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Free Radical Scavengers In Anaesthesiology And Critical Care

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Abstract
Free radicals are highly reactive and unstable compounds. These highly reactive molecules cause oxidative damage to cellular components such as DNA, proteins and lipids. They play central role in the mechanism of cell injury and cell death. Free radical scavengers either prevent these reactive species from being formed, or remove them before they can damage vital components of the cell. Oxidative stress defines an imbalance in production of oxidizing chemical species and their effective removal by protective antioxidants and scavenger enzymes. Evidence of massive oxidative stress is well established in critical illnesses characterized by tissue ischaemia-reperfusion injury and by an intense systemic inflammatory response such as during sepsis and acute respiratory distress syndrome, acute lung injury. Several clinical trials have been performed in order to reduce oxidative stress by supplementation of antioxidants alone or in combination with standard therapies. Antioxidant supplementation at an early stage of illness may lead to improved therapies in the treatment of critically ill patients. Several intravenous anaesthetic drugs act as reactive oxygen species scavengers. Anaesthetic preconditioning is of particular interest to anaesthesiologist, in which lasting protection of myocardium is elicited by brief exposure to a inhalational anaesthetic agent. These anasthetics may also mediate protective effects in other organs, such as the brain and kidney It is important for the anaesthesiologist to understand the mechanism of damage caused by free radicals and how free radical scavengers work so that this knowledge can be applied to varied pathological conditions. The topic was hand searched in text books and electronically searched from PubMed and Google scholar using text words.

Keywords: Anaesthesiology, antioxidants, critical care, free radicals, oxidative stress

Introduction

Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals. Inturn, these radicals can start chain reactions that damage cells. Most of the potentially harmful effects of oxygen are due to reactive oxygen species (ROS), which have a tendency to donate oxygen to other substances. Many such reactive species are free radicals and have a surplus of one or more free-floating electrons rather than having matched pairs and are, therefore, unstable and highly reactive.[1] Types of free radicals include superoxide radicals (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl ions (OH) and lipid peroxyl radical (LOO).[2]

Several protective systems operate in mammalian cells to prevent formation of free radicals or to scavenge excessive amounts already formed. These are known as preventive and chain breaking antioxidants or radical scavengers like catalases, glutathione peroxidase, superoxide dismutase (SOD), α-tocopherol (Vit. E), ascorbic acid (Vit. C), β carotene (Vit. A), selenium. Although about 4000 antioxidants have been identified, the best known are Vit. E, Vit. C and the carotenoids. Many other non-nutrient food substances, generally phenolic or polyphenolic compounds, display antioxidant properties and thus may be important for health.

Excessive generation of ROS is one of the mechanism incriminated in the pathogenesis of generalized (i.e. sepsis, transplantation, ischaemia/reperfusion injury, burns) or local (i.e. asthma,

chronic obstructive pulmonary disease) inflammatory reactions. Ischaemia/reperfusion injury (IRI) occurs in a number of pathological conditions, including myocardial infarction, stroke, aortic surgery, cardiopulmonary bypass, organ transplantation, resuscitation and critical care. Massive and abrupt release of oxygen radicals after reperfusion triggers oxidative damage. Before critical surgeries or after resuscitation, it would be wise to find a suitable prophylactic treatment to avoid ischaemia/reperfusion damage.[3] Commonly used anaesthetic agents protect against renal IRI. Erguin Y *et al*. reported protective effect of propofol and ketamine in IRI in skeletal muscle in rats.[4] Pharmacological interventions like methylprednisolone, multivitamin antioxidant infusion, Vit. E infusion, amrinone, prostaglandin E 1, pentoxifylline, mannitol, trimetazidine, dextrose, allopurinol, and OKY046 have shown some promise in decreasing liver damage caused by occluded blood supply in liver resection surgery performed under vascular control.[5] The oxidative stress is more evident in patients with sepsis, systemic inflammatory response syndrome (SIRS), who develop multiple organ failure (MOF) and die.[6] ROS are central to cardiac IRI. They contribute to myocardial stunning, infarction and apoptosis and possibly to genesis of arrhythmias. Anaesthetic preconditioning (APC) is of particular interest to anaesthesiologists. In this phenomenon, lasting protection of myocardium is elicited by brief exposure to inhalational anaesthetic agent. Free radicals are known to act as second messengers in the preconditioning cell-signalling pathway.[7] Inhalational anaesthetics have been shown to enhance generation of free radicals in cardiac cells, probably by causing mild uncoupling of the mitochondrial electron transport chain. Hepatotoxicity attributable to halothane may result partly from conversion of halothane to free radicals by cytochrome P450 enzymes, but there is no evidence of similar reactions involving other inhalational anaesthetics in other organs. Stephan G. De Hert *et al*. concluded from experimental data that clinical concentrations of inhalational anaesthetics protect the myocardium from IRI, as shown by decreased infarct size and a more rapid recovery of contractile function on reperfusion.[8] Local anaesthetics lidocaine and procaine dose dependently preserve endothelium-dependent vasorelaxation against ROS attack potentially via H_2O_2 scavenging.[9]

The aim of this article is to highlight relevance of free radicals and free radical scavengers to anaesthesia practice, as scant literature is available relating this relevance. There is no dearth of literature relating this relevance to critical care, which is summarized in this article. Ischaemic and hypoxic insults to the brain during surgery and anaesthesia result in life threatening complications including stroke.

Several protective systems operate in mammalian cells to prevent formation of free radicals or to scavenge excessive amounts already formed. Free radical scavengers either prevent reactive oxygen species from being formed, or remove them before they can damage vital components of the cell. They are known as preventive and chain breaking antioxidants. The first group includes catalases, glutathione peroxidases and superoxide dismutase (SOD) i.e. enzymatic mechanism of inactivation of ODFR (oxygen derived free radicals). The second group, chain breaking antioxidants or 'radical scavengers' are compounds capable of transferring hydrogen to free radicals. This group includes physiological antioxidants like ascorbic acid, α tocopherol and β carotene. The preventive antioxidants eliminate the species involved in the initiation of free radical chain reaction, whereas the chain breaking antioxidants repair oxidizing radical directly. Antioxidants are classified into two broad divisions, depending on whether they are soluble in water (hydrophilic) e.g. Vit. C or in lipids (hydrophobic) e.g. β carotene and Vit. E which are membrane bound. Water soluble antioxidants react with oxidants in the cell cytosol and the blood plasma, while lipid soluble antioxidants protect cell membranes from lipid peroxidation. These compounds may be synthesized in the body or obtained from diet. About 4000 antioxidants have been identified. Some of the antioxidants like glutathione, ubiquinol and uric acid are produced during normal metabolism in the body. Several essential minerals including selenium, copper, manganese and zinc are necessary for the formation or activity of peroxidases, SOD and catalase. Hence, if the nutritional supply of these minerals is inadequate, enzymatic defences against free radicals may be impaired.

Lidocaine and procaine dose dependently preserve endothelium-dependent vasorelaxation against ROS attack potentially via H_2O_2 scavenging.[9] Lidocaine is more effective than bupivacaine and ropivacaine in protecting human erythrocytes submitted to an oxidative stress.

Oxidative stress is important in the pathogenesis of ALI/ARDS. Patients with ARDS showed a significant decrease in plasma levels of α-tocopherol, ascorbate, β-carotene and selenium and elevated levels of lipid peroxidation products. Free radical scavenging has protective effect in pulmonary oxygen toxicity and ARDS. FRS Edaravone has protective effect in acute pancreatitis associated lung injury in rat lungs.

Oxygen free radical scavengers (SOD, allopurinol) are being assessed in experimental haemorrhagic and septic shock models.[10] Treatment with SODmimetics has been shown to prevent the cellular energetic failure associated with shock and ischaemia-reperfusion and to prevent tissue damage associated with conditions. Salvemini D *et al*. presented a study to support the potential development of SODmimetics as novel and effective agents in the area of critical care medicine.[11] Treatment with melatonin has been shown to prevent *in vivo* the delayed vascular decompensation and the cellular energetic failure associated with shock, inflammation and ischaemia/reperfusion injury. Recently it has been demonstrated that melatonin inhibits the activation of poly (ADP-ribose) synthetase and prevents the organ injury associated with shock, inflammation and ischaemia/reperfusion.[12]

Conclusions

As oxidative stress might be an important part of many human diseases, the use of free radical scavengers in pharmacology is being intensively studied, particularly as treatment for stroke and neurodegenerative diseases. Commonly used anaesthetic agents protect against ischaemia/reperfusion injury. An intense study of oxygen radical-mediated mechanism may lead to improved therapies in the treatment of critically ill patients. Antioxidants are also widely used as ingredients in dietary supplements in the hope of maintaining health and preventing diseases such as cancer and coronary heart disease. Further studies will be required to determine if the cellular protective effects of anaesthetic agents translate into meaningful improvements in perioperative outcome.

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