OXIDATIVE STRESS AND VASCULAR DAMAGE IN HYPOXIA PROCESSES. MALONDIALDEHYDE (MDA) AS BIOMARKER FOR OXIDATIVE DAMAGE.

Pilar Muñiz¹, María Jesús Coma², Joaquín Terán³

¹Department of Biochemistry and Molecular Biology. Faculty of Sciences. Universidad de Burgos. ²Research Unit, ³Multidisciplinary Sleep Unit. Hospital Universitario de Burgos. Burgos. España


mjcoma@hubu.es

SUMMARY

Changes in the levels oxidative stress biomarkers are related with different diseases such as ischemia/reperfusion, cardiovascular, renal, aging, etc. One of these biomarkers is the malondialdehyde (MDA) generated as result of the process of lipid peroxidation. This biomarker is increased under conditions of the oxidative stress. Their levels, have been frequently used to measure plasma oxidative damage to lipids by their atherogenic potential. Its half-life high and their reactivity allows it to act both inside and outside of cells and interaction with proteins and DNA involve their role in different pathophysiological processes.

This paper presents an analysis of the use of MDA as a biomarker of oxidative stress and its implications associated pathologies such as cardiovascular diseases ago.

Keywords: Oxidative stress. Biomarker. Malondialdehyde. Ischemia

RESUMEN:

Cambios en los niveles biomarcadores de estrés oxidativo, moléculas que se forman resultado de la interacción de ROS, están asociados a diferentes enfermedades como procesos de isquemia/reperfusión, enfermedades cardiovasculares, renales, envejecimiento, etc.

Uno de estos biomarcadores es el malondialdehído (MDA) que se genera resultado de la peroxidación lipídica. Este biomarcador de peroxidación lipídica, generado en situaciones de estrés oxidativo, ha sido utilizado frecuentemente para medir en plasma el daño oxidativo a lípidos por su potencial aterogénico. Su vida media y alta reactividad le permite actuar tanto en el interior como en el exterior de las células interactuando con proteínas y DNA implicado en diferentes procesos fisiopatológicos.

En este trabajo se hace un análisis del uso del MDA como biomarcador de estrés oxidativo y sus implicaciones en patologías como las asociadas a las enfermedades cardiovasculares.
INTRODUCTION

Hypoxia is characterised by profound episodes of absence of oxygen followed by a rapid oxygenation process that could be considered as an analogue to ischaemic and reperfusion processes that promote the production of reactive oxygen species (ROS) and oxidative stress. In intermittent hypoxia processes, there is activation of the inflammatory response, which participates in the production of ROS. In this sense, an elevated number of transcription factors and pathways that are modulated by ROS are involved during hypoxia and include, hypoxia inducible factor 1 alpha (HIF1A), NFkB AP1 (activator protein 1), and nuclear factor Nrf2 1-3.

The implication of oxidative stress and inflammation and their potential role in producing endothelial dysfunction and cardiovascular diseases have been the subject of review by several authors 4-7.

Oxidative stress biomarkers can be classified as molecules that are modified due to an interaction with ROS and antioxidant molecules that change in response to an increase in the oxidative state. Lipids, proteins, DNA, and carbohydrates are examples of molecules that could be modified by an excess of ROS.

The increases in lipid peroxidation are produced as a result of increases in oxidative stress. During hypoxia processes there is an increased production of radicals, such as superoxide, which can stimulate the Haber-Weiss reaction, and thus the lipid peroxidation process. The lipid peroxidation index generated in oxidative stress situations has frequently been used to measure oxidative damage in plasma. The peroxides, generated in vivo via peroxidation of polyunsaturated fatty acids, interact with proteins and are potentially atherogenic 6.

LIPID PEROXIDATION

Lipids are molecules that are susceptible to oxygen due to their molecular structure with an abundant amount of hydrogen double bonds. Free radicals initiate and cause lipid peroxidation, particularly those in the cell membrane, and are associated with different pathophysiological changes, mainly vascular damage.

Peroxidation is an autocatalytic radical process 8 that consists of three stages; the first being initiation, followed by propagation, and lastly termination of the peroxidation that is the result of the interaction of the lipid radicals and/or the formation of non-radical species due the action of the peroxyl radical. Lipid peroxidation is mainly initiated by hydroxyl radicals, generated via reactions catalysed by transition metals, such as the Fenton reaction.

In the initiation stage, the free radicals capture a hydrogen atom of methylene carbon of the fatty acids, leaving a non-paired electron in the carbon to be converted into a lipid radical. The radical generated on the carbon suffers a molecular readjustment to form a conjugated diene that is capable of being combined with oxygen to form a peroxyl radical that can remove a new hydrogen atom and start a chain reaction that continues until the substrate is exhausted, or the process is interrupted by antioxidants. The resulting lipid peroxides are fairly stable compounds, but their decomposition may be catalysed by transition metals and metal complexes, giving rise to new radicals capable of stimulating further lipid peroxidation or the formation of oxidation end-products with a range of toxicities, such as malonaldehyde (MDA), hydroxynonenal and hexanal9-10.

Lipid peroxidation can have various effects on cell functions, either directly, by reacting with proteins and nucleic acids, or indirectly through receptor signalling pathways. Thus, lipid peroxidation of the membranes result in changes in flow, increasing patency, and decreasing the membrane potential 2 that can lead to cell death.

Malonaldehyde (MDA) is one of the most used lipid peroxidation markers. It is produced in vivo via peroxidation of polyunsaturated fatty acids, and is the main and most studied product of lipid peroxidation. It is believed that the peroxides are decomposed during lipid peroxidation into aldehydes such as MDA, which is highly toxic. Its half-life and high reactivity enables it to act inside and outside the cells, interacting with proteins and DNA 11 involved in different pathophysiological processes.

The interaction of MDA with proteins such as lysine residues in apolipoprotein B-100 results in the formation of a coloured product that can be measured in a spectrophotometer or by HPLC. Despite not being a very specific method and that artefacts may be produced during the analytical processes, it is the method most used as a biomarker of lipid peroxidation due to its simplicity and low cost. HPLC is one of the methods used that has shown to give good results for the determination of MDA in biological samples.

Furthermore, its interaction with a DNA sample shows potential genotoxicity 11, on generating DNA adducts that give rise to mutations and changes in gene expression 17-18.

The determination of malonaldehyde (MDA) is one of the most used methods. It is based on the fact that, during peroxidation the peroxides are broken down into aldehydes like MDA, which can be detected using the reaction with thiobarbituric acid in acid conditions that leads to the formation of a coloured product that can be measured in a spectrophotometer or by HPLC. Despite not being a very specific method and that artefacts may be produced during the analytical processes, it is the method most used as a biomarker of lipid peroxidation due to its simplicity and low cost. HPLC is one of the methods used that has shown to give good results for the determination of MDA in biological samples.
results and provides specificity 19-20.

REFERENCES


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Comment of the reviewer Prof. Dra. Victoria Valls Belles. Professor of Phisiology, Faculty of Medicine. Universidad Jaime I. Valencia

A review on the use of MDA as an oxidative stress biomarker in vascular hypoxia is an interesting work. It describes the mechanism of action by which lipid peroxidation is induced, as well as some of the molecular mechanisms involved in oxidative damage in hypoxia processes and its relationship with cardiovascular disease.

Within the review, highlight the reference method used for its determination, that using the HPLC technique being the most accurate.

Comment of the reviewer Prof. Dr. Juan Vicente Sánchez Andrés. Professor of Phisiology, Faculty of Medicine. Universidad Jaime I. Valencia. España.

The work synthesises the process from hypoxic stress to vascular damage, with special emphasis on the analytical methodology. The effects of lipid peroxidation are rigorously detailed, highlighting the up-to-datedness of literature references and, thus the validity of the data presented.

The validity of the markers selected should be highlighted for their practical and experimental usefulness. In summary, it is a valuable article with an appropriate balance of up-to-datedness and synthesis that makes its publication recommendable.