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ACTIVITY OF CERULOPLASMIN IN GUINEA PIGS' TRACHEA IN LATE PERIODS OF EXPERIMENTAL ALLERGIC ALVEOLITIS DEVELOPMENT AND THEIR CORRECTION WITH THIOTRIAZOLIN

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Abstract

We have investigated the results of alterations in indices of pro-oxidant (conjugated diene and malondialdehyde) and antioxidant (ceruloplasmin) systems in guinea pigs' trachea in experimental allergic alveolitis development.

The results of our experimental work have showed a significant accumulation of lipid peroxidation products in the trachea's tissue in late periods (on 44th and 54th days). The state of antioxidant defence was characterized by moderate decrease of ceruloplasmin activity. A potential role of oxidative stress in the pathogenesis of allergic alveolitis has been demonstrated. Increased oxidant levels and decreased antioxidant defences can contribute to the progression of this immune complex pathology. Reduction of conjugated diene and malondialdehyde content and elevation of ceruloplasmin activity have been reported in animals with this experimental model of disease after using of thiotriazolin.

Key words: experimental allergic alveolitis, peroxide lipid oxidation, ceruloplasmin, thiotriazolin.

Introduction

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a syndrome caused by an exaggerated immune response to the inhalation of a variety of antigenic particles found in the environment. A number of offending agents have been identified, many of which are associated with a name referring to the resulting clinicopathologic condition (ie, farmer's lung, hot tub lung, byssinosis, etc) [1, 3]. The development of disease and the clinical presentation is influenced by several factors, such as the nature and the amount of the inhaled antigen; the intensity and frequency of exposure; and the host immune response, which is likely determined by a genetic background [2]. HP has been conventionally classified as acute, subacute, and chronic. Chronic HP may mimic other fibrotic lung diseases, such as idiopathic pulmonary fibrosis. Recognition of the antigen is important for diagnosis; avoidance of further exposure is critical for treatment. During inflammatory processes, activated macrophages and neutrophils can release a great amount of hydrogen peroxide and superoxide via the phagocytic isoform of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The massive production of antimicrobial and tumoricidal reactive oxygen species (ROS) in an inflammatory environment plays an important role in bodily defences but when inflammation becomes chronic it induces persistent activation of macrophages and neutrophils that become a persistent source of oxidative damage of DNA and cell components [4-9]. Chronic inflammation induced production of ROS in the lung may predispose individuals to lung diseases [9]. Additional research is needed to understand why the disease develops only in a minority of exposed individuals and why cases of chronic HP may progress without further antigen exposure.[10]

The aim of the research was to study lipid peroxidation processes and the condition of antioxidant protection in guinea pigs' trachea in different periods of experimental allergic alveolitis (EAA).

MATERIALS AND METHODS OF INVESTIGATION

All experiments on laboratory animals were conducted following the principles of bioethics according to the regulations of *European Convention for the protection of vertebrate animals* used for experimental and other scientific purposes (Strasbourg, 1986), European Union Directive 2010/63/EU, Law of Ukraine № 3447-IV "On protection of animals from cruel treatment", general ethic principles of experiments on animals, approved by the first national congress of Ukraine on bioethics (2001).

The experiment was conducted on 40 female guinea pigs weighing 0.18-0.20 kg. The animals were divided into 4 groups:

I – intact guinea pigs (n=10);

II – guinea pigs (n=10) with EAA (44th day from the start of injecting antigen).

III – guinea pigs (n=10) with EAA (54th day from the start of injecting antigen).

IV – guinea pigs (n=10) with EAA (54th day from the start of injecting antigen) after treatment with thiotriazolin.

Experimental allergic alveolitis (EAA) was induced by the method of O.O. Orehov and Y.A. Kyrylov [10]. Prior, the animals had been immunized with Freund's complete adjuvant (0.2 ml intramuscularly into a hind leg). In 2 weeks, 0.2 ml of 1% BCG solution was introduced intravenously every 10th day. Later, the animals were decapitated; the level of lipid oxidated peroxides and activity of ceruloplasmin were detected in lung homogenate on the 44th 54th days after EAA. The content of conjugated dienes was determined by the method of V.B. Havrylov and M.I. Myshkorudina [11], malondialdehyde (MDA) – by E.N. Korobeinikov method [12], and ceruloplasmin – by V.H. Kolb and V.S. Kamyshnikov method [13].

All digital results were statistically processed using arithmetical mean (M), margin of error of arithmetical mean (m), and Student's criterion "t". The calculations were performed using means of statistical and graphic analysis of electron tables Microsoft Excel (Microsoft office programs). Statistically reliable were the results with $p \leq 0.05$.

RESULTS OF INVESTIGATION AND THEIR DISCUSSION

Data from experimental studies have shown that in the late period (44th) of EAA development rising the content of DC in trachea was observed. It was characterized by 62,84% ($p < 0.01$) respectively with control group of animals. And this increasing has achieved a highest level by 115,59% ($p < 0.01$) on 54th day of the experiment relatively to group of intact guinea pigs. Results of our investigations have been detected that a gradual elevation of MDA level in the trachea was revealed on the 44th day of allergic alveolitis development by 39,23% ($p < 0,01$) and 64,38 ($p < 0,01$) on 54th day respectively, in comparison with intact animals, that points out on aggravation of lipid peroxidation processes. Peroxidation of lipids disturbs the integrity of cell membranes and leads to rearrangement of membrane structure.

Condition of antioxidant defence we estimated on ceruloplasmin activity in the trachea of guinea pigs. It enzyme inhibits of free-radical reactions. Our experimental investigations have showed that this marker of antioxidant system had on 44th day the level of physiological norm on on 44th day after start of antigen inection. Reduction ceruloplasmins` activity in animal`s trachea was observed just on the latest day of experiment – on 54th day by 40,35%

($p < 0,01$) in comparison of healthy animals . That fact shows us about significant ability of antioxidant system to deactivate overproduced reactive oxygen species with exhaustion of ability to maintain oxidative balance on late period of this experimental model of disease.

Antioxidant thiotriazolin has caused corrective effect on changed indicators as pro- as antioxidant systems. Thiotriazolin was used for 10 days(from 44th to 54th days) intramuscularly at a dose of 100 mg / kg. Reduction of CD and MDA content in trachea by 48,96% ($p < 0,01$) and 34,08% ($p < 0,01$) respectively against the group of guinea pigs which didn't received this drug have been reported (Fig.1) Activity of ceruloplasmin had a different direction. It's level has elevated by ($p < 0,01$) in comparison with animals without treatment.

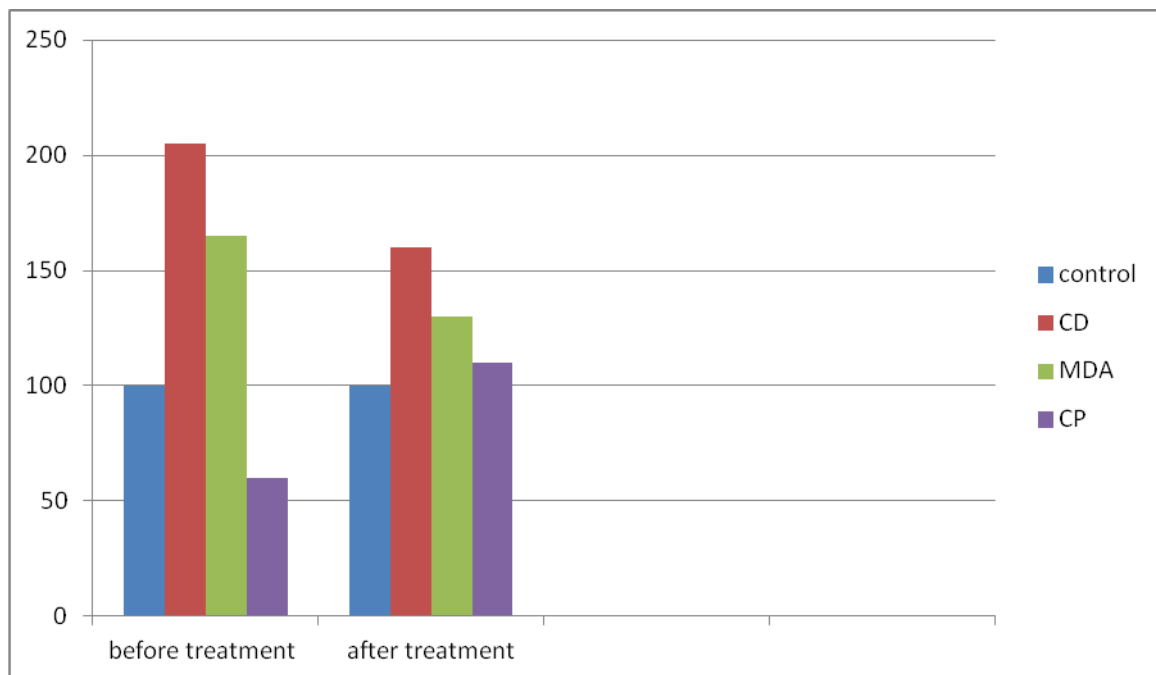


Fig.1. Action of thiotriazolin on condition of pro-oxidant and antioxidant systems in the animals' trachea in experimental allergic alveolitis (in % of control)

CONCLUSIONS

As oxidative stress has been associated with the pathogenesis of exogenic allergic alveolitis novel clinical trials to verify the effectiveness of antioxidants in these diseases are urgently required. In conclusion, research into oxidant/antioxidant balance in diffuse lung diseases is a promising field that can provide insights into pathogenetic mechanisms and open new therapeutic perspectives.

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