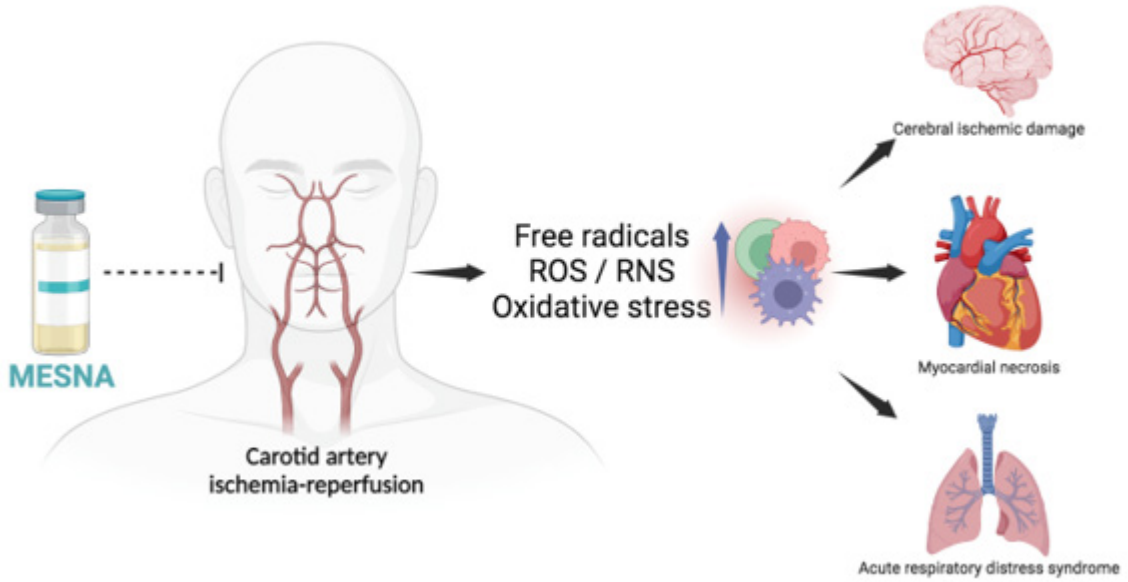

Figure 1: MESNA prevents cerebral and myocardial tissue damage as well as acute respiratory distress syndrome, by inhibiting the deleterious effects of free radicals, oxidative stress, and inflammation.

Several life-threatening disorders such as myocardial infarction, ischemic stroke, and acute kidney injury may emerge following carotid artery ischemia-reperfusion, where free radicals are prevalent [13]. Ischemia in the chronic stage can lead to carotid artery disease, which may result in interruptions in the blood flow to the brain and paralysis [14].

Carotid artery ischemia-reperfusion induced brain damage

Ischemia-reperfusion in the carotid artery reduces cerebral blood flow, and thus, the oxygen levels in some areas of the brain drop. The reperfusion that occurs after ischemia results in oxidative stress in regions with low oxygen levels. However, excessive production of ROS in cells disrupts the endogenous antioxidant system [15, 16].

Reperfusion causes oxidative stress in the region exposed to ischemia, and as a result, the blood-brain barrier is compromised [17], and cerebral edema develops over time. Cerebral ischemia, which worsens with oxidative stress, exacerbates brain injury by altering the neuro-inflammatory pathways [18, 19].

Furthermore, several enzymes are inactivated by superoxide, one of the free radicals that tends to increase during carotid ischemia-reperfusion. Cerebral ischemic damage, vasospasm following a subarachnoid hemorrhage, atherosclerosis, meningitis, stroke, and Alzheimer's disease or vascular dementia may occur as a result of this vascular dysfunction [20, 21]. All these pathological events occur due to sudden death of brain tissues due to ischemia resulting from reduced blood flow in the carotid artery [22].

Carotid artery ischemia-reperfusion can also affect remote organs. Remote organ injury (ROI) may occur in reperfusion after local ischemia of the carotid artery [23-25]. Ischemia-reperfusion injury also disrupts organ perfusion in distant tissues, causing tissue hypoxia, resulting in cellular damage and/or cell death [26].

Carotid artery ischemia-reperfusion-induced heart and lung damages

Prolonged ischemia resulting from carotid artery ischemia-reperfusion can cause myocardial necrosis and cell death due to excessive oxidative stress [27]. ROS adversely affects myocardial calcium and heart rhythm, thus leading to arrhythmia. Also, disruption of vascular blood flow can cause atherosclerosis, a chronic and progressive disease that can trigger myocardial ischemia and infarction [28, 29].

After carotid artery ischemia reperfusion, several reactive oxygen species (ROS) restrict blood flow to the lungs and impair breathing [30, 31]. High levels of ROS contribute to the

advancement of acute respiratory distress syndrome (ARDS) as well as lung damage. Oxidative stress triggers the release of cytotoxic substances, which cause pulmonary edema by promoting endothelial and epithelial damage in the lungs [32]. However, different antioxidant mechanisms aid in the reduction of cell damage caused by ROS [28, 33].

Protective effects of MESNA

MESNA is a chemo-protective agent that neutralizes ROS. MESNA suppresses hemorrhagic cystitis by inhibiting the excess hydrogen peroxide produced during treatment with anticancer drugs like Oxazaphosphorine [11, 34, 35]. Because of its direct suppressive action on hydrogen peroxide generation, thiol containing MESNA might be used as an antioxidant to reduce the damaging effects of free radicals [11].

According to studies, MESNA is well tolerated by most patients and can prevent neurotoxicity as well as cell death caused by caspase activation [36]. In physiological states, superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase, and other antioxidant enzymes can protect tissues from ROS cytotoxicity via catalysis, therefore maintaining a neutral equilibrium. During cerebral ischemia-reperfusion, particularly during the reperfusion phase, the generation of free radicals rise, leading to the breakdown of antioxidant systems. However, MESNA has been shown to protect the brain from severe damage due to its antioxidant and anti-inflammatory effects [37]. Furthermore, it has been shown in several studies that the removal of excess ROS from cells successfully prevents the formation of atherosclerotic plaques. Because MESNA reduces ROS, it may also suppress the formation of atherosclerotic plaques.

Conclusion

No proven preventative drugs or measures have been presented in studies until now for carotid artery ischemia-reperfusion. This review proposes that MESNA may play a key protective role in carotid artery ischemia-reperfusion, which can be attributed to its antioxidant effects. Hence, we suggest that further studies be conducted to confirm this hypothesis and extend the research.

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Ethical approval

This article does not contain any studies with animals performed by any of the authors.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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