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PRACA POGLĄDOWA
REVIEW

Malondialdehyde (MDA) – product of lipid peroxidation as marker of homeostasis disorders and aging

Dialdehyd malonowy – produkt peroksydacji lipidów jako marker zaburzeń homeostazy i wieku

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ABSTRACT

Malondialdehyde (MDA) found in the body comes from two sources: food consumed and lipid peroxidation occurring in the tissues. The formation of MDA and the scale and rate of lipid oxidation in the tissues of living organisms is influenced by a number of endo- and exogeneous factors. The products of lipid peroxidation, in particular MDA, exhibit cytotoxic, mutagenic and carcinogenic properties. They can also inhibit enzymes associated with defending cells against oxidative stress. Not only do the occurring processes contribute to the development of many diseases, but they are also a part of the aging process. The body defends itself to some extent against the effects of free radicals by trapping and neutralising them. The main source of antioxidants is food products of plant origin. Lifestyle, the components of which are diet and physical activity, is an important element in preserving health understood as physical and psychological well-being. Dietary habits and a diet rich in antioxidants are modifiable factors which not only prevent age-associated diseases, but also delay aging processes.

KEY WORDS
lifestyle, free radicals, aging

STRESZCZENIE

Dialdehyd malonowy (MDA) w organizmie człowieka pochodzi z dwóch źródeł: spożywanego pokarmu i peroksydacji lipidów występujących w tkankach. Powstawanie MDA, a także wielkość i szybkość utleniania lipidów w tkankach organizmów żywych, zależy od wielu czynników endo- i egzogennych. Produkty peroksydacji lipidów, szczególnie

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MDA, wykazują właściwości cytotoksyczne, mutagenne i rakotwórcze. Mogą one również hamować enzymy związane z obroną komórki przed stresem oksydacyjnym. Mogą nie tylko przyczyniać się do rozwoju wielu chorób, ale stanowią również część procesu starzenia się. Organizm broni się w pewnym stopniu przed działaniem wolnych rodników, neutralizując je. Głównym źródłem przeciwutleniaczy jest żywność – produkty pochodzenia roślinnego. Styl życia, na który składają się dieta i aktywność fizyczna, jest ważnym elementem w zachowaniu zdrowia rozumianego jako dobre samopoczucie fizyczne i psychiczne. Nawyki żywieniowe i dieta bogata w przeciwutleniacze są modyfikowalnymi czynnikami, które nie tylko zapobiegają chorobom związanym z wiekiem, ale także opóźniają procesy starzenia.

SŁOWA KLUCZOWE
styl życia, wolne rodniki tlenowe, starzenie

INTRODUCTION

Ageing is a physiological process, meaning the gradual decrease of the reserves of functional capability of individual systems and of the whole organism.
At present, more than 13% of people in the world are at the age of 65 and over. An increase in the number of persons in this age is forecasted. It is assumed that 23% of the population will be of this age by 2035 [1]. 'The 2015 Ageing Report' [2] indicates that Polish society is one of the fastest aging populations of the European Union. The percentage of people 65 + in 2013 was 14.5%, while in 2060 seniors will constitute 33% of the population. The percentage of people over 80 years old will also increase. Public expenditure in Poland related to the ageing population will rise from 20.9% of GDP in 2013 to 22.2% of GDP in 2060. The biggest increase in expenditures will cover the area of health and long term care. It is necessary to promote healthy ageing, early detection and prevention of health problems as well as to ameliorate and treat already existing disorders.
Demographics data require an attentive look at the ageing process in humans. It is particularly important is to understand the complex mechanisms of ageing and death of cells. One of the known mechanisms responsible for this process is the free-radical theory. In this paper, we have synthesized current knowledge on the role of free radicals, particularly analysing the importance of malondialdehyde in aging.

Free-radical theory of aging

The ageing process is caused, among others, by the activity of free radicals in the body. The free-radical theory of ageing was first proposed by Harman [3]. According to this theory, the process starts around age 40, when defence mechanisms become less effective, leading to oxidative damage caused by free radicals. Free radicals are molecules containing unpaired electrons which are highly reactive. However, a wider group of chemical compounds is responsible for oxidative stress, known as 'reactive oxygen species' (ROS), some of which are not free radicals sensu stricto. Harman defined ageing as two simultaneous processes: a progressive decline in biological functions and decreased resistance to multiple forms of stress [3].
The influence of reactive oxygen species causes damage to mitochondrial and nuclear DNA, lipids, and proteins. These defects accumulate with age, and in addition to this, the defence system grows weaker. Numerous authors postulate that this process significantly affects the lifespan of the cell [4,5,6].
ROS are generated under the influence of various internal (unmodifiable) factors, such as cellular respiration, enzymatic processes catalysed by certain enzymes, and the autoxidation of biologically active compounds as a result of phagocytosis and hydroxylation of drugs in the liver.
The formation of free radicals is also sped up by external factors such as reactions of oxygen with engine fuel, smog, or the incineration of organic substances (environmental pollution). One may therefore indicate modifiable environmental factors responsible for the process of free radical formation. Behaviour, habits and dietary preferences also are important. These factors may be classified as modifiable since they are elements of lifestyle which we can control. Free radical formation occurs in food, which upon consumption becomes a source of these molecules in the body. The peroxidation of polyunsaturated fatty acids, components of vegetable oil, may be an example. Polyunsaturated fatty acids are also essential components of cellular membranes (as constituents of phospholipids). Peroxidation also occurs in physiological conditions and causes oxidation of these fatty acid chains [5]. Malondialdehyde (MDA) (Fig. 1) is one of the end products of this process [6,7].

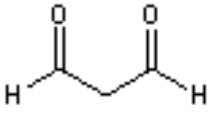

Fig. 1. Structure of malodialdehyde (MDA).
Ryc. 1. Wzór strukturalny dialdehydu malonowego.

MDA found in the body comes from two sources: food consumed and lipid peroxidation occurring in the tissues. The formation of MDA, and the scale and rate of lipid oxidation in the tissues of living organisms, is influenced by a number of endo- and exogeneous factors.

The products of lipid peroxidation, in particular MDA, exhibit cytotoxic, mutagenic and carcinogenic properties. Many of the biological consequences of their actions are, for example: loss of proliferation potential of cells, changed gene expression, mutations, molecular heterogeneity, impairment of intercellular communication, and organ dysfunction [8,9,10]. They can also inhibit enzymes associated with defending cells against oxidative stress. This leads to greater oxidative damage in these cells. Accumulation of this damage may change the metabolism of the cell, leading to the loss of its integrity. The hydrophobicity of the lipid interior is affected, and the two-layer structure of the membranes is disturbed. Not only do the occurring processes contribute to the development of many diseases, but they are also a part of the process of ageing [11,12,13,14]. MDA, generated in the process of peroxidation of polyunsaturated fatty acids present in the membrane phospholipids, exhibits high reactivity to proteins and nucleic acids. From the sites of its formation, it permeates easily into remote tissues and due to the ability to form covalent bonds to these compounds, it may modify their structure and properties. The resulting change in the properties of cell membranes cause loss of integrity. This in turn leads to perturbation of their proper functioning and results in the dysfunction of individual organs [15,16,17]. The concentration of MDA in serum is considered to be a measure of lipid peroxidation.

MDA and diseases

MDA is a well-established marker used to investigate the oxidative damage of lipids in the course of many human diseases [18]. In Gil et al. [19] involving 194 healthy men and women between 18 to 84 years old, it was found that plasma MDA levels increased with age, indicating accelerated oxidation during ageing. The latest observations by Indian researchers [20] who studied 100 healthy men (without chronic diseases, non-smokers, and non-alcoholic) and measured their MDA/total antioxidant capacity (TAC) ratio, are also very interesting. In this study it was presented that the MDA/TAC ratio increased with age, and the oxidative stress indicators correlated with body weight. This is another study showing the close relationship between an improper body mass index and the rate of ageing. Moreover, Jho and Rizvi proved that age is the strongest risk factor for the accumulation of RCO [21]. Ageing, beyond the gradual physiological impaired functioning of many organs, is often associated with the occurrence of many diseases. The most common health problems of postmenopausal age are cancer, heart failure and neurodegenerative disorders [22, 23,24]. The causes of these disorders are not fully understood, but in many cases it is believed that oxidative stress plays a significant role. In particular, the antioxidant potential of the body decreases with age. With age, we observe a decrease in the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px), and the accumulation of reactive oxygen species [25].

It is believed that the products of body fluid peroxidation constitute a group of potentially mutagenic and carcinogenic compounds that may damage DNA. As an endogenous genotoxic factor forming as a result of lipid peroxidation and biosynthesis of prostaglandins, these compounds may contribute to the growth of tumours [26]. This is a complex process resulting e.g. from the reaction of MDA with bases in the DNA structure, which leads to the formation of compounds known as adducts. It is supposed that their presence in DNA is likely to contribute to the initiation of mutagenesis and carcinogenesis processes [27]. The pathogenic role of peroxidation of fatty acids in the development of colorectal cancer, for example, has been confirmed [28]. Similar observations apply to breast and lung cancer. In another study, high serum levels of MDA were observed in patients with breast and lung cancer compared to the control group [29]. This confirms the hypothesis about the role of oxidative stress in carcinogenesis.

Cardiovascular disorders belong to the most frequent diseases occurring in old age. Many authors [30, 31,32,33] have demonstrated elevated plasmatic concentrations of MDA in the case of persons with recent myocardial infarction during the first days of the illness, and then an MDA level increase in the following days. These changes correlated with the levels of MB fraction of creatine phosphokinase. It is assumed that the generated MDA may be transported with LDL lipoproteins. Malondialdehyde, closely connected to lipoproteins, would facilitate the bonding of cholesterol esters with the blood vessel wall and the formation of an atherosclerotic plaque.

According to Li et al. [34], oxidative stress, indicated by plasma MDA, is also a major factor linked to renal function decline with age. Li et al. in their study showed that plasma MDA had a significant relation to the prevalence not only of chronic kidney disease, but also mild kidney function insufficiency . On the other hand, Ostałowska, Kasperczyk et al. [35] concluded that in rheumatoid arthritis (RA) patients, increased lipid peroxidation was associated with a tendency for alterations in the antioxidant system including increased activities of all of the antioxidant enzymes. This thereby suggests potential adaptation to the in-

creased ROS in the blood and synovial fluid of RA patients.

Another common problem in the elderly population is age-related macular degeneration (AMD), which is associated with progressively increasing amblyopia, and the loss of central vision. The pathogenesis of AMD is unknown, but in a cross-sectional study in Turkey, it was shown that the plasma MDA level was significantly higher in patients with AMD (compared to the control group) [36,37,38]. This confirms the previous assumptions about the role of oxidative stress in the retina in the pathogenesis of AMD. The retina is very susceptible to damage by reactive oxygen species, because it is rich in polyunsaturated fatty acids which can be oxidized. The human brain contains a large amount of polyunsaturated fatty acids as well. Since the brain consumes up to 20% more oxygen than the rest of the body and displays low antioxidant activity, it seems to be vulnerable to oxidative stress. Consequently, there are numerous reports on the role of oxidative stress in the pathogenesis of neurodegenerative diseases characteristics for the elderly, including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS). Autopsy studies of patients with dementia have found among others lipid peroxidation markers, like MDA and 4-hydoksynonenal (4-HNE) in the cortex and hippocampus (in patients with Alzheimer's disease), in the substantia nigra (patients with Parkinson's disease) and in spinal fluid of patients with ALS [39,40,41].

In neurology dysfunctions, oxidative stress plays an important role not only in degeneration disorders. Bulut et al. in their study showed that MDA serum levels were significantly higher in patients with attention-deficit hyperactivity disorder (ADHD) [42].

The above reports show that the accumulation of free radicals is the pathogenetic link to many diseases.

CONCLUSION

Living organisms have developed a number of defence mechanisms against the harmful activity of free radicals. The body defends itself to some extent against the effects of free radicals by trapping and neutralising them. Antioxidants can be divided into two groups: enzymatic, such as superoxide dismutase, catalase and glutathione peroxidase; and non-enzymatic. Due to the decreased activity of endogenous antioxidants in elderly patients, correct supplementation of exogenous antioxidants in this age group is important.

The main source of antioxidants is food products of plant origin. The major exogenous antioxidants are vitamin E, C, A and β-carotene. These components can be provided with a properly balanced diet, rich in vegetable oils, especially sunflower oil, fresh vegetables and fish [5,43]. Reports on the advantages of caloric restriction are also very interesting. Pamplona and Barja proved that caloric restriction decreases the ageing rate and the mitochondrial production of ROS [44]. Lifestyle, the components of which are diet and physical activity, is an important element in preserving health understood as physical and psychological well-being. Lifestyle components are modifiable factors that may be shaped by an individual. Dietary habits and a diet rich in antioxidants are modifiable factors which not only prevent age-associated diseases, but also delay ageing processes.

PIŚMIENNICTWO

1. Demography Report 2010. Older, more numerous and diverse Europeans, European Commission, 2011; www.healthyageing.eu/file resources/ /EUL14135_ Demographyreport_ web.pd.

2. European Commission (DG ECFIN) and Economic Policy Committee (Ageing Working Group). The 2015 Ageing Report. Economic and budgetary projections for the 28 EU Member States 2013–2030. Luxembourg: Publications Office of the European Union, 2015.

3. Harman D. Aging: a theory based on free radicals and radiation chemistry. J. Gerontol. 1956; 11(3): 288–300.

4. Dmitriev L.F., Titov V.N. Lipid peroxidation in relation to ageing and the role of endogenous aldehydes in diabetes and other age-related diseases. Ageing Res. Rev. 2010; 9(2): 200–210.

5. Niedworok E., Bielaszka A. Comparison of the Effect of Vitamins A and E on Aging Processes of Edible Vegetable Oils. Polish J. of Environ. Stud. 2007; 16(6): 861–865

6. Marnett L.J, Bienkowski M.J, Raban M., Tuttle M.A. Studies of the hydrolysis of14C-labeled tetraethoxypropane to malondialdehyde. Anal. Biochem. 1979; 99: 458–463.

7. Valko M., Rhodes C.J., Moncol J., Izakovic M., Mazur M. Free radicals, metals and antioxidants in oxidative stress – induced cancer. Chem. Biol. Interact. 2006; 160: 1–40.

8. Marnett L.J. Oxy radicals, lipid peroxidation and DNA damage. Toxicol 2002; 181–182: 219–222.

9. Blair I.A. Lipid hydroperoxide-mediated DNA damage. Exp. Gerontol. 2001; 36: 1473–1481.

10. Niederhofer L.J., Daniels J.S., Rouzer C.A., Greene R.E., Marnett L.J. Malondialdehyde, a product of lipid peroxidation, is mutagenic in human cells. J. Biol. Chem. 2003; 278(33): 31426–31433.

11. Chen J.I., Petersen D.R., Schenker S., Henderson G.I. Formation of malondialdehyde adducts in livers of rats exposed to ethanol: role in ethanol-mediated inhibition of cytochrome c oxidase. Alcohol Clin. Exp. Res. 2000; 24(4): 544–552.

12. Casado A., Encarnación López-Fernández M., Concepción Casado M., de La Torre R. Lipid peroxidation and antioxidant enzyme activities in vascular and Alzheimer dementias. Neurochem Res. 2008; 33(3): 450––458.

13. Siu G.M., Draper H.H. Metabolism of malonaldehyde in vivo and in vitro. Lipids 1982; 17(5): 349–355.

14. Raghavan S., Subramaniyam G., Shanmugam N. Proinflammatory effects of malondialdehyde in lymphocytes. J. Leukoc. Biol. 2012; 92(5): 1055–1067.

15. Yang I.Y., Chan G., Miller H., Huang Y., Torres M.C., Johnson F., Moriya M. Mutagenesis by acrolein-derived propane deoxyguanosine adducts in human cells. Biochemistry 2002; 41: 13826–13832.

16. De Bont R., Van Larebeke N. Endogenous DNA damage in humans: a review of quantitative data. Mutagenesis 2004; 19: 169–185.

17. Veneskoski M., Turunen S.P., Kummu O., Nissinen A., Rnnikko S., Levonen A.L., Hörkkö S. Specific recognition of malondialdehyde and malondialdehyde acetaldehyde adducts on oxidized LDL and apoptotic cells by complement anaphylatoxin C3a. Free Radical Biol. Med. 2011; 51(4): 834–843.

18. Rani V., Yadav U.C. Free radicals in Human Health and Diseases. Springer. India 2015.

19. Gil L., Siems W., Mazurek B., Gross J., Schroeder P., Voss P., Grune T. Age-associated analysis of oxidative stress parameters in human plasma and erythrocytes. Free Radic. Res. 2006; 40: 495–505.

20. Suresh D.R., Sendil K., Annam V., Hamasaveena Age related changes in malondialdehyde: total antioxidant capacity ratio- a novel marker of oxidative stress. Int. J. Pharm. Bio. Sci. 2010; 1(2): 1–6.

21. Jha R., Rizvi S.I. Carbonyl formation in erythrocyte membrane proteins during aging in humans. Biomed Pap. Med. Fac. Univ. Palacky Olomunc 2011; 155(1): 39–42.

22. Mahla V.K., Mahla M., Gupta R.C., Rawtani J. A study to evaluate the effect of menopause on oxidative stress. International Journal of Physiology 2014; 2(1): 118–123.

23. Casado A., Encarnación López-Fernández M., Concepción Casado M., de La Torre R. Lipid peroxidation and antioxidant enzyme activities in vascular and Alzheimer dementias. Neurochem. Res. 2008; 33(3): 450––458.

24. Dzięgielewska-Gęsiak S., Wysocka E., Michalak S., Nowakowska-Zajdel E., Kokot T., Muc-Wierzgoń M. Role of lipid peroxidation products, plasma total antioxidant atatus, and Cu-, Zn-superoxide dismutase activity as biomarkers of oxidative stress in elderly prediabetics. Oxid. Med. Cell. Longev 2014; 2014: ID987303, p. 1–8.

25. Karolkiewicz J. Effects of oxidative stress and free-radical mediated damage on cell structure and function – connection to aging process. Gerontol. Pol. 2011; 19(2): 59–67.

26. Klaunig J., Kamendulis L., Hocevar B. Oxidative stress and oxidative damage in carcinogenesis. Toxicol Pathol. 2010; 38(1): 96–109.

27. Sosa V., Moliné T., Somoza R. Paciucci R., Kondoh H., Lleonart M.E. Oxidative stress and cancer: An overview Ageing Res. Rev. 2013; 12: 376–390.

28. Parše M. Oxidative stress in the pathogenesis of colorectal cancer: cause or consequence? Biomed Res. Int. 2013; ID 725710.

29. Gönenç A., Ozkan Y., Torun M., Simşek B. Plasma malondialdehyde (MDA) levels in breast and lung cancer patients. J. Clin. Pharm. Therap. 2001; 26(2): 141–144.

30. Aznar J., Santos M.T., Valles J., Sala J. Serum malondialdehyde-like material (MDA-LM) in acute myocardial infarction. J. Clin. Pathol. 1983; 36: 712–715.

31. Lee R., Margaritis N., Channon K.M., Antoniades C. Evaluating Oxidative Stress in Human Cardiovascular Disease: Methodological Aspects and Considerations. Curr. Med. Chem. 2012; 19(16): 2504–2520.

32. Antoniades C., Antonopoulos A.S., Bendall J.K., Channon K.M. Targeting redox signaling in the vascular wall: from basic science to clinical practice. Curr. Pharm. Des. 2009; 15: 329–342.

33. Walter M.F., Jacob R.F., Bjork R.E., Jeffers B., Buch J., Mizuno Y., Mason R.P. Circulating lipid hydroperoxides predict cardiovascular events in patients with stable coronary artery disease: the PREVENT study. J. Am. Coll. Cardiol. 2008; 51(12): 1196–1202.

34. Li G., Chen Y., Hu H., Liu L., Hu X., Wang J., Shi W., Yin D. Association between age-related decline of kidney function and plasma malondiadehyde. Rejuvenation Res. 2012; 15(3): 257–264.

35. Ostalowska A., Koczy B., Słowińska L., Kasperczyk A. Oxidative stress and enzymatic antioxidant status of blood and synovial fluid in rheumatoid arthritis patients. Ann. Acad. Med. Siles. 2016; 70: 196–205.

36. Wiktorowska-Owczarek A., Nowak J.Z. Pathogenesis and prophylaxis of AMD: focus on oxidative stress and antioxidants. Postepy Hig. Med. Dosw. 2010; 64: 333–343.

37. Wang H., Zhao B., Vrcek I., Johnston J.M. Role of Malondialdehyde in the Age-Related Macular Degeneration. In: Oxidative Stress in Applied Basic Research and Clinical Practice. Ed. Sttraton et al. Springer Science + Business Media. LLC 2012, s. 85–93.

38. Ates O., Azizi S., Alp H.H., Kiziltunc A., Beydemir S., Cinici E., Kocer I., Baykal O. Decreased serum paraoxonase 1 activity and increased serum homocysteine and malondialdehyde levels in age-related macular degeneration. Tohoku J. Exp. Med. 2009; 217: 17–22.

39. Gutowicz M. The influence of reactive oxygen species on the central nervous system. Postepy Hig. Med. Dosw. 2011; 65: 104–113.

40. Andersen J.K. Oxidative stress in neurodegeneration: cause or consequence? Nat. Med. 2004; 10 Suppl: S18–28.

41. Hensley K., Maidt M.L., Sang H., Markesbery W.R., Floyd R.A. Electrochemical analysis of protein nitrotyrosine and dityrosine in the Alzheimer brain indicates region-specific accumulation. J. Neurosci. 1998; 18, 8126–8132.

42. Bulut M., Selek S., Gergerlioglu S., Savas H.A., Yilmaz R.H., Yuce M., Ekici G. Malondialdehyde levels in adult attention-deficit hyperactivity disorder. J. Psychiatry Neurosci. 2007; 32(6): 435–438.

43. MeiLian T., NingNing X., Ming Fang Y., JinFeng Ch., XingChu Y. Effects of sunflower artificial aging on seed vigor and physiological characteristics. Agricultural Sci Tech. 2010; 11(4): 39–43.

44. Pamplona R., Barja G. Mitochorndrial oxidative stress, aging and caloric restriction: the protein and methionine connection. Biochim. Biophys. Acta. 2006; 1757: 496–508.