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# Situations Leading to Oxidative Stress in Dairy Cattle

Review Article

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## ABSTRACT

Free radicals are normally produced by living organism, at controlled production rate they perform physiological functions as signal transduction molecules. However, situations leading to an overproduction that surpasses antioxidant capacity creates oxidative stress. Consequently, damage to the cell membrane, protein, DNA and cell death are observed. Dairy cattle are susceptible to oxidative stress. Situations such as infections, metabolic disorders and heat stress are known to cause oxidative stress in cattle by depleting body antioxidants concentrations or by increasing endogenous free radical production. The organism response to oxidative stress by activating cell factors that after evaluating the damage to cell, a repair or death signal will be programmed. The objective of this review is to empower the reader with knowledge related to oxidative stress and to provide information on the situations leading to this type of stress and the cellular response to it in dairy cattle.

**KEY WORDS** antioxidants, bovine, cellular response, oxidants.

## INTRODUCTION

Oxidative stress is "the state at which oxidative forces exceed the antioxidant system due to loss of balance between them" (Yoshikawa and Naito, 2002). An imbalance of this nature may result in reduced concentrations of antioxidants or increased production of free radicals. Free radicals are oxidative forces; they are atoms, molecules or compounds with a short life and an unpaired electron that makes them unstable and highly reactive (Bhattacharya, 2014), capable of treating life in high and uncontrolled concentrations. Fortunately, living organisms counteract free radicals with antioxidants, which significantly delay, prevent or inhibit damage of a substrate by free radicals (Halliwell and Gutteridge, 1995). The term "substrate" includes everything found in a live organism (Halliwell *et al.* 1995).

There are several types of free radicals (Halliwell and Whiteman, 2004), but the most relevant in biological systems are reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Aprioku, 2013). A regulated amount of free radicals is normally produced in living organisms; these are not harmful, but they are used as signal transduction molecules. Common endogenous sources of free radicals include mitochondrial production of ATP (Jastroch *et al.* 2010), degradation of purines by xanthine oxidase (Kuppusamy and Zweier, 1989), phagocytosis of microorganisms (Knight, 2000), inflammation (Mittal *et al.* 2014) and oxidation of very long-chain fatty acids (Reddy, 2001). Situations leading to additional production of ROS and consequently to oxidative stress in farm animals include heat stress, inflammation, dietary imbalances, respiratory diseases, and parasites (Celi and Gabai, 2015). Once pro-

duced, additional free radicals will damage cells by extracting an electron from a substrate (lipids, proteins or DNA), making them more stable and less reactive.

Oxidative stress opens a novel field of research in ruminant medicine (Celi, 2011). However, there is evidence of oxidative stress involved in events that compromise dairy cattle welfare. The objective of this paper is to review existing knowledge related to oxidative stress and to provide information on the situations leading to this type of stress.

**Oxidation of lipids**

Damage by ROS or lipid oxidation also termed peroxidation, occurs when a free radical steals an electron (hydrogen) from a lipid. Polyunsaturated fatty acids (PUFA) from the cell membrane are highly susceptible to oxidative damage due to the presence of methylene groups, which are characterized by a weak carbon-hydrogen bond (Bochkov *et al.* 2010). Basically, a ROS will generate a lipid radical by abducting a hydrogen molecule from PUFA. The lipid radical that reacts with oxygen will generate a lipid peroxy radical, which will abstract another electron from the nearest PUFA creating a new lipid radical and a lipid hydroperoxide. The new lipid radical will react with oxygen as indicated above. This is a self-sustained process that could convert all the cell membrane PUFA into lipid hydroperoxides. Additionally, hydroperoxides can react with free transitional metals such as $Fe^{2+}$ and $Cu^{+}$ to produce a lipid alcoxyl radical, which can abstract an electron from another PUFA, creating a new lipid radical (Esterbauer *et al.* 1990).

Peroxidation results in structural changes in the cell membrane. According to Greenberg *et al.* (2008), fatty acid peroxidation will change the normal fluid mosaic of the cell membrane to one with protruded fatty acids known as the whisker model, which may serve to elicit cell phagocytosis from macrophages.

In addition to hydroperoxides, peroxidation will render endoperoxides (Valko *et al.* 2006) that can be fragmented to generate reactive carbonyl species such as malondialdehyde (MDA) and 4-hydroxy–trans-2-nomenal (HNE), depending on the type of fatty acid oxidized. Oxidation of lipids containing ω-6 PUFAS will give rise to HNE, while those containing three or more methylene interrupted double bonds will produce MDA (Esterbauer *et al.* 1991). Due to its short life, ROS will normally react with the nearest substrate, but reactive carbonyl species have a longer half-life and are able to migrate through membranes and cytosol, extending damage to other cell constituents as well as the membrane (Pamplona, 2008). MDA is mutagenic (Niedernhofer *et al.* 2003); it impedes the mechanism of DNA repair after damage (Feng *et al.* 2006) and alters physiological functions of proteins (Rittié *et al.* 2002) by forming adducts with DNA and proteins.

Elevated concentrations of MDA have been reported in cows affected with mastitis (Ranjan *et al.* 2005). In fact, a positive correlation between MDA and somatic cells counts was reported by Suriyasathaporn *et al.* (2006), indicating that antioxidant capacity of cows is compromised during mastitis. Interestingly, Weiss *et al.* (2004) found that udder infection leads to decreased concentrations of the antioxidant vitamin C, evidence that oxidative stress is involved in the pathology of mastitis (Atakisi *et al.* 2010). A source of ROS leading to lipid peroxidation and formation of MDA could be bacterial lipopolysaccharides. Lipopolysaccharides are components of the outer cell membranes of bacteria and are considered endotoxins, capable of inducing an inflammatory response in animal cells (Raetz and Whitfield, 2002). They are released during bacterial growth, division, and lysis. Clinical mastitis has been induced in cows challenged with intra-mammary infusion of lipopolysaccharides (Zimov *et al.* 2011), and increased MDA concentrations have been measured in bovine mammary epithelial cells cultured with lipopolysaccharides (Shi *et al.* 2016).

Another source of lipid peroxidation in cattle is parasitic infection (Ellah, 2013). Cows infected with lungworms and fasciolosis have decreased antioxidant capacity and augmented lipid peroxidation, while infected animals have higher concentrations of MDA than those not infected (Bahrami *et al.* 2014; Silva *et al.* 2016). Lipid peroxidation could result from over production of ROS during host defense by phagocytes. Phagocytes use NADPH-oxidase system in their cell membrane to generate superoxide during phagocytosis (Roos, 1991). Nitric oxide also generated during parasite infection by phagocytes can react with superoxide to form peroxynitrite. Both nitric oxide and peroxynitrite are used as weapons to kill parasites (Brunet, 1991; Linares *et al.* 2001), but peroxynitrite produces MDA on the side (Radi *et al.* 1991).

**Protein oxidation**

Protein oxidation is defined as "covalent modification of a protein induced by direct reaction with reactive oxygen species or indirect reaction with secondary by-products of oxidative stress" (Zhang *et al.* 2013), which leads to oxidation of amino acid residue side chains, peptide bond cleavage, formation of cross-like aggregates and ultimately to alterations in protein structure and functionality (Stadtman and Levine, 2003). All the amino acid residues of a protein are susceptible to oxidative damage, but cysteine and methionine are considered the most sensitive (Berlett and Stadtman, 1997). However, only with these two did reversible oxidation occur, giving them antioxidant properties. According to Yan (2014), irreversible oxidation of amino acid residues may result in loss of protein function. However, on the contrary, reversible oxidation serves as a

protein function regulator. According to Levine *et al.* (1996), under oxidative stress conditions, preferential oxidation of methionine allows the protein to maintain its biological function.

Abstraction of hydrogen from the α-carbon of the amino acid generates a carbon-centered radical that can also abstract hydrogen from thiols or react with iron to render peroxyl radicals. Peroxyl radicals are converted to alkyl peroxides by reaction with superoxide or by abstraction of a hydrogen molecule from other molecules. Alkyl peroxide produces an alkoxyl radical by reacting with a hydroperoxyl radical, which can undergo protein peptide bond cleavage by α-amidation or diamide pathway. Other radicals resulting from protein oxidation include thiyl radicals generated by hydrogen abstraction from free thiol groups or cleavage of disulfide linkages, chloramines produced by hypochlorous acid reacting with proteins and carbonyl groups by oxidation of lysine, proline, arginine and threonine (Hawkins and Davies, 2001; Stadtman and Levine, 2003).

Protein oxidation has been evaluated in dairy cattle by assessing the status of advanced oxidation protein products (AOPP). AOPP are produced by hypochlorous acid that reacts with proteins during neutrophil activation (Bordignon *et al.* 2014). Cows with high concentrations of AOPP had a higher embryo mortality incidence after artificial insemination, probably due to a pathogen eliciting an inflammatory response in the uterus (Celi *et al.* 2011; Celi *et al.* 2012). Moreover, parasitic infection has also increased AOPP blood serum concentrations.

**DNA oxidation**

Oxidative damage to DNA occurs at a basic sites, purine and pyrimidine bases. Abasic sites are produced by hydrolysis of the N-glycosylic bond, while free radical attack at positions 1, 2 or 4 of the sugar residues gives rise to oxidized a basic sites (Häring *et al.* 1994). Oxidative damage can also be inflicted on purine and pyrimidine bases. The oxidative damage products of purines and pyrimidines are discussed by Cadet and Wagner (2013) and, according to David *et al.* (2007), due to the high susceptibility of guanine to oxidative damage; 7,8-dihydro-8-oxo-2′-deoxyguanosin is the most studied product of oxidative DNA damage.

Oxidative damage to DNA in dairy cattle was reported by Ellah *et al.* (2014). According to these authors, dairy cows during the dry period experience greater oxidative DNA damage than during other phases of lactation. In a different study, Ellah *et al.* (2016) found that during the transition period, the concentration of DNA oxidative damage products was greater during pre-partum than after parturition. These studies suggest that oxidative stress is more severe during the dry period. However, Sharma *et al.* (2011) and Gong and Xiao (2016) agree that the first weeks post-partum are the most stressful for dairy cattle.

They reported increased lipid peroxidation and reduced antioxidant capacity in cows during the first days of lactation compared with cows 30 days after calving. In concordance with these findings, Omidi *et al.* (2016) reported higher antioxidant capacity in cows at the end of lactation. Thus, it seems that oxidative stress is established before and after parturition.

The degree of oxidative damage is expected to be greater after parturition, when a negative energy balance predisposing lipid mobilization will favor free radical formation (Piccione *et al.* 2007; Pedernera *et al.* 2010). In addition, cows in early lactation that experience a negative energy balance have lower concentrations of antioxidants such as vitamin C, tocopherol and glutathione (Cigliano *et al.* 2014; De Bie *et al.* 2016). On the other hand, Mandebvu *et al.* (2003) suggest that antioxidant capacity in dry cows may be compromised due to the low content of antioxidants in rations formulated at this stage of lactation. In addition, low activity of the hepatic antioxidant paraoxonase-1 has been found in cows during the transition period (Turk *et al.* 2008).

Reactive oxygen species can also induce DNA strand break. The mechanism leading to strand break begins with hydrogen being stolen from sugar (2-deoxyribose), causing the formation of a carbon base radical, which in the presence of oxygen is converted to a peroxyl radical. This can abstract hydrogen molecules from neighboring sugars and lead to strand break (Kryston *et al.* 2011). In dairy cattle, increased hepatic DNA strand break has been identified as the transition period progresses, resulting in hepatocytes apoptosis (Tharwat *et al.* 2012). The latter indicates that during this period liver functionality is compromised, explaining the reduction in the previously mentioned hepatic antioxidant production.

**Cellular responses to oxidative stress**

The increase in the production of reactive oxygen species is counterattacked by well-organized response elements. One of them is the nuclear factor E2-related factor (Nrf2). Under non-oxidative stress conditions Nrf2 is found in the cell cytoplasm bound to its regulator, the kelch-like ECH protein 1 (Keap1), but an increase in reactive oxygen production causes oxidation of Keap1 and the release of Nrf2. This can be translocated to the cell nucleus where it associates with Maf proteins (sMaf) and bind to antioxidant responsive elements (ARE), which in turn control the expression of several antioxidants, including glutathione, thioredoxin and NADPH (Gorrini *et al.* 2013; Hayes and Dinkova-Kostova, 2014).

Activation of Nrf2 helps to ameliorate oxidative stress. In dairy cattle, activation of Nrf2 in mammary epithelial cells exposed to heat shock stress reduces the production of reactive oxygen species and improves cell survival (Jin *et al.* 2016). Like heat stress, high concentrations of NEFA and ketosis are known to induce oxidative stress damage. NEFA produces oxidative stress damage and apoptosis in hepatocytes by activating p38 mitogen-activated protein kinase (MAPK) and the subsequent increased expression of transcription factor p53 and the down regulation of Nrf2 (Song *et al.* 2014). The guardian of the genome, p53, protects the cell from oxidative damage under low level of oxidative stress, but induces cell death when oxidative stress increases (Liu and Xu, 2011).

As a result of incomplete metabolism of NEFA in liver, the cows develop ketosis, which is characterized by a high blood concentration of ketone bodies during periods of negative energy balance. Ketone bodies such as β-hydroxybutyrate produce similar damage to hepatocytes such as NEFA (Song *et al.* 2016). In addition, Gessner *et al.* (2013) found that after calving the mRNA for genes controlled by Nrf2 declined. Thus, the cellular antioxidant response to oxidative insult is compromised in cows with negative energy balance after parturition.

The nuclear factor–κB (NF–κB) is also activated during oxidative stress events. Similar to Nrf2, NF–κB is sequestered in the cell cytoplasm bound to a protein IκB. However, increased production of reactive oxygen species breaks the bond between NF–κB and IκB, allowing translocation of NF–κB to the cell nucleus, where it stimulates the expression of pro-inflammatory factors (Gloire *et al.* 2006).

In dairy cattle, oxidative stress and activation of NF–κB has been observed in cows with acidosis, together with a down regulation of Nrf2 (Abaker *et al.* 2017). Another situation leading to NF–κB turn on is ketosis. Shi *et al.* (2014) reported that hepatocyte damage induced by β-hydroxybutyrate was mediated by increased activation of NF–κB and expression of pro-inflamatory factors (tumor necrosis factor-α and interluekin-6). Interestingly, the expression of these pro-inflammatory factors was reduced by antioxidant treatment.

The mitogen activated protein kinase (MAPK) is turned on by increased reactive oxygen species concentrations. It is integrated by three subfamilies, the extracellular signal-regulated kinases (ERK), C-Jun N-terminal kinases (JNK) and p38. The first subfamily is normally involved in the cell survival process and the last two are implicated in apoptotic cell death, but not always (Wada and Penninger, 2004). Cell treatment with hydrogen peroxide resulted in cell apoptosis and activation of the three subfamilies of MAPK, but cell death was decreased by inhibition of ERK and the contrary occurred when JNK was inhibited (Wang *et al.* 1998). In dairy cattle, Tian *et al.* (2014) suggest that the oxidative stress damage and apoptotic cell death induced by β-hydroxybutyrate in abomasum smooth muscle cells is responsible for abomasum displacement. The latter occurred under the upregulation of p38 and JNK, but down-regulation of ERK.

## CONCLUSION

Oxidative stress disrupts cell homeostasis and compromise dairy cattle health. Participation of oxidative stress in situations such as metabolic disorders, bacterial and parasitic infections suggest that antioxidant therapy could improve dairy cattle health affected by these situations. Knowledge of the physiology of oxidative stress in disrupting cell homeostasis and dairy cattle health will help to determine the best dose and time for antioxidant supplementation to prevent oxidative stress damage.

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