ejpmr, 2021,8(7), 296-299

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

HOW OXIDATIVE STRESS LEADS TO COPD PROGRESSION AND IT'S BASED THERAPIES

Sachindra Kumar*, Preet Verma, Amit Kishor Srivastava, Rohit Mohan and Amresh Gupta

Department of Pharmacology, Goel Institute of Pharmacy and Science 226028 Utter Pradesh, India.

***Corresponding Author: Sachindra Kumar**
Department of Pharmacology, Goel Institute of Pharmacy and Science 226028 Utter Pradesh, India.
DOI: https://doi.org/10.17605/OSF.IO/UFG58

Article Received on 13/05/2021 **Article Revised on 03/06/2021** **Article Accepted on 23/06/2021**

ABSTRACT

Chronic obstructive pulmonary disease is a group of lung disease which generally causes limitation in airflow and make difficulty in breath, it is a progressive and irreversible lung disease and oxidative stress play critical role in COPD progression because overproduction of oxidant either endogenous or exogenous is generate the oxidative stress these oxidative Stress will be damage majorly protein-lipid and DNA, directly and indirectly, damage lungs tissue also and produce inflammation as well as activate the redox-sensitive transcription factor and lead to COPD progression. this study we suggest treating the COPD with the help of antioxidant or we can enhancing endogenous antioxidant most medical studies conduct they have using glutathione generating antioxidant such as carbocysteine, N- acetylcysteine and erdosteine which inhibits the progression of COPD but in this study, we are suggest more antioxidant such as NADPH oxidase inhibitor, a mitochondria-targeted antioxidant superoxide dismutase mimetic.

KEYWORD: COPD, Oxidative Stress, Antioxidant, Inflammation, Nrf2 activator.

INTRODUCTION

Chronic obstructive pulmonary disease is a major health concern in worldwide because more than 328 million people will be affected by COPD. it is 3rd leading cause of death also. COPD is a group of disease it has two conditions chronic bronchitis which are inflamed the airway and increase the production of mucus another condition is emphysema which destructs the structure of alveolar sac and airspace become enlarge both conditions have a problem in breathing because airflow limitation occurs here due to airflow limitation gas exchange phenomenon cannot occur properly and patient body develop hypoxia due to deficiency of oxygen and hypercapnia because CO2 cannot release properly under these circumstances patient cannot breathe well. It currently population over 45 years of age 10% will be affected through COPD but 50% have heavy smokers. So cigarette smoking is the most common cause of COPD another cause such as air pollution alpha one antitrypsin deficiency. These factors cause oxidative stress which is playing a critical role in COPD progression. Oxidative stress will be neutralized by endogenous antioxidants but excessive production of ROS appears to drive the pathogenic mechanism of COPD and its progression. This suggests if we reducing the oxidative stress through antioxidant or enhanced the endogenous antioxidant like GSH may be a useful therapeutic approach. However difficult to find safe and effective antioxidant for COPD because the level of oxidative stress in the lungs are so high. Restore the normal redox balance in the lungs is the aim of the therapy.

Oxidative Stress in Lungs

Cigarette smoke, biomass smoke air pollution in the most common cause of oxidative stress in the lungs. These oxidative stress damage epithelial linings and activate the alveolar macrophages and also activate the adaptive immune system. If the epithelial lining is damaged by oxidative stress it will produce an immune response and the number of the immune cell such as neutrophils, macrophages, eosinophils, and some cytokine, chemokine will be increased. Activation of anti-proteases and surfactant, mitochondrial respiration lipid peroxidation alveolar epithelial injury apoptosis and remodeling of extracellular matrix. Increased level of ROS in the airway reflect by using biomarkers of oxidative stress like hydrogen peroxide, F2 isoprostanes, MDA, Protein carbonyl. By Fenton reaction, these oxidative stress can increase hydroxyl ions and hydrogen peroxide. Increasing the level of reactive oxygen species has been producing inflammatory response by activating redox-sensitive transcription factor (NFkB), chromatin remodeling signal transduction and express some inflammatory mediator. Reactive oxygen species is also released by the lungs' epithelial cells which activate inflammatory mediators. Inflammation is the primary feature of COPD development which is characterized by activation of epithelial cells and alveolar macrophages activate. They have responded in the recruitment and

activation of white blood cells such as neutrophils, eosinophils, lymphocytes, and monocytes. The activation of the immune cell such as macrophages neutrophils and eosinophils which are rapidly converted generate superoxide anion to hydrogen peroxide with the help of superoxide dismutase (SOD). However, NADPH oxidase is the primary ROS generating enzyme, which is commonly present in the epithelial cell and pathogen or bacteria come into our body these enzyme complex become active and try to kill or remove the pathogen via oxidative process these phenomena is also called oxidative burst or respiratory burst in these process hydrogen peroxide in presence of chloride ion produce hypochlorous acid which are toxic f6 pathogen. Many oxidative reactions Irons play a critical role. Free from iron have ferrous from which are catalyzed by Fenton reaction and generate the OH which damages the lung tissue.

Cigarette Smoke Derived Ros

Smoking of cigarette is caused oxidative stress include toxic gases results indirectly lung tissue damaged as Well as activate the inflammatory response in lung tissue. Cigarette smoke contains more than 4700 chemical compounds that are highly toxic in nature and react with oxide ions to form hydroxyl radical and hydrogen peroxide. Cigarette smoke in aqueous phase undergoing Redox recycling for a considerable duration in the epithelial lining fluid of smokers. However, in tar phase have an effective metal chelator that can bind to Iron and produce tar-fe2+ and generated hydrogen peroxide.

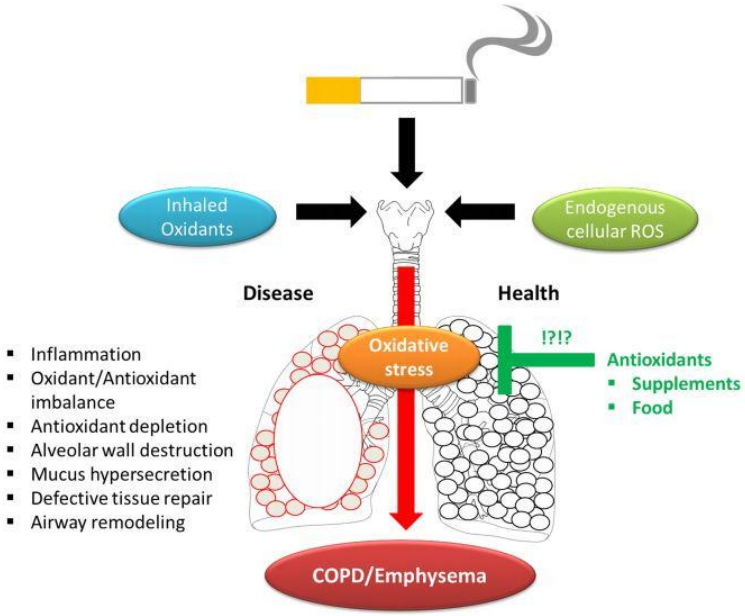

Fig: - Oxidative stress- pathogenesis of COPD. From Michael Seimetz, Djuro Kosanovic, Himal Luitel at el.

Depletion of Antioxidant

Smoking in COPD leads to reduce the antioxidant capacity in plasma and occurs transiently after smoking cessation. However antioxidant capacity will be reduced several days. When decreasing the number of antioxidants they will be significantly increased the ROS and increased the number of neutrophils eosinophils lymphocytes which lead to the immune or inflammatory response. As compared with plasma in the epithelial lining antioxidant glutathione (GSH) is present in higher concentration and plays a protective role together with its redox enzyme. Antioxidant enzymes. So if antioxidant activity reduces and increases the oxidative stress redox-sensitive transcription factor becomes active which leads to phosphorylation of p65NF kB - as well as IkBa in the lung tissue.

Therapeutic Implications

A. Strategies for reducing oxidative stress

Above we have discussed oxidative stress Play critical role in the pathogenesis of COPD so if we reduce the oxidative stress with the help of antioxidant this therapy may act as an important therapeutic strategy.

B. Thiol-base antioxidant

The thiol compound is a mucolytic agent as it breaks down mucus and reduces mucus viscosity. Glutathione concentration also increasing through antioxidant properties which are reduced with the progression of COPD. In some study indicate N-acetyl cysteine reduces the progression of COPD but low dose NAC (BRONCOS bronchitis randomized on N-acetyl cysteine study n=523 giving 600mg daily) showed no reduction in disease progression but when using a higher dose of NAC 600mg two times a day and there are show reduction in pathogenesis about 20% carbocisteine also another thiol mucolytic drug with antioxidant efficacy responsible in reduction of COPD exacerbation and erdosteine also have some properties to treating the COPD overall thiol based mucolytic compound can reduce the progression of COPD.

C. Dietary antioxidant

If we do not take property antioxidants will be associated with worse lung function and the development of COPD dietary antioxidants such as vitamin C (ascorbic acid) Vitamin E flavonoids and resveratrol are helpful in improving lung function. In Mediterranean condition, some antioxidant and there have some retrospective evidence which reduces the progression of COPD

D. Antioxidant mimetic

Antioxidant mimetic compounds which are generally to designed to restore endogenous antioxidants such as GSH, SOD mimetic like AEOL 10150 and AEOL 10113 and it will contain manganese molecule like M40419. So these are drug which has capacity to reduce the inflammation in various in vivo studies of animal models. AEOL 10150 is basically used to treat radiation pneumonia and there some derivatives also used currently in COPD patients. Another antioxidant mimetic like GPX includes selenium and non-selenium enzyme which are breakdown the H^2O^2 so GPx has the capacity to reduce COPD and plasma we are suggesting GPx has useful therapeutically.

E. NOX inhibitors

NADPH oxidase is a membrane-bound enzyme that is the major source of oxidative stress in COPD. Basically, NADPH is responsible for the generation of superoxide anions. NOX inhibitors use to inhibit the oxidative stress like apocynin are non-selective NOX inhibitors when it was given systemically to mice in cigarette smoke model they have reduced chemokine, inflammatory cytokine in BALF sample and when given nebulization of apocynin in COPD patient result they will be reduce breathing problem some other polyphenol like resveratrol and quercetin also have NOX inhibit activity setanoxib is also used as a NOX inhibitor this drug in under the clinical trials.

CONCLUSION

In COPD patients increased oxidative stress in the lungs which are a major cause of chronic inflammation and disease pathogenesis and their progression and exacerbation so have the antioxidant capacity to neutralize the oxidative stress. Thiol-base antioxidant which is used to reduce mucus and act as a mucolytic agent and reducing the exacerbation of COPD however antioxidant mimetic such as SOD and GPx mimetic are effectively suppressing the progression of COPD. So antioxidants can suppress the activation of redox-sensitive transaction factor (NFkB) dimer if NFkB dimer inhibited transcription factor not activate and exacerbation of COPD will be inhibited.

REFERENCES

1. Rahman I. The role of oxidative stress in the pathogenesis of COPD: implications for therapy. Treat Respir Med, 2005; 4(3): 175-200. doi: 10.2165/00151829-200504030-00003. PMID: 15987234.
2. Barnes, P., Oxidative stress-based therapeutics in COPD. Redox Biology, 2020; 33: 101544.
3. Richter, C., Gogvadze, V., Laffranchi, R., Schlapbach, R., Schweizer, M., Suter, M., Walter, P. and Yaffee, M. Oxidants in mitochondria: from physiology to diseases. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1995; 1271(1): 67-74.
4. Rahman, I. and MacNee, W. Role of transcription factors in inflammatory lung diseases. Thorax, 1998; 53(7): 601-612.
5. Rahman, I. and MacNee, W. Role ofu oxidants/antioxidants in smoking-induced lung diseases. Free Radical Biology and Medicine, 1996; 21(5): 669-681.
6. Rahman, I. and MacNee, W., Oxidative stress and regulation of glutathione in lung inflammation. European Respiratory Journal, 2000; 16(3): 534.
7. Snider, G., Chronic Obstructive Pulmonary Disease: Risk Factors, Pathophysiology and Pathogenesis. Annual Review of Medicine, 1989; 40(1): 411-429.
8. PRYOR, W. and STONE, K., Oxidants in Cigarette Smoke Radicals, Hydrogen Peroxide, Peroxynitrate, and Peroxynitrite. Annals of the New York Academy of Sciences, 686(1 Tobacco Smoki), 1993; 12-27.
9. Nowak, D., Antczak, A., Krol, M., Pietras, T., Shariati, B., Bialasiewicz, P., Jeczkowski, K. and Kula, P. Increased content of hydrogen peroxide in the expired breath of cigarette smokers. European Respiratory Journal, 1996; 9(4): 652-657.
10. Dekhuijzen, P., Aben, K., Dekker, I., Aarts, L., Wielders, P., van Herwaarden, C. and Bast, A., 1996. Increased exhalation of hydrogen peroxide in patients with stable and unstable chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine, 154(3): 813-816.
11. Barnes, P., Oxidative stress-based therapeutics in COPD. Redox Biology, 2020; 33: 101544.
12. Salvi, S. and Barnes, P., Chronic obstructive pulmonary disease in non-smokers. The Lancet, 2009; 374(9691): 733-743.
13. Halpin, D. and Tashkin, D., Defining Disease Modification in Chronic Obstructive Pulmonary Disease. COPD: Journal of Chronic Obstructive Pulmonary Disease, 2009; 6(3): 211-225.
14. Bartoli, M., Novelli, F., Costa, F., Malagrinò, L., Melosini, L., Bacci, E., Cianchetti, S., Dente, F., Di Franco, A., Vagaggini, B. and Paggiaro, P., Malondialdehyde in Exhaled Breath Condensate as a Marker of Oxidative Stress in Different Pulmonary Diseases. Mediators of Inflammation, 2011; 1-7.
15. Seimetz, M., Kosanovic, D. and Himal Luitel, H., [online] PVRI. Available at: <https://pvrinstitute.org/en /professionals/publications/pvri-chronicle-vol-2-issue-1/the-two-faces-of-antioxidants-in-pulmonary-

vascular-disease-focus-on-copd/> [Accessed 12 June 2021], 2021.
16. Domej, W., Oetll, K. and Renner, W., Oxidative stress and free radicals in COPD – implications and relevance for treatment. International Journal of Chronic Obstructive Pulmonary Disease, 2014; 1207.
17. Kluchova, Z., Petrasova, D., Joppa, P., Dorkova, Z., and Tkacova, R. The association between oxidative stress and obstructive lung impairment in patients with COPD. Physiol Res., 2007; 56: 51-56.
18. Park, H.S., Kim, S.R., and Lee, Y.C. Impact of oxidative stress on lung diseases. Respirology, 2009; 14: 27-38.
19. Heffner, J.E., and Repine, J.E. Pulmonary strategies of antioxidant defense. Am Rev Respir Dis., 1989; 140: 531- 554.
20. Brug, J., Schols, A., and Mesters, I. Dietary change, nutrition education and chronic obstructive pulmonary disease. Patient Educ Couns, 2004; 52: 249-257.
21. Carey, I.M., Strachan, D.P., and Cook, D.G. Effects of changes in fresh fruit consumption on ventilatory function in healthy British adults. Am J Respir Crit Care Med, 1998; 158: 728-733.
22. Denny, S.I., Thompson, R.L., and Margetts, B.M. Dietary factors in the pathogenesis of asthma and chronic obstructive pulmonary disease. Curr Allergy Asthma Rep, 2003; 3: 130-136.
23. Strachan, D.P., Cox, B.D., Erzinclioglu, S.W., Walters, D.E., and Whichelow, M.J. Ventilatory function and winter fresh fruit consumption in a random sample of British adults. Thorax, 1991; 46: 624-629.
24. Tabak, C., Arts, I.C., Smit, H.A., Heederik, D., and Kromhout, D. Chronic obstructive pulmonary disease and intake of catechins, flavonols, and flavones: the MORGEN Study. Am J Respir Crit Care Med, 2001; 164: 61-64.