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Bovine Endotoxicosis – Some Aspects of Relevance to Production Diseases. A Review*

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Andersen PH: Bovine Endotoxicosis – some aspects of relevance to production diseases. A review. Acta vet. scand. 2003. Suppl. 98, 141-155. – This review describes some circumstances where endotoxins of Gram negative bacteria may be related to the pathogenesis of some common production diseases. Decisive evidence for the pathogentical role of endotoxins remains scarce, and therefore an interdisciplinary background covering epidemiological, biological, biochemical, clinical and experimental aspects is given.

Several authors have suggested that endotoxins play a significant role for the development of diseases such as laminitis, abomasal displacement, sudden death syndrome of feed-lot steers ect. While the biological, biochemical and clinical pictures of bovine endotoxicosis is quite well known, and certainly may resemble the clinical and biochemical pictures seen in some of the before mentioned diseases, it is however still not clear how or when endotoxins would gain parenteral access. This review describes excerpts of the biology of endotoxins, key clinical signs and the biochemistry associated to these. It is described how ruminal acidosis may facilitate the translocation of endotoxin from the intestinal/ ruminal contents to the portal and eventually the systemic bloodstream. The function of the liver hence becomes central, and the role of hepatic fatty infiltration around parturition is discussed. The review finally suggest that acute ruminal acidosis may be viewed as an analogue to the human syndrome Gut-Derived Infectious Toxic Shock (GITS), where shock is propagated primarily by the translocation of bacterial endotoxin from the gut.

Introduction

It has often been stated that the development of endotoxemia is a significant factor in the pathogenesis of various clinical conditions, from ruminal acidosis and "sudden death syndrome" in feed-lot cattle, to laminitis in dairy cattle, Gram negative infections, shock and death (*Dougherty et al.* 1975, *Boosman et al.* 1991, *Cullor* 1992, *Katholm & Andersen* 1992, *Singh et al.* 1994, *Cullor & Smith* 1996). Decisive evidence for the presence of endotoxemia is relatively scarce, but circumstantial evidence is more common, because in many respects the clinical and biochemical symptoms of bovine endotoxicosis are similar to those observed in various of the production diseases mentioned above.

Failure to detect endotoxins in the blood of clearly sick cows has frustrated many researchers and it has been questioned whether the presence of endotoxemia is necessary for the development of endotoxicosis. It is becoming increasingly evident that the toxicity of endotoxin is caused by the response of the host or-

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ganism, rather than by the properties of endotoxin per se (*Morrison and Ulevitch* 1978, *Green and Adams* 1992).
The classic Koch's postulates state that in order to be recognized as the cause of a disease an organism should consistently be isolated from affected patients, and such, when injected into healthy animals, as to reproduce the relevant disease. Production diseases do not easily satisfy these postulates, and during the 1970s the concept 'one disease - one cause' has therefore been dropped in favour of the term 'multi-factorial disease'.
The role of endotoxin in the development of production diseases should therefore be investigated and discussed with the utmost respect for the complexity and multifactorial nature of this group of cattle diseases.

Production diseases and endotoxemia

Epidemiological investigations have associated high concentrate feeding regimens to production diseases such as laminitis, abomasal displacement, the fatty liver syndrome and "sudden death" of feed-lot steers (*Coppock* 1972, *Coppock* 1974, *Dougherty* 1976, *Nagaraja* 1979, *Hesselholt et al.* 1982, *Gerloff* 1985, *Gerloff et al.* 1986). The very high production of milk and meat in modern production systems is maintained by rations containing large quantities of concentrates which are likely to induce an acidotic ruminal environment (*Dunlop* 1972). The combination of ruminal acidosis and high carbohydrate feeding has often been supposed to play a central role in the pathogenesis of production diseases, because high carbohydrate feeding results in an increased number of Gram-negative bacteria. This again has led to the discovery that ruminal acidosis is associated with a significant increase in ruminal endotoxin concentration (*Dougherty and Cello* 1949, *Nagaraja et al.* 1978, *Nagaraja et al.* 1978, *Andersen et al.* 1994). Endotoxicosis has therefore been believed by several scientists to play a role in the etiology of feeding-related production diseases (*Krogh* 1961, *Dougherty et al.* 1975, *Huber et al.* 1978, *McManus et al.* 1978). However, the precise pathogenetic role of endotoxin in this disease complex has not yet been determined (*Andersen and Jarløv* 1990). This mini review therefore aims at elucidating some of the aspects of relevance to complex of production diseases in cattle.

What is endotoxin?

Endotoxins (s. lipopolysaccharides) are structural parts of the bacterial cell wall and in general comprise three major regions: the side chain, the core polysaccharides and lipid A (Figure 1, modified from *Rietschel* 1996). The side chain differs widely between Gram-negative bacterial strains and will be characteristic of a given bacterial strain. It is composed of repeating units of oligosaccharides; and the type, sequence and linkage of these saccharides determine the antigenic specificity. The side chain is therefore known as 'the O-specific side chain' and is used for serological typing of Gram-negative bacteria (*Rietschel et al.* 1982, *Rietschel* 1996).
Lipid A is a highly conserved structure of the endotoxin molecule. Lipids are attached to a backbone consisting of phosphorylated glucosamine-disaccharides. Only small variations occur among bacterial strains, and most natural and synthetic variants of lipid A possess the endotoxic activity of endotoxin. However, the role of the substructures of endotoxin, such as the inner core (2-keto-3-deoxyoctulosonic acid), the core polysaccharides and the O-antigens is still discussed, because in a variety of ways these components may contribute to the toxicity of lipid A (*Rietschel et al.* 1971, *Lüderitz et al.* 1973).
Administration of endotoxin to cattle in vivo sets off a vast cascade of physiological and

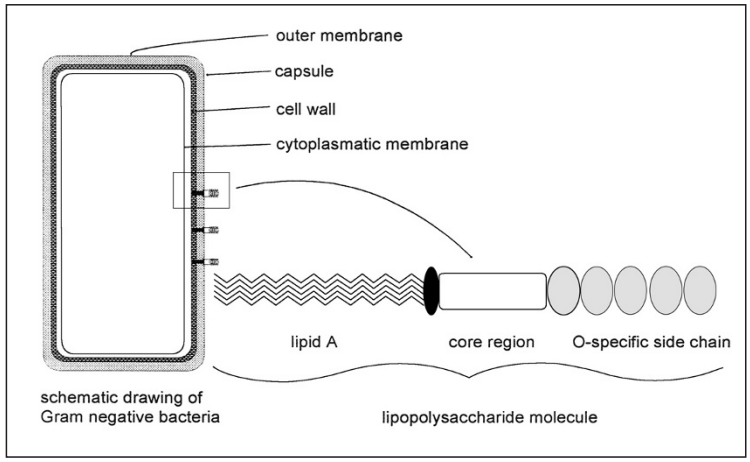

Figure 1. Endotoxins (s. lipopolysaccharides) are structural parts of the bacterial cell wall and in general comprise 3 major regions: the side chain, the core polysaccharides and lipid A (Modified from *Rietschel* 1996).

pathophysiological events, which have been described extensively in the literature (Wray and *Thomlinson* 1972, *Maxie et al.* 1979, *Groothuis et al.* 1981, *Lohuis et al.* 1988, *Lohuis et al.* 1988, *Luthman et al.* 1988, *Cullor* 1992, *Green & Adams* 1992, *Cullor & Smith* 1996).

Clinical signs of endotoxicosis in cattle

Early signs of moderate and severe endotoxicosis are urination, defecation and salivation, which probaly are results of an activation of the sympatico-adrenal response (*Griel et al.* 1975). In the cattle studied, pulse frequencies increased to up to twice the initial rate, and the respiration rate increased 3-4 times, following experimentally induced endotoxicosis. This was interpreted as an early vasoconstrictory response, which eventually results in cold ears and skin. The pulmonary responses in the cow seem to be quite marked in comparison to other species and the bovine lung is probably a target organ for circulating endotoxin (*Templeton et al.* 1988). An explanation for this may be that cattle have more smooth muscles in the pulmonary tree, compared to other species. Smooth muscle cells produce large amounts of prostanoid mediators when stimulated by endotoxin (*Tikoff et al.* 1968). The initial respiratory distress is probably caused by a thromboxane-induced constriction of pulmonary arterioles. From other studies it is known that such episodes are associated with pulmonary hypertension. After 5-10 minutes the respiratory distress ceased, although the respiration rate in some instances may remain elevated for several hours, due to the formation of a pulmonary edema. This formation is probably caused by the liberation of prostacyclin (*Bottoms et al.* 1982, *Hüttemeier et al.* 1982, *Templeton et al.* 1985, *Ward et al.* 1987, *Templeton et al.* 1988). Also low doses of endotoxin which do not result in shock are able to induce hyperventilation, possibly induced by vasoconstriction. Such findings have been described in both bovine and equine studies (*Lavoie et al*. 1990, *Clark et al.* 1991, *Constable et al.* 1991). Ruminal contractions decrease in number and strength and reticulo-ruminal stasis develop, often within 15-30 minutes. Reticulo-ruminal stasis is of particular interest in relation to the pathogenesis of production diseases associated with gastrointestinal atonia, such as displaced abomasum and 'off feed'. The occurrence of reticulo-ruminal stasis is a well known conse-

quence of administration of endotoxin and has been described by several other authors (van *Miert et al.* 1976, *van Miert et al.* 1977, *van Miert et al.* 1978, *Veenendaal et al.* 1980).
The capacity of endotoxins to induce gastro-intestinal atonia has also been demonstrated in other species, e.g. the equine large intestine and cecum (*Clark and Moore* 1989, *King and Gerring* 1991). On the basis of these findings it can be conjectured that endotoxin-induced gastro-intestinal hypomotility might be of significance in the development of bovine indigestion.

Fever

It is a very old observation that the body temperature rises after administration of endotoxin (*Centanni* 1894). This elevated body temperature is a true pyrogenic response, in contrast with hyperthermia. Until the 1950s the word "pyrogen" was almost synonymous with endotoxin. Later, two categories of pyrogens were described: endogenous (EP, LEM, LAF ect.) and exogenous (*Sanderson* 1876, *Bornstein et al.* 1963, *Beisel & Sobocinski* 1980). Most bacteria and toxins act as exogenous pyrogens, whose effect is secondary to an activation of the endogenous pyrogens (*Kluger & Rothenburg* 1980). In the 1980s the endogenous pyrogens were called 'interleukins', and later other cytokines were shown also to act as endogenous pyrogens. In common laboratory animals, small doses of endotoxin induce a monophasic fever response, while moderate to large doses may induce a biphasic fever response (*Dinarello* 1991). The initial fever response, which is due to a direct effect on the thermoregulatory center in the hypothalamus, is believed to have a latency time of approximately one hour. If a second peak occurs, it will appear approximately four hours after the endotoxin administration (*van Miert et al.* 1977, *van Miert et al*. 1978, *Veenendaal et al.* 1980, *Verheijden et al.* 1983, *Lohuis et al.* 1988).

Significantly elevated rectal temperatures is not always observed in the bovine. It seems to be depending on the dose of endotoxin administrered. Very high and very low doses do not elicit a fever response. This might be controversial, because traditionally fever has been a prerequisite for the clinical diagnosis of endotoxicosis. If fever can be absent from the clinical picture of endotoxicosis, the category of feeding-induced disorders is no longer excluded from the group of possible endotoxin related disorders.
When it comes to the lacking pyrogenic effect of the high doses, these findings are supported by those of a few other studies (*Luthman et al.* 1988), in which a dose of 2 µg/kg b.w. endotoxin produced hypothermia and shock. A considerably lower dose (0.25 µg/kg b.w.) did not induce fever. These authors suggested in another study that fever was not the most suitable parameter for the monitoring of endotoxin response in calves (*Luthman et al.* 1989).
Kenison et al. (1991) have reported that 90 kg calves dosed intravenously with 1 µg/ kg b.w. did not attain a well defined fever response.
In conclusion, quite a few reports do not support the contention that fever is a consistent systemic sign of endotoxicosis in cattle. The orchestration of the cytokines involved in the bovine fever response may therefore differ from that of common laboratory animals, in connection with which most such experiments have been conducted. This area needs further investigation, as it could yield important knowledge on the orchestration and timing of the bovine inflammatory response.

The biochemical and hematological response of acute endotoxicosis

Biochemically described, endotoxicosis consists of an initial endocrine-metabolic stress response (hyperglycemia, hyperlactemia and increases in plasma cortisol concentration),

followed by a somewhat dose-dependent response including leukopenia, thrombocytopenia, hypoglycemia and hypozincemia. (See references (*Griel et al.* 1975, *Luthman et al.* 1988, *Cullor* 1992). This second response is a general reaction to a rapid activation of the inflammatory cascade, and is generally referred to as the "acute phase" response.

Leukopenia

Leukopenia is a result of adherence, margination and/or aggregation of granulocytes, platelets and monocytes to endothelial surfaces. The adherence is activated by endotoxin-induced activation of complement but may also happen independently of the complement cascade (*Reece and Wahlstrom* 1973, *Culbertson Jr. & Osburn* 1980, *Deldar et al.* 1984). This effect seem to be somewhat dose related. If the endotoxin dose is small, the leukopenic phase is transient and followed by a later phase of leukocytosis. This is probably due to a release of mature leukocytes from the bone marrow.

Thrombocytopenia

Thrombocytopenia is a result of both aggregation and margination of the blood platelets. The platelets are marginated in the lung and the liver of dog and mouse (*Cicala & Page* 1992, *Endo & Nakamura* 1992). Furthermore, endotoxin initiates an intra-vascular coagulation process, which includes formation of both fibrin and fibrin degradation products (*Morrison & Ulevitch* 1978). This reaction has been related to the Schwartzman reaction and to disseminated intravascular coagulopathy, DIC, (*Thomson et al.* 1974, *Hamilton et al.* 1978, *Buntain* 1980). We did not detect fibrin deposits autopsy in any of our experimental cows, these appears for some, as yet obscure reason, to be rare in cattle, at least at autopsy. *Boosman et al.* (1991) measured various coagulation parameters in cows with experimentally induced endotoxicosis, but observed neither DIC nor clinical signs of laminitis. As was the case for induction of fever, the tendency to achieve clinical signs related to DIC in response to endotoxin seems to vary among species. Most experiments on DIC are conducted in rats, rabbits or dogs, where multiple organ failure as a result of disseminated fibrin thrombosis formation is common. The coagulopathies of cattle in relation to inflammatory response need further investigation.

Hypozincemia

Hypozincemia is a result of the redistribution of zinc from plasma to hepatocytes which occurs in cattle in response to endotoxin and inflammation (*Groothuis et al.* 1981, *Depelchin et al.* 1985, *Luthman et al.* 1988, *Erskine & Bartlett* 1993). Zinc (and also iron) are removed from the circulation and stored in the liver, and this correlates with the induction of metallothionein (*Fukushima et al.* 1988). The response contributes to the non-specific defence of the cow by depleting invading microorganisms of zinc and/or stimulating the production of superoxides in leukocytes; and this has antibacterial effects (*Beisel et al.* 1974, *Kluger* 1979, *Fukushima et al.* 1988, *Sternlieb* 1994).

Acid-base balance

The acid-base balance may be disturbed during the acute phases of endotoxemia: respiratory vasoconstriction causes a respiratory acidosis, which is later accompanied by a metabolic acidosis, such metabolic change being due to hyperlactemia. However, despite respiratory distress, metabolic acidosis was only observed in cases of experimentally induced endotoxicosis in cows suffering from hepatic lipidosis (*Andersen et al.* 1996). This contrasts with findings in horses (*Beadle & Huber* 1977, *Moore et al.* 1981, *Moore & Morris* 1992). Development of metabolic alkalosis displayed a much more

consistent pattern, probably due to hypochloremia caused by chloride trapping in the atonic upper gastro-intestinal tract. This pattern is compatible with acid-base determinations in blood from naturally occurring cases of coliform mastitis (*Katholm & Andersen* 1992).

Serum calcium concentrations

Serum calcium concentrations are also affected by endotoxicosis. It has been suggested that low plasma calcium is an important contributing factor in the development of gastro-intestinal hypotonia and disorders of multifactorial etiology, such as displaced abomasum (*Coppock* 1974). The total calcium concentration in plasma of normal cows ranges between 2.4 and 3.1 mmol/l (*Kaneko* 1980), and 2 mmol/l is considered the lower limit of a normal calcium concentration. Decreases to concentrations below this limit are currently associated with signs of hypocalcemia (*Waage & Hansen* 1993). Total calcium concentration may decrease to below 2 mmol/l in experimental endotoxicosis. This accords with findings of other investigators (*Reece & Wahlstrom* 1973, *Fredricksson* 1984, *Fredricksson et al.* 1984, *Andersen* 1985, *Luthman et al.* 1989). Inconclusive attempts to relate some cases of milk fever to endotoxicosis have been made (*Aiumlamai et al.* 1992). Also, in natural occurring cases of coliform mastitis, calcium concentration is generally low (*Katholm & Andersen* 1992). Low calcium concentration could be an effect of the absorption of gastro-intestinal endotoxin. Fat tissue is also mobilized around parturition. Marked lipolysis has been associated with the induction of hypocalcemia, because during this process calcium is relocated to the adipocytes. However, endotoxicosis (0.2 µg/kg) in 5 calves produced neither significant lipolysis nor hypocalcemia (*Luthman & Bengtsson* 1989).

Besides these classic biochemical alterations, a wide range of other biochemical and clinicochemical parameters may change as endotoxicosis progresses. These parameters are indicators of cell damage (e.g. enzyme leaks), altered hepatic metabolism (during acute phase reaction) and DIC.

Mediators of endotoxicosis

The clinical and biochemical signs mentioned above are inititated, orchestrated and either limited or propagated by cellular mediators. Such mediators are directed at protecting the host and eliminating the endotoxin. Many fine reviews are given on mediators of endotoxicosis, the follwing section will highlight only a few points related to production diseases.

Eicosanoids and reticulo-ruminal hypomotility

The prostaglandins, and especially the PgE's, affect the tonus and motility of the gastrointestinal tract. In goats, systemic administration of these prostaglandins induces, among other effects, hypomotility and diarrhoea (*Veenendaal et al.* 1980) and cessation of ruminal contractions (*van Miert et al.* 1977). Many common systemic diseases in farm cows (e.g. coliform mastitis and endometritis) are associated with stasis or hypomotility of the forestomachs (*Lohuis et al.* 1988). PGE_2 has been supposed to mediate this response, because the intracerebroventricular administration of PGE_2 induces cessation of ruminal contractions in goats (*van Miert et al.* 1983). Pre-treatment with non-steroidal anti-inflammatory drugs did not totally abolish the inhibition of ruminal motility. The effects on reticuloruminal stasis of other mediators of inflammation, such as catecholamines, kinin, serotonin and histamin (*Ahrens* 1967, *van Miert* 1971, *Koers et al.* 1976, *Veenendaal* 1979) have also been investigated, but the significance of these mediators in the development of the clinical signs of ruminal acidosis seems unclear (*Ahrens* 1967, *van Miert et al.* 1976, *Gravert et*

al. 1986). A study by *Vlaminck et al.* (1985) indicated that administration of endotoxin to healthy cows may induce a delay and a decrease in the emptying of the abomasum, besides the induction of reticulo-ruminal stasis. Endotoxin may then play a role also in the pathogenesis of displaced abomasum.

Traditionally, the ocurrence of fever has been closely associated with reticulo-ruminal hypomotility (*van Miert* 1979), but it is important to notice that dysfunction of the forestomach may occur independently of the occurrence of fever. A study in cattle showed that forestomach motility decreased before the plasma PGE_2 concentration increased (Eades, 1993). This may in part be explained by the fact that PGE_2 may also be produced and act locally in the gastrointestinal muscles. Also prostacyclin may reduce motility. If these prostaglandins were produced locally in the ruminal wall, measurable plasma concentrations might be detected later when a spill-over from the local production had occurred. The prostaglandin liberation would be sufficient for local activity at the production site long before plasma concentrations exceeded the base-line values. Portal vein plasma concentrations of prostaglandin mediators (*Andersen et al.* 1994) were larger than the corresponding mediator concentration in peripheral blood, rendering some support to that point of view.

Cytokines

Alterations of cytokine concentrations are well described as a consequence of endotoxicosis (*Maury* 1986, *Feist et al.* 1989, *Adams et al.* 1990, *Young* 1990, *Kenison et al.* 1991, *Gerros et al.* 1993). Besides participating in inflammatory cascades, the cytokines have profound effects on metabolism and immunity (*Zentella et al.* 1990). This is fascinating when seen in the perspective of the pathogenesis of production diseases.

During inflammation, the liver acutely (i.e. within few hours) increases the production of acute phase proteins, such as haptoglobin, a1-acid glycoprotein, α1-protease inhibitor, fibrinogen, ceruloplasmin and amyloid A, at the expense of synthesis of for example albumin (*Conner et al.* 1986, *Eckersall & Conner* 1988). This shift in protein synthesis is initially mediated by IL-1 and TNF, and then amplified by a second wave of IL-1 and IL-6, synthesized by fibroblasts and endothelial cells (*Conner et al.* 1989. *Dofferhoff et al.* 1990. *Fey et al.* 1994). Glucocorticoids are involved in the synthesis of plasma acute phase proteins in the liver. Glucocorticoids are also potent down-regulators of pro-inflammatory cytokines and inhibit expression of their cellular receptors (*Fantuzzi & Ghezzi* 1993). It might therefore be worth noting that we still don't know if a high cortisol level is a sign of a sufficient defense mechanism, or of detrimental stress.

Tolerance to endotoxin

Tolerance occurs if a cow is exposed to endotoxin in sublethal doses, either repeatedly or continuously, for a period of time (*Beeson* 1947, *Milner* 1973). Endotoxin tolerance is a transient stage of hyporesponsiveness during which the biological responses to endotoxin are diminished or absent. After tolerance is induced, endotoxin administered in even lethal doses does not elicit detrimental biological responses.

The nature of tolerance is not yet fully understood. Several processes are involved: induction of a self-limiting inflammatory process, a raised immune function and increased production of mediators (*Kimmings et al.* 1996). Tolerance is traditionally divided into 'early' and 'late' tolerance (*Greisman et al.* 1969, *Milner* 1973). The early phase occurs within a few hours of the challenge, is transient and nonspecific regarding to type of endotoxin, is not asso-

ciated with the occurrence of anti-endotoxin antibodies, and cannot be transferred with plasma. The mechanisms of the early phase are complex, involving production of acute phase proteins which bind endotoxin, induction of endotoxin receptor blockage, and alterations of the macrophage activity (Henricson et al., 1990). The priming endotoxin stimulus may lead to a production of immature monocytes, with only few active receptors available. The endotoxin challenge may also induce the production of anti-inflammatory serum factors, such as IL-10, type I and II soluble TNF receptors or cortisol, which downregulate the endotoxin response (*Kimmings et al.* 1996).

In cows, the significance of the early hyporesponsive stage remains to be thoroughly described. Thorough description of this stage may be imperative in the understanding of the individual cow's ability to create a response to endotoxin and perhaps other diseases.

The late phase occurs after days of repeated endotoxin administration.This form of tolerance lasts for longer and is related both to the development of antibodies to the O-chain, and (probably) the production of antibodies to the endotoxin common core, specifically to lipid A. As the O-chain has a great variability and as the common core is a very constant part of the endotoxin molecule, antibodies against lipid A have a greater cross protective effect than antibodies directed against the O-chain. Danish cows do have antibodies to lipid A in varying amounts, showing that endotoxicosis is not an uncommon finding among cattle (Andersen et al. 1996).

Liver function in cattle

It is generally agreed that endotoxins are not contaminants of systemic blood in healthy individuals and that impairment of liver function may result in systemic endotoxemia in otherwise healthy humans (*Bjørneboe et al.* 1972, *Prytz et al.* 1973). This seems to be the case for ruminants too.

The liver is an effective barrier to the passage of bacteria and endotoxin from the intestine (*Nolan* 1975, *Munford* 1978). Human investigators have focussed on the role of endotoxin in the development of liver disease, while the problem in cattle seems to be that the detoxificatory function of the liver is critical in the prevention of dissemination of the inflammatory response induced by intestinal endotoxin.

Bovine liver function may decrease in the period around calving, due to triglyceride accumulation in the hepatocytes, hepatic lipidosis. Hepatic lipidosis has been associated with poor performance and increased occurrence of disease. The condition may be quite frequent in high-yielding dairy cows, where the dry cows are fed high-energy rations and/or are overconditioned at partum (*Reid* 1980, *Reid & Roberts* 1983, *Gerloff* 1985, *Gerloff et al.* 1986, *West* 1990).

Hepatic lipidosis is associated with a decreased capacity for endotoxin clearance in the liver, as demonstrated by *Andersen et al.* (1996a), where endotoxin was administered to cows with spontaneously developed subclinical fatty liver. There was a marked increase in the time it took for endotoxin to disappear from plasma. In the human clinic, alcoholic fatty liver and cirrhosis are associated with an increase in the concentration of antibodies against intestinal bacteria, such as E. coli, and the patients have an increased frequency of endotoxemia (*Bjørneboe et al.* 1972, *Prytz et al.* 1973, *Prytz et al.* 1976). A similar association may occur in cows with hepatic lipidosis. Whether hepatic lipidosis, together with concurrently increased exposure to gastro-intestinal endotoxins, is responsible for observed increases in the concentration of antibodies to the common core of endotoxins (*Andersen et al.* 1996b) cannot be determined. However, the investigation supports the view

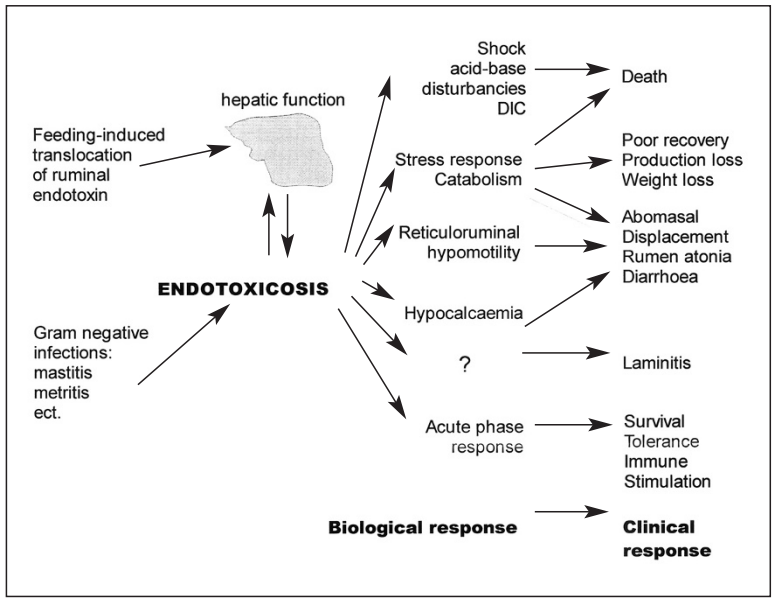

Figure 2. Proposed relationships between route of endotoxin exposure, hepatic function, biological reponse and clinical response in bovine endotoxicossis.

that endotoxin is quite commonly implicated in the pathophysiology of bovine diseases.

Also, the ability of the liver to initiate an acute phase response seems to be very important. The liver should be able to react to cytokine stimulation from e.g. portal endotoxicosis and switch from production of "household" proteins to production of acute phase reactants (*Fey et al.* 1994). The influence of hepatic lipidosis on the acute phase responses has yet to bee investigated in the cow.

Evidence of endotoxin translocation in Danish dairy herds

Screening of the natural occurrence of IgG antibodies to lipid A in Danish cattle has demonstrated that this part of the endotoxin molecule is a common challenge to the immune system (*Andersen et al.* 1996b). Exposure to endotoxin is therefore obviously a relatively common feature among Danish cattle; and it was shown that the presence of antibodies recognizing lipid A was epidemiologically related both to the occurrence of diseases which were of an infectious nature, such as mastitis and reproductive disorders, and to the occurrence of digestive disorders. Further studies are needed in order to elucidate whether translocation of endotoxin from the gastrointestinal tract may result in increased levels of antibodies to endotoxin, and how this would relate to health and productivity.

GITS in cattle

This review indicates a relationship between a common subtype of septic shock, GITS (Gut-Derived Infectious-Toxic Shock, described in the human clinic by *Lebek & Cottier* 1992), and the endotoxicosis described in ruminal acidosis. In GITS the bacterial invasion is assumed to stem from the intestinal microflora. A generalized infection is not a prerequisite for GITS and the disorder is predominantly propagated by bacterial endotoxin.

Conclusion

Ruminal acidosis is a common and central production disease. This disease may increase the translocation of endotoxin from the gastro-intestinal contents to the systemic circulation. Some cows may handle this challenge well, while others may suffer from a generalized endotoxin induces inflammatory response, which includes decreased motility of the forestomachs, leukopenia, hypocalemia and other characteristic derangements. The capacity of the immune system, including the clearance capacity of the liver, play important roles in the defense of endotoxin mediated diseases. A summary of the the proposed relationship between endotoxicosis and production diseases is given in figure 2.

Understanding of the part played by endotoxin in the pathogenesis of ruminal acidosis may form the basis of new therapies, aiming both at correction of the metabolic disorder and at modulating the systemic aseptic inflammation induced by endotoxin.

The causative factors involved in the individual variations in susceptibility to endotoxin and experimentally induced ruminal acidosis need further investigation. It is possible that the cytokine network, which regulates the acute phase response and the early inflammatory response, is involved in the regulation of the bovine reaction to metabolic stress, tissue mobilisation and immune competence in the early post-partum period.

Investigation of these interrelationships may provide a basis for the identification of indicators of health which can be used in future screenings both for herd-health and genetically determined conditions.

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