NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), FREE RADICALS AND REACTIVE OXYGEN SPECIES (ROS): A REVIEW OF LITERATURE

Karam-Allah S. Mahmood[1], Jawad H. Ahmed[2], Abdullah M. Jawad[3]

ABSTRACT

A wide controversy exists regarding the effect of NSAIDs on the oxidative status. Each member of these NSAIDs has been shown to act both as antioxidant or pro-oxidant in different test systems, using different concentrations and various oxidative stress-inducing agents. This review tackles this problem and tries to look for factors that might be responsible for this variation in results.

INTRODUCTION

The mechanism behind the great inter-individual variation in response to non-steroidal anti-inflammatory drugs (NSAIDs) and also behind their recent uses in chemoprevention of cancer is still poorly understood. One possible explanation might be through their effect on free radicals and reactive oxygen species and, thus, on the oxidative status.[1] Free radicals can be generated by oxidizing or reducing reactions. A free radical is defined as any species capable of independent existence that contains one or more unpaired electrons.[1] By this definition, oxygen which has two unpaired electrons is a free radical, whereas hydrogen peroxide (H_2O_2), which has no unpaired electrons, is not a free radical, but classified as reactive oxygen species (ROS).[2] Excessive reactive species can deplete the endogenous antioxidant system, giving rise to a condition known as oxidative stress. During the condition of oxidative stress, the generation of free radicals can have several consequences. Free radicals can react with and cause damage to DNA, lipids and proteins.[3] Examples of free radicals and ROS include: superoxide anion (O^{-}_2), hydroxyl radical ($OH^{\cdot}$), hydrogen peroxide (H_2O_2), nitric oxide and nitric dioxide, and peroxynitrite.[3]

Biological sources of free radicals and ROS

Many reactive species produced by biological system are intermediate products of several enzymatic and non-enzymatic reactions that are beneficial to the body. ROS and reactive nitrogen species (RNS) are formed during normal physiological processes that occur when the cell is not under stress.[4] The endogenous sources for ROS production in human and in animals may be as follows:[5]

- Mitochondrial respiratory chain (O^{-}_2).
- Inflammation and phagocytosis (O^{-}_2, $OH^{\cdot}$, H_2O_2, HOCl).
- Xanthine oxidase (O^{-}_2).
- Vascular NAD(P)H oxidase (O^{-}_2).
- Cycloxygenase ($LOO^{\cdot}$).
- Free iron and copper as metal ions ($OH^{\cdot}$).
- Reaction between O^{-}_2 and NO to yield peroxinitrites.
- Reaction between H_2O_2 and peroxinitrites (singlet oxygen).
- Auto-oxidation of catecholamine.
- Ischemia/reperfusion (ROS and RNS).
- Prolonged severe emotional stress (ROS and RNS).

Classification of antioxidant defences

Cells have complex antioxidant systems and chemical sequesters that help prevent oxidative damage caused by high free radical concentrations. These defence systems are classified as endogenous (e.g. Superoxide dismutase, Catalase, Glutathione peroxidase) and exogenous antioxidants (vitamin C, vitamin E, beta-carotenes and flavonoids).[6-8]

The role of metal ions in the induction of oxidative stress

Several metals, in their reduced forms, can catalyze the production of radicals from H_2O_2 via Fenton reaction. The transition metals of interest are those that have variable valence which allow them to undergo changes in oxidation state involving one electron. This is true for iron, cupper and manganese but not zinc which has only one valence which, unlike iron, cupper and manganese, prevents it from promoting radical reactions.[9-11] Fenton reaction occurs when a mixture of H_2O_2 and ferrous salt (Fe^{+2}) reacts with many organic molecules, as was first observed by Fenton in 1894. The reactivity is most likely due to formation of the hydroxyl radical ($OH^{\cdot}$).[11]

[1]MSc(Pharmacology), Directorate of Basrah
[2]MBChB, PhD (UK), Assistant Professor, Department of Pharmacology, College of Medicine, University of Basrah, Iraq
[3]MBChB ,PhD (UK), Professor, Department of Pharmacology, College of Medicine, University of Basrah, Iraq.