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CHANGES IN DOMESTIC ANIMALS AFTER ENDOTOXIN ADMINISTRATION – A REVIEW*

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Abstract

Lipopolysaccharides (LPS, commonly known as endotoxins) are components of cell walls of gram-negative bacteria. Lipopolysaccharides are complex glycolipids composed of lipid A, a core polysaccharide, and repeating units of O-specific polysaccharides. Lipid A is associated with the majority of toxic effects of gram-negative bacteria. It interacts with target cells, such as macrophages and activated neutrophils, initiating the inflammatory cascade. The effects of LPS depend mostly on organism reaction to endotoxins, their concentration in blood and also on the state of the animal before the occurrence of endotoxemia. The effect of endotoxin on the reproductive functions of domestic animals has been partly elucidated. This paper presents data on clinical, hematological and biochemical changes in endotoxemia as well as effects of injection of endotoxin in the reproductive systems in boars, rams, and stallions. The results show that these males respond to endotoxins in a similar way, concerning clinical symptoms, body temperature and leukocyte count in blood. Endocrine and seminal changes are different and the range of these changes also depends on the dose and endotoxin exposure time.

Key words: endotoxemia, clinical symptoms, blood parameters, hormonal changes, semen quality, boar, ram, stallion

Gram-negative bacteria of the genera *Escherichia*, *Salmonella*, *Shigella*, *Proteus*, *Pseudomonas*, and other contain complex lipopolysaccharides (LPS), commonly known as endotoxins. Lipopolysaccharides are heteropolymers composed of a hydrophobic part (Lipid A) and a hydrophilic part (polysaccharide). The distal part of the LPS directed towards the environment is an O-specific chain called antigen O. This type of lipopolysaccharide is found in many bacteria of the family *Enterobacteriaceae*. Lipid A, anchoring the LPS in the outer membrane, is responsible for

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the toxic properties and biological activity of the molecule (Rietschel and Brade, 1993).

Lipopolysaccharides are potent stimulators of many non-specific and specific reactions of the organism. The body's response to the presence of LPS consists in activating immunologically competent cells (monocytes, macrophages, granulocytes, B cells) and non-immune cells, such as endothelial cells. The group of lipopolysaccharide and serum protein – lipopolysaccharide binding protein (LBP) binds efficiently (via the CD14 receptor) to granulocytes and macrophages, stimulating the synthesis of pro-inflammatory cytokines, among which dominate: tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1α and IL-1β), interleukin-6 (IL-6) and interleukin-8 (IL-8). They are released a few minutes after the exposure of mononuclear phagocytes to endotoxin. Under the influence of LPS, TNF-α. is synthesized and released at first whereas IL-1 and IL-6 appear in blood later. Apart from the TNF-α and IL-6, IL-1 is the best-known endogenous pyrogen that triggers a febrile reaction by affecting the thermoregulatory centre, where an increase in PGE_2 synthesis occurs. TNF-α is responsible for the first phase of fever, whereas IL-1 is related to the second phase. The increase in the internal body temperature affects all animals exposed to the influence of endotoxins, but its extent is dependent on the dose of LPS (Bieniek et al., 1988; Morris et al., 1990; Wiśniewski et al., 1993; Olson et al., 1995; Studziński et al., 1995; Barton et al., 1996; Danek, 2002; Tadros and Frank, 2012).

Biological effects and symptoms caused by endotoxins can be found in relation to the role played by LPS in the initiation of arachidonic acid cascade and the release of a number of its products (cyclooxygenase line) to thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) as well as prostaglandins E_2 (PGE_2) and $F_{2\alpha}$ ($PGF_{2\alpha}$). These factors mediate in the manifestation of hemodynamic dysfunctions occurring in the initial phase of endotoxemia, fever, gastrointestinal motility inhibition and to leukotrienes (LT) in the lipooxygenation line. LT-C_4 D_4 E_4 cause bronchospasm, increase vascular permeability, induce chemotaxis and activate neutrophils and macrophages, as well as stimulate the production of the TNF-α and IL-1. Platelet Activating Factor (PAF) is a lipid mediator released under the influence of LPS. It is secreted by many cells, including macrophages, monocytes, neutrophils, eosinophils, endothelial cells and platelets. PAF is chemotactic and stimulating for neutrophils and monocytes, it also causes activation and aggregation of thrombocytes. It induces bronchospasm and coronary and pulmonary arteries constriction. By increasing capillary permeability it also contributes to swelling and blood thickening (Bottoms et al., 1982; Ogletree et al., 1986; Olson et al., 1990; Klosterhalfen et al., 1991; Morris, 1991; Bottoms and Adams, 1992; Green and Adams, 1992; Snapper et al., 1998; Doherty et al., 2003).

The development of endotoxemia occurs when endotoxin is released from the bacterial cell surface, which takes place during cell division or cell death. Afterwards, the endotoxin enters the blood from infection pockets localized in organs or tissues. Endotoxins released from Gram-negative bacteria, which are a part of the bacterial flora of the gastrointestinal tract, can play an important role in the development of this process. The destruction of the intestinal barrier promotes movement of large amounts of endotoxin to the peripheral blood and induces endotoxemia.

During the course of endotoxemia in animals there are many behavioural, clinical, hematological and biochemical changes, depending on the size of dose received and the degree of sensitivity to endotoxin. These changes are a result of internal organs damage and disorders of many body systems, especially of cardiovascular system, respiratory system and digestive system in pigs (Olson et al., 1992 a; 1992 b; Eriksson et al., 1998; Kutzsche et al., 2000; Castegren et al., 2012), sheep (Demling et al., 1986; Godsoe et al., 1988; Warner et al., 1988; Noshima et al., 1993; Foley and Schlafer, 1994; Perkowski et al., 1996; Snapper et al., 1998) and horses (Olson et al., 1985; Fessler et al., 1989; Collatos et al., 1994; Dąbrowska et al., 1995; Oikawa et al., 2004; Tetens et al., 2004). Endotoxins also have an adverse effect on female reproductive functions. Endotoxin can cause numerous changes in the reproductive cycle and can be a reason of spontaneous abortion, as demonstrated in pigs (Cort et al., 1986; Cort and Kindahl, 1990; Kucharski et al., 2002), sheep (O'Brien et al., 1981; Schlafer et al., 1994) and horses (Fredriksson et al., 1986; Daels et al., 1987; 1991; Santschi et al., 1991; Alexander and Irvine, 2002).

Spermatogenic epithelium is sensitive to changes of temperature, mineral deficiency, drugs (anabolic steroids), metals (cadmium, lead), X-rays, dioxins, alcohols and infectious diseases. These factors adversely affect spermatogenesis and may cause a decrease in male fertility. In laboratory animals, endotoxins may induce such signs of impaired fertility. Endotoxemia associated with the release of a number of inflammatory cytokines leads to hypogonadism and decrease in the level of androgens in the blood of male laboratory animals, e.g. IL-1β is a potential inhibitor of testosterone biosynthesis because of its impact on protein synthesis – Steroidogenic Acute Regulator (StAR), and later on steroidogenesis enzymes (an enzymatic complex containing cytochrome P-450 – P450ssc, Cholesterol Side-Chain Cleavage Enzyme – SCC). Acute or prolonged impairment of testosterone production in endotoxemia in mice can therefore lead to disturbances in spermatogenesis, failure of accessory glands and consequently reduced fertility of these animals (Lin et al., 1991; Mauduit et al., 1991; Bosmann et al., 1996; Biswas and Yenugu, 2011; Collodel et al., 2012).

The aim of this review is to discuss the changes in some species of domestic animals and especially boars, rams and stallions, which have been influenced by bacterial endotoxins in experimental studies.

Changes in boars after administration of endotoxin

Various clinical and hematological changes occur in endotoxemia in boars (Wallgren, 1989). Within 30 min. after intravenous administration of *S. typhimurium* endotoxin, temporary restlessness, lameness and tremors have been observed in boars. This led to the development of febrile response, as indicated by a significant increase in rectal temperature reaching a maximum in the third hour after the administration (an increase of 1.6°C to 2.6°C). Boars exposed to LPS also responded by increased heart and respiratory rates and numerous hematological changes, especially leukopenia (Table 1).

In endotoxemia in boars the concentration of prostaglandin metabolite 15-ketodihydro-$PGF_{2\alpha}$ increases and numerous hormonal imbalances occur (Ta-

ble 2). This is reflected in changes in the concentration of gonadotropin, luteinizing hormone (LH) and testosterone (T) in blood plasma. The initial increase in T found in experimental studies in boars was associated with a massive release and discharge of androgen in the circulation. Except for the T release some changes in boar semen quality are observed including the increase in prevalence of many morphological defects of sperm. These changes are an adverse effect of endotoxin on spermatogenic epithelium and on sperm maturation in the epididymis (Wallgren, 1989; Wallgren et al., 1993).

Table 1. Clinical and hematological changes after administration of endotoxin in boars (Wallgren, 1989)

Indicator	The change after administration of LPS
Anxiety	+ ab
Chills	+ ab
Lameness	+ ab
Vomiting	+ a
Rectal temperature	↑ ab
Number of pulse	↑ ab
Number of breaths	↑ ab
Number of white blood cells	↓ ab
Number of neutrophils	↓ ab
Number of lymphocytes	↓ ab

Explanatory note: + – occurrence, ↑– growth, ↓– fall.
a – LPS *S. typhimurium* (2.0 µg/kg b.w.).
b – LPS *S. typhimurium* (2.5 µg/kg b.w.).

Table 2. The concentration of prostaglandin $F_{2\alpha}$, luteinizing hormone and testosterone in blood and semen characteristics after administration of endotoxin in boars (Wallgren, 1989; Wallgren et al., 1993)

Indicator	The change after administration of LPS
$PGF_{2\alpha}$ (BP)	↑ ab
LH (BP)	↑ a (ab-NC)
T (BP)	↑ ab ↓ a
Semen volume	NC ab
Sperm count in ejaculate	NC ab
Motile sperm cells	NC ab
Sperm cells with proximal droplet	↑ a
Sperm cells with coiled tail	↑ ab
Sperm cells with abnormal heads	↑ ab
Sperm cells with bulging nucleus	↑ b

Explanatory note: ↑ – growth, ↓– fall, NC – no changes, BP – blood plasma.
a – LPS *S. typhimurium* (2.0 µg/kg b.w.).
b – LPS *S. typhimurium* (2.5 µg/kg b.w.).

Bacteria-released endotoxin has a negative effect also on the freezability of boar sperm. LPS binds to Toll-like receptor-4 (TLR-4) expressed on the sperm surface, resulting in induction of apoptosis (Okazaki et al., 2010).

Changes in rams after administration of endotoxin

In endotoxemia in rams, as well as in boars, series of behavioural, clinical and hematological changes occur (Wallgren et al., 1989; Sokkar et al., 2003). After an intravenous administration of endotoxin of *E. coli* or *S. typhimurium* lethargy, chills and sometimes diarrhoea were observed in rams. Diarrhoea occurred after the third injection of LPS (at 0.3 μg/kg of body weight at intervals of 12 h and after the 24th hour in the ram which was given a single dose of LPS equal to 3.0 μg/kg of body weight). In these animals, contractions of rumen can occur, which disappears after 12 hours after a single injection and immediately after the third injection of endotoxin. The symptom of febrile response was an increase in rectal temperature (maximum in the 4th-5th hour, after a single dose of endotoxin in the range from 0.4°C to 1.8°C). The next administration of LPS did not result in a substantial increase in rectal temperature. Rams influenced by LPS also responded by increased heart and respiratory rates and a number of hematological changes, among which the most characteristic are leukopenia and neutropenia, with a maximum decrease of neutrophils in the 2nd hour after the administration of endotoxin (Table 3).

Table 3. Clinical and hematological changes after administration of endotoxin in rams (Sokkar et al., 2003; Wallgren et al., 1989)

Indicator	The change after administration of LPS
Apathy/Depression	+ abd
Chills	+ abd
Lack of appetite	+ abcd
Loss of weight	+ d
Diarrhoea	+ ab
Rumen contractions reduction	+ ab (d-ND)
Rectal temperature	↑ abc(d-ND)
Number of pulse	↑ abc(d-ND)
Number of breaths	↑ abc(d-ND)
Number of white blood cells	↓ abcd
Number of neutrophils	↓ abc(d-ND)
Number of lymphocytes	↓ abc (d-ND)

Explanatory note: + – occurrence, ↑ – growth, ↓ – fall, ND – no data.
a – LPS *S. typhimurium* (0.3 μg/kg b.w., every 12 h for 10 days).
b – LPS *S. typhimurium* (3.0 μg/kg b.w.).
c – LPS *S. typhimurium* (0.6 μg/kg b.w., every 24 h for 5 days).
d – LPS *E. coli* (0.6 μg/kg b.w. for 10 days and 6 μg/kg b.w. after 15-day break).

Endotoxemia in these males results in an increase in the concentration of prostaglandin metabolite 15-ketodihydro-$PGF_{2\alpha}$ and numerous hormonal disorders that are

reflected in changes in the concentration of luteinizing hormone (LH) and testosterone (T) in blood plasma (Table 4). Changes in T levels were a result of the original adverse effect of LPS on Leydig cells whereas changes in LH were a secondary effect of disturbances in the production of testosterone. The increase in T found in other studies is connected, according to the author, with a massive release of LH and androgen biosynthesis intensification. In addition to the hormonal imbalance, numerous changes in semen quality are observed in rams, including the increase in prevalence of many morphological sperm abnormalities. Undoubtedly, these changes are a result of an adverse effect of endotoxin on spermatogenic epithelium and sperm maturation in the epididymis (Wallgren et al., 1989; Sokkar et al., 2003).

Table 4. The concentration of prostaglandin $F_{2\alpha}$, luteinizing hormone and testosterone in blood and semen characteristics after administration of endotoxin in rams (Sokkar et al., 2003; Wallgren et al., 1989)

Indicator	The change after administration of LPS
$PGF_{2\alpha}$ (BP)	↑ abc (d-ND)
LH (BP)	↓ abc (d-ND)
T (BP)	↓ abc ↑ d
Semen volume	NC bc (d-ND)
Sperm count in ejaculate	NC bc (d-ND)
Motile sperm cells	↓ abc (d-ND)
Sperm cells with proximal droplet	↑ abcd
Sperm cells with abnormal head	↑ abcd
Sperm cells with damaged acrosome	↑ d
Sperm cells with knobbed acrosome	↑ d
Sperm cells with acrosomal deficiency	↑ d

Explanatory note: ↑ – growth, ↓ – fall, BP – blood plasma, ND – no data, NC – no changes.
a – LPS *S. typhimurium* (0.3 μg/kg b.w., every 12 h for 10 days).
b – LPS *S. typhimurium* (3.0 μg/kg b.w.).
c – LPS *S. typhimurium* (0.6 μg/kg b.w., every 24 h for 5 days).
d – LPS *E. coli* (0.6 μg/kg for 10 days and 6 μg/kg b.w. after 15-day break).

In an *in vitro* study, LPS at concentrations less than its spermicidal effect, changes progressive motility of ram epididymal sperm (Mirshokraei et al., 2010).

Changes in stallions after administration of endotoxin

Many behavioural, clinical, hematological and biochemical changes are observed in endotoxemic stallions (Danek, 2000 a; 2002; 2005; 2006; 2011; Danek, unpublished data). Apathy, recumbency, chills, occasionally loose stools, and increased body temperature are indicative of the stallion's response to endotoxin administration. In stallions the highest temperature increase (an increase of up to 2.3°C) is found in the 4th hour after intravenous administration of a single dose of *Escherichia coli* endotoxin at a dose of 0.3 μg/kg b.w.

The symptom of thermoregulatory disorders in stallions' reproductive organs was an increase of scrotal skin temperature, with the maximum increase (an increase of up to 2.0°C) in the 3rd hour after administration of endotoxin. Another important symptom of endotoxemia was an increase in the pulse rate and the respiratory rate. Changes in these ratios depend on the endotoxin dose. The maximum increase of heartbeat and respiratory rate occurs in the 2nd hour after administration of LPS. Characteristic symptoms of endotoxemia such as leucopenia and neutropenia also occur in stallions after administration of endotoxin. The maximum decrease in the number of neutrophils in the peripheral blood leukocytes appeared in the 1st and 2nd hour respectively after administration of endotoxin (Table 5).

Table 5. Clinical, hematological and biochemical changes after administration of endotoxin in stallions (Danek, 2000 a, 2002; 2005; 2006; 2011; Danek, unpublished data)

Indicator	The change after administration of LPS
Apathy	+ ab
Restlessness	+ b
Chills	+ ab
Sweating	+ ab
Loose stool	+ b
Rectal temperature	↑ ab
Scrotal skin surface temperature	↑ (a-ND) b
Number of pulse/heart beats	↑ ab
Number of breaths	↑ ab
Number of leukocytes/neutrophils in blood	↓ ab
PCV	↑ ab
PLT	↓ (a -ND) b
Fibrinogen (BP)	↑ b
GLU (S)	↑ (a -ND) b
AP (S)	↑ (a -ND) b
LDH (S)	↑ (a-ND) b
Total cholesterol (S)	↓ b

Explanatory note: + – occurrence, ↑ – growth, ↓ – fall, ND – no data, S – serum, BP – blood plasma.
a – LPS *E. coli* (0.05 μg/kg b.w.).
b – LPS *E. coli* (0.3 μg/kg b.w.).

After administration of endotoxin in stallions, numerous disorders occur in biosynthesis of steroid hormones that are released in the circulation and accumulated in blood and semen. This results in the changes in testosterone (T) and estradiol-17β ($E_2\beta$) in serum and stallion seminal plasma (Danek, 2003; 2006; 2011). The administration of endotoxin causes a decrease in testosterone and estradiol-17β in serum at the 6th hour of research and a decrease in T and an increase of $E_2\beta$ in seminal plasma.

Table 6. The concentration of testosterone and estradiol-17β in blood and semen and characteristic of semen after administration of endotoxin in stallions (Danek, 2000 b, 2003, 2006, 2008, 2011)

Indicator	The change after administration of LPS
T(S)	↓ ab
$E_2\beta$ (S)	↓ ab
T (SP)	↓ b
$E_2\beta$ (SP)	↑ b
Motile sperm cells	↓ ab
Concentration of sperm	↓ b
Sperm midpiece with distal droplet	↑ ab
Sperm cells with coiled tails	↑ ab
Sperm cells with loose heads	↑ b
Sperm cells with large heads	↑ b
Sperm cells with small heads	↑ ab
Total protein (SP)	↑ ab
Albumin (SP)	↑ (a-ND) b
Aspartate aminotransferase (SP)	↑ ab

Explanatory note: ↑ – growth, ↓ – fall, S – serum, SP – seminal plasma, ND – no data.
a – LPS *E. coli* (0.05 μg/kg b.w.).
b – LPS *E. coli* (0.3 μg/kg b.w.).

Numerous changes in semen quality (Danek, 2000 b, 2003, 2008) can be also found, including a decline in sperm motility and concentration, an increase in sperm morphological defects (sperm cells with a cytoplasmic drop, sperm with loop with a single switch, loose head, giant sperm) and an increase in total protein concentration, albumin and activity of aspartate aminotransferase (AST) in seminal plasma (Table 6).

Conclusions

The recent studies have presented various effects of bacterial endotoxin in domestic animals. Lipopolysaccharide (LPS) is a strong stimulator of many specific and non-specific organism reactions. The results of current research confirmed that the LPS can initiate a variety of pathophysiological responses in these animals. The reactions to endotoxin in sexually active subjects could be specific. In females, reproductive effects of endotoxemia include alterations in the estrous cycle and inability to maintain pregnancy. In males, numerous disorders occur after administration of endotoxin that affect reproductive functions, especially semen quality (increase in the percentage of spermatozoa with abnormalities).

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