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The application of mesenchymal progenitor stem cells for the reduction of oxidative stress in animals

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Abstract: Oxidative stress is the primary cause of lowering of the body's immune status. It arises as a result of intense metabolic processes in humans and animals that involve a decrease in antioxidant enzymes activity at the expense of increased production of free radicals and reactive oxygen species (ROS). Consequently, this leads to oxidation of lipids, proteins, DNA, and RNA, causing cell proliferation reduction, faster cell aging, and subsequent degradation. Currently, there is a search for methods to maintain an oxidation–antioxidant balance. The results of many authors' research point to the effectiveness of the use of mesenchymal stem cells (MSCs) in the treatment of various clinical disorders. Numerous studies indicate that, compared to other cells, MSCs have ability to regulate cell adhesion molecules. They also have specific immunogenic and immunosuppressive properties that determine their application in clinical research and regenerative medicine.

Key words: Oxidative stress, stem cells, mesenchymal stem cells, animals, reduction

1. Introduction

Every cell in both humans and livestock is involved in oxidation-reduction reactions. Their main products are oxygen free radicals, molecules having at least one unpaired electron in their structure (Betteridge, 2000; Czajka, 2006; Uttara et al., 2009). Under normal conditions, an organism seeking the balance equilibrium removes reactive compounds using protective substances and enzymes. Disturbances that occur in the accumulation of these are referred to as oxidative stress (Nisar et al., 2013; Konvičná et al., 2015).

The organism is exposed to oxidative stress especially when subjected to intense physical and metabolic exertion. In the case of livestock, oxidative stress occurs as the result of continuous improvement and sharp selection in order to increase productivity (Jóźwik et al., 2012). According to Kimothi and Ghosh (2005), interracial mating is an alternative for alleviating the effects of oxidative stress, but research results of another author (Tanaka et al., 2008) did not confirm the above dependence.

Metabolic disorders increase the incidence of oxidative stress. In dairy cows, the predisposing factor is dietary mistakes committed in the last few months of lactation and in the dry period (Blowey, 2005). In addition, fat increased mobilization from the subcutaneous tissue in the perinatal period leads to increased production of lipid peroxide and reactive oxygen species (Konvičná et al., 2015), which contributes to a reduction in the antioxidant capacity of an organism in early lactation (Turk et al., 2005). Similar results were observed in sheep and goats (El-Deeb, 2015).

The oxidation–antioxidant imbalance may be an effect of 'stressor' activity. According to Dimitrios et al. (2003), their short-term impact in the form of psychological, physiological, or environmental stimuli activates an organism to induce neurohormonal regulatory mechanisms, which leads to homeostasis. In turn, animals that have been chronically exposed to stress are characterized by higher susceptibility to pathogens, which represents the effect of reducing the adjustment mechanisms (Kock et al., 1987; Ziegler, 1991).

An innovative method of oxidative stress reducing in animals can be an application of stem cells, which are isolated from bone marrow, peripheral blood, and umbilical cord or adipose tissue. Mesenchymal stem cells (MSCs) have an ability of rapid multiplication, tissue repair, and regeneration. Moreover, MSCs can exhibit an immunosuppressive effect. According to Gala et al. (2010), an important feature of MSCs is their ability to synthesize and secrete cytokines. From the immunological point of view, cytokine proteins produced by leukocytes affect the

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growth, proliferation, and cell activation determining humoral and cell mediated immunity. An important feature is also high ductility, which makes it possible to differentiate tissue cells, e.g., osteoblasts, chondrocytes, and myocytes, and they have the ability to regenerate damaged tissues (Barry and Murphy, 2004; Wei et al., 2013).

Currently, stem cells are increasingly often used in the experimental treatment of various clinical disorders including degenerative bone and joint diseases especially osteoarthritis, osteoporosis, and osteonecrosis. The results reported by Brehm et al. (2014), Marędziak et al. (2016), and others show the great potential of MSCs' application in degenerative arthritis in animals. Moreover, Broeckx et al. (2014) observed up to 45% shorter period of recovery in horses treated using intraarticular injection of MSCs isolated from peripheral blood.

2. Formation of oxidative stress

The main causes of oxidative stress are free radicals and reactive oxygen species (ROS), which are formed by the metabolic processes at the stage of the cell. Some of them may also be derived from an external environment (industrial chemicals, air pollutants, ozone) (Lobo et al., 2010). In the state of equilibrium, these compounds enhance the organism's cellular response against infectious agents (Nisar et al., 2013), support embryos' implantation in the uterine wall and fetal development, and protect the uterus against infectious agents after birth (Mutinati et al., 2013). In excess, they lead to damage to the structure of lipids, nucleic acids, and proteins (Lobo et al., 2010).

During normal metabolism, the oxygen molecule is reduced to the superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and water (H_2O) under the effect of NADPH oxidase. The resulting free radicals are systematically removed by natural mechanisms of the body using antioxidant enzymes: superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) (Lobo et al., 2010). The conditions of low concentrations of substances inhibiting oxidation reactions and the severe metabolic function cause an increased activity of NADPH oxidase, according to Martynowicz et al. (2004); it contributes to the formation of large amounts of cytotoxic free radicals of oxygen. In addition, the oxidation reduced glutathione (GSH) concentration of antioxidants decreases and increases in the use of agents responsible for the process of glucose molecule transfer. Lack of glucose metabolism availability leads to disruption of energy metabolism, weakening of the immune function and antioxidant capacity, and calcium imbalance (Celi, 2011).

3. Oxidative stress in ruminants

In all animals, oxidative stress is mainly caused by high temperatures (heat stress) (Chauhan et al., 2014), noise, and improper maintenance system and nutrition. In the case of dairy cows, sheep, and goats, the perinatal period is very important, when the organism's metabolic activity achieves the highest level (Konvičná et al., 2015). A rapid increase in fetus weight is noted in the last days before birth. Many observations point to the fact that the placenta has a major impact on the homeostasis in the final stage of pregnancy. Mitochondria present in its structure use large quantities of oxygen, which promotes the formation of free radicals and reactive oxygen species (Berchieri-Ronchi et al., 2015). In addition, the gradual development of glandular tissue lists for the upcoming colostrogenesis and lactogenesis processes determines the needs of larger cells and tissues for irrigation and oxidation (Celi and Gabai, 2015).

In ruminants the rumen is a kind of a chamber within which a sample feed is subjected to decomposition with the involvement of the bacterial microflora. According to Celi (2011), digestive disorders stage in the rumen leads to an increased risk of oxidative stress. Acidosis presents a particular danger (Guo et al., 2013), since it involves overproduction of volatile fatty acids and lactic acid. This mainly results in a decrease in rumen fluid pH, and the results of some authors studies (Emmanuel et al., 2008) also indicate the degradation of gram-negative bacteria. During the disintegration of the cell walls they release significant amounts of lipopolysaccharides affecting lipid metabolism, which leads to reduced triglycerides accumulation in the liver (Feingold et al., 1992). Weakened metabolic functions of the liver become the cause of its steatosis, and consequently lead to the deepening of negative energy balance and ketosis in dairy cows. Furthermore, animal feeding with feedstuff rich in starch with a low concentration of effective neutral detergent fiber (NDF) in the last 3 weeks of pregnancy contributes to the release of significant amounts of endotoxin in the rumen, which stimulates the production of inflammatory cytokines, ROS, and bioactive lipids (Rietschel et al., 1994; Celi and Gabai, 2015).

Body condition is an important factor predisposing for metabolic disorders (Berchieri-Ronchi et al., 2015). Fatness in sheep, goats, and especially cows at the end of lactation and during the dry period will often cause a decrease in feed intake during the last 10–14 days before birth. In addition, the gradual development of mammary gland tissue and the colostrogenesis process increase the organism's demand for nutrients. Under such conditions, there is an intensive mobilization of lipids. According to El-Deeb (2015), rapid metabolism and release of excessive amounts of free fatty acid increase the production of ROS.

A similar relationship was also demonstrated in the results of studies by other authors (Bernabucci et al., 2005; Loor et al., 2006; Schäff et al., 2012).

Oxidative stress impairs physiological processes, which leads to destabilization and consequently to diseases that weaken the immunity of the organism (Jóźwik et al., 2012). In sheep, goats, and particularly in dairy cows, a decrease in antioxidant activity leads to an increase in the incidence of subclinical mammary gland inflammations. They are primarily responsible for neutrophils, which are formed during the oxidation reaction (Karyak et al., 2011). According to other authors, an increase in the amount of nitric oxide (NO) and a decrease in the level of ascorbic acid in the blood are observed in cows with mastitis (Sordillo et al., 2009).

Currently, there are few reports suggesting a direct effect of oxidative stress on reproduction. However, there are some data suggesting that the basis of reproductive system disorders in cows are metabolic disorders and dietary mistakes during the perinatal period. According to Miller et al. (1993), improper feeding and antioxidant deficiencies in the ration during the transition period contribute to reduced muscle tension, which leads to placenta retention. According to Brzezińska-Ślebodzińska et al. (1994), deficiency of vitamin E and selenium in the last weeks of pregnancy increases the production of lipid peroxide, and thus the frequency of retained placenta and postpartum metritis. The oxidant–antioxidant imbalance may also contribute to sexual cycle disorders. ROS and large amounts of superoxide dismutase (SOD) are present in the corpus luteum structure, serving a regulatory function. The violation of the organism's homeostasis is an effective factor blocking corpus luteum activity, leading to premature degradation (Sugino, 2006).

4. Oxidative stress in laboratory animals

There are many factors that determine oxidative stress in laboratory animals. The results of the study conducted by Demirel et al. (2009) suggest an increased level of malondialdehyde (MDA), NO, and glutathione peroxidase (GSH-Px) as indicators of impaired antioxidant activity in the serum of rats exposed to noise of 100 dB for 20 days. On the other hand, Noeman et al. (2011) argue that a high fat diet leads to obesity in mice and rats, and thus to decreased activity of antioxidant enzymes and reduced glutathione (GSH), as well as increased level of MDA and protein carbonyl group (PCO) in the tissues of the kidney, liver, and heart, which clearly shows the presence of oxidative stress. In the case of mice, deficiency transcription factor was observed (p53, JunD, Foxos, and HIF-2alpha), which is responsible for the regulation mechanisms involved in antioxidant secretion (Pouyet and Carrier, 2010). However, Chan et al. (2001) showed deficiency of the p45NF-E2 gene, which causes an accumulation of elevated levels of reactive oxygen intermediates in red blood cells. According to Nocchi et al. (2014), one of the main symptoms of oxidative stress in mice is impaired bladder activity associated with the deterioration of contractile response. Under conditions of ROS overproduction induced by the addition of melamine to the diet of female mice, Dai et al. (2015) reported ovarian damage in the form of abnormal oocyte maturation. Reckziegel et al. (2011) demonstrated that prolonged exposure to cigarette smoke in mice activates the release of free radicals, which cause an increase in lipid peroxidation in the brain and red blood cells and a decrease in plasma ascorbic acid level. In turn, Choi et al. (1998) reported that one of the oxidative stress symptoms in hamsters is mitochondrial dysfunction, accompanied by a reduction in SOD and an increase in the concentration of glutathione peroxidase and glutathione reductase.

5. Methods of oxidative stress reduction in animals

The primary method of oxidative stress reduction in animals is the supply of compounds with antioxidant properties, which protect the cells of the body and interact with free radicals and reactive oxygen species (ROS). The study by Araújo et al. (2013) showed that creatine as a dietary supplement for rats supports the antioxidant activity of the body. A similar relationship was indicated in the observations of other authors (Souza and Pereira, 2008; Guimarães-Ferreira et al., 2012). In turn, the results of the study by Tsuda et al. (2000) show that cyanidin administered with the feedstuff acts as an antiregulating agent of liver function. Moreover, Furukawa et al. (2015) analyzed the oxidative stress process in obese rats. In their opinion, the injection of NADPH oxidase inhibitor effectively lowers the amount of free radicals produced during lipolysis of adipose tissue. Reckziegel et al. (2011) obtained positive results in the case of an application of aqueous extract from walnut shells in mice exposed to cigarette smoke. They mainly observed an increase in antioxidant activity and a decrease in physical activity and anxiety.

It was demonstrated that addition of vitamins and minerals to the ration for ruminants in the perinatal period effectively reduces the incidence of oxidative stress (Singh et al., 2009). In the case of dairy cows, an increase in the share of vitamin E and selenium in the dry period helps to reduce lipid peroxidation at the beginning of lactation and protect cell structures against ROS-dependent damage, including lipids and membranes, proteins, and DNA (Nisar et al., 2013). Similar conclusions were drawn by Konvičná et al. (2015). Apart from the addition of vitamin E and

selenium to basic feed, it is also important to supplement with vitamin C, beta-carotene, zinc, and beta-flavonoids, which strengthen the resistance of cows' mammary glands. According to Castillo et al. (2013), the results show a decrease in somatic cells count in milk. In turn, the results of Aoki et al. (2010) show the efficacy of disaccharides in the ration of dairy cows. They mainly observed reduced amount of lipid peroxides and increased antioxidant properties of milk. The study conducted by Puppel et al. (2015) demonstrated that dietary supplementation of cows with fish oil and flax is beneficial not only for the organism's metabolic profile but also the fatty acids profile and antioxidant properties of milk.

6. Stem cells

Stem cells are unspecialized cells of the body that exhibit a high ability for multipotency, self-renewal, and differentiation into mesoderm lineages, ectodermic cells, and endodermic cells (Wei et al., 2013). In mammals, stem cells can be divided due to their origin into embryonic and somatic ones. Initially, due to the tolerance of all cell lines the most effectiveness shows embryonic stem cells applicable for biological research and regenerative medicine. However, ethical considerations concerning the method of their acquisition meant that the studies and observations consisted of MSCs (Maumus et al., 2011) initially isolated only from the bone marrow. Currently, they can be obtained from peripheral blood or the umbilical cord or directly from the adipose tissue (Horwitz et al., 2005). Kern et al. (2006) and Vidal et al. (2008) showed regenerative properties due to the ease of these cells' growth in vitro and a putative role in cell adhesion molecules regulation, as well as proliferative and differentiative potential. The results of the study by Law and Chaudhuri (2013) point to their specific immunomodulatory properties. Furthermore, MSCs are not immunogenic, which makes it necessary to check and match the histocompatibility of the donor and recipient. Moreover, MSCs immediately after transplant by chemokines and their receptors effectively move to the regeneration site. According to Maumus et al. (2011), the ability of these cells to differentiate and secrete cytokines, as well as growth factors, determines their immunosuppressive properties. This means that MSCs, blocking B and T lymphocytes, can reduce immune reactivity at a time when the immune response would be detrimental for the organism itself (to protect against transplant rejection).

7. Mesenchymal stem cells and oxidative stress

Due to the high distribution potential and repeatability of isolation procedures, MSCs used in cell therapy are derived mainly from the bone marrow and adipose tissue (Maumus et al., 2011). Damage to structures of cell membrane proteins, lipids, and DNA generated by the action of oxidative stress leads to accelerated cell aging and then to their degradation. The genetic reason is telomere shortening during the process of cell replication. The results reported by Estrada et al. (2013) indicate the efficacy of stem cells in the treatment of diseases caused by oxidant–antioxidant imbalance. According to them, catalytic subunit MSCs, human telomerase reverse transcriptase (hTERT) present in the structure of the telomerase, controls the length of telomere division, preventing both elongation and shortening. This action increases the lifetime of the cells, inhibiting thus the aging process. In addition, Brandl et al. (2011) reported that MSCs showed a higher tolerance in the conditions of oxidative stress compared to fibroblasts and chondrocytes. On the other hand, Fan et al. (2011) demonstrated that stem cells exposed to the long-term action of hydrogen peroxide had decreased ability to proliferate.

So far, many studies have been conducted on laboratory animals to determine the relationship between MSCs and oxidative stress. According to Calió et al. (2014), MSCs isolated from bone marrow reduce apoptosis and ROS production in the cells of rats exposed to spontaneous hypertension. Furthermore, Vanella et al. (2012) reported that heme oxygenase 1 (HO-1) already present in the structure of MSCs exhibits strong antioxidant properties. Indeed, it inhibits the production of superoxide anion ($O_2^{\bullet -}$), which exhibits a high predisposition for lipid peroxidation and increases the sensitivity of cells to hydrogen peroxide (H_2O_2). On the other hand, Ayatollahi et al. (2014) demonstrated the protective effect of stem cells implanted in rats with a damaged liver. The recorded indicators include elevated levels of glutathione (GSH), which plays an essential role in detoxification of hydrogen peroxide, free radicals, and reactive oxygen species, which cause oxidative stress. Transplantation of stem cells also led to the stabilization of liver enzymes (AST and ALT), supporting their function in degradation and detoxification of harmful substances. Positive results were also obtained in rats suffering from osteoporosis. In older individuals, which received stem cells in the form of injection, an increase in gene expression dismutase 1 (SOD1) was noted, which affects the reduction of reactive oxygen species (Tan et al., 2015). Studies by Sun et al. (2015) show that the MSCs isolated from bone marrow contributed to restoring the integrity of the intestinal epithelial barrier in the rat that had been damaged by prolonged exposure to oxidative stress. The basic mechanism of this process occurs through restoration of the expression of E-cadherin, which acts as an

adhesive protein. In normal condition E-cadherin, which is located on the cell surface, interacts with the adjacent cell and her cadherin, what leads to the formation of the actin skeleton, which is an integral part of the adhesion complex. According to many authors, the presence of this complex is important, because it allows the regulation and constant control of the process of growth, differentiation, and cell migration. It is also a stimulus for the induction of anti-inflammatory cytokines, which are responsible for the immune response of the organism. Furthermore, the observations of other authors (Quintanilha et al., 2014; Yang et al., 2015) showed an increase in the production of cytokines and chemokines as a result of the injection of mesenchymal stem cells derived from bone marrow (BMSCs). In studies by Quintanilha et al. (2014) it was found that the activation of these proteins in mice with advanced liver injury was associated with increased levels of matrix metalloproteinase (MMP-9) in liver tissues, and the phenomenon of overexpression of Nrf2. In turn, Yang et al. (2015), in the case of inflammation of the colon of rats, observed high levels of trinitrobenzenesulfonic acid (TNBS), which has strong oxidizing properties. As stated, this acid leads to the release of enzymes from the group of proteases (caspase3, caspase8, and caspase9) that are responsible for acceleration of the process of cell apoptosis. It also acts as a mediator in the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which mediates transcription of proinflammatory genes. Transplantation of mesenchymal-type stem cells leads to inhibition of the inflammatory response induced by TNBS and thus to reduction in the level of interleukin-1β (IL-1β) and increase in interleukin-10 (IL-10). An important repair mechanism for oxidative stress damage was membrane blebs, EVS secreted by the plasma membrane of BMSCs. Their structure contains growth factors, apoptotic pathways factors, and anti-inflammatory substances, which according to Marędziak et al. (2016) are responsible for the high therapeutic potential of MSCs. In addition, they reported reductions in disease activity index (DAI), myeloperoxidase (MPO), and MDA and increased levels of SOD and GSH, which indicate the positive impact of stem cells in the reduction of oxidative stress.

Another important feature of stem cells is their ability to differentiate into other specialized cells of the body, as evidenced in the results reported by Huang et al. (2015). In that study, MSCs were isolated from bone marrow and then were administered by injection to rats suffering from lung fibrosis. The pathogenesis of the disease involves blocking the function of pulmonary alveolar epithelial cells (PAECs), which are responsible for identifying and presenting a particular antigen. What is essential is that these cells produce and secrete surfactant proteins (SPs): SP-A, SP-B, SP-C, and SP-D, which regulate morphological, physical, and biochemical function and they decide on the efficiency of the immunoregulatory cells of the lung (Zissel et al., 2000). The MSCs after transplantation migrate to the site of tissue damage and then differentiate into the alveolar epithelial cells type II (AEC II), which is the basic mechanism of the regeneration process (Huang et al., 2015). A similar ability of MSCs to differentiate into other cells was observed by Lv et al. (2014). During the research BMSCs were transplanted into rats in which strong diabetes was found. The factor responsible for the induction of the disease was cytokine-transforming growth factor beta (TGF-β), which according to Stępień-Wyrobiec et al. (2008) is involved in angiogenesis, degradation of the extracellular matrix, and regulation of the apoptotic pathway. The authors observed a high level of TGF-β contributed to the increase in the expression of the glucose carrier GLUT1, which caused the severity of metabolic processes, and thereby led to the formation of oxidative stress. Under such conditions, pancreatic cells lose their ability to secrete insulin, necessary to regulate blood glucose levels. Therapy that involves stem cells reduces the expression of GLUT1; what is more it allows reduction in albumin and creatinine levels in the urine, which indicates the stabilization of kidney function.

8. Summary

The high susceptibility to disease observed in laboratory and livestock animals is an effect of oxidative stress. Oxidants created during this process react with cells of the organism, causing their damage and degradation. So far, many studies have been carried out that aimed to reduce the production of compounds responsible for disorders in oxidant–antioxidant balance. It should be noted that oxidative stress prevention should not be limited only to the reduction of harmful substances (free radicals, reactive oxygen species). Its basic task should be regeneration of previously damaged cellular structures, which lead to the weakening of immunodeficiency of the organism. The rationale and philosophy supporting the use of stem cells therapy is that preventing oxidative stress is preferable to treating it, following the dictum: 'an ounce of prevention is worth a pound of cure'. The research conducted by many authors on laboratory animals indicates that MSCs exhibit immunosuppressive and immunoregulatory properties. In addition, the authors confirm their proliferation abilities, reduction of apoptosis risk and liver enzyme stabilization. The wide spectrum of positive effects of stem cell therapy in laboratory tests should predispose the application of MSCs in clinical studies of farm animals.

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