

Sub-Acute Ruminant Acidosis and non-structural carbohydrates: a study model in nutritional immunology^x

Acidosis Ruminant Sub-Aguda y carbohidratos no estructurales: un modelo de estudio en inmunología nutricional

Acidose ruminant subaguda e carbohidratos não estruturais: um modelo de estudo em imunologia nutricional

Luis Miguel Gómez ^{1,2,3}, MVZ, MSc, cPhD, Sandra Lucía Posada ², Zoot, MSc, PhD, Martha Olivera ³, MV, Dr. Sci. Agr ^{3*}

**Corresponding author: Martha.olivera@udea.edu.co. Profesora Titular, Facultad de Ciencias Agrarias, Universidad de Antioquia, AA 1226, Medellín, Colombia*

¹ Departamento de Investigación y Desarrollo, Grupo Nutri-Solla, Empresa Solla S.A. Carrera 42 No. 33-80 Itagui, Colombia. ² Grupo de Investigación en Ciencias Agrarias-GRICA, Facultad de Ciencias Agrarias, Universidad de Antioquia UdeA, Calle 70 No. 52-21, AA 1226, Medellín, Colombia. ³ Grupo de Investigación Biogénesis, Facultad de Ciencias Agrarias, Universidad de Antioquia UdeA, Calle 70 No. 52-21, AA 1226, Medellín, Colombia.

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Abstract

Nutritional immunology combines two areas of knowledge that did not interact until recently. One of the best examples studied to date is the bovine rumen. The symbiotic relationship between the host and rumen microorganisms can be altered causing a breakdown of immunological tolerance and imbalance of animal homeostasis. Dietary inclusion of supplements rich in non-structural carbohydrates is required for high yielding cows to meet their energy requirements. However, the use of those diets can lead to substantial changes in the rumen ecosystem, reducing the pH and promoting the development of subacute rumen acidosis. This generates lysis of gram-negative bacteria, release of lipopolysaccharides, breaking of immune tolerance, and activation of a cascade of inflammatory mediators with systemic effects that affect milk yield and quality. The gastrointestinal tract is the most important place where lipopolysaccharides are produced and its translocation mechanism from the rumen to peripheral circulation is still controversial. This review proposes a biological model integrating nutritional and immunological aspects of production, absorption, and mechanisms of action of lipopolysaccharides and its effects on milk production and compositional quality.

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Key words

Immunogens, lipopolysaccharides, nonstructural carbohydrates, nutritional immunology, SARA.

Resumen

La inmunología nutricional combina dos áreas del conocimiento que no interactuaban hasta hace algunos años. Uno de los mejores ejemplos estudiados hasta la fecha lo constituye el rumen bovino. La relación simbiótica entre hospedero y microorganismos ruminales puede alterarse provocando una ruptura de la tolerancia inmunológica y un desequilibrio en la homeostasis del animal. Para cubrir los requerimientos energéticos de las vacas de alta producción lechera es necesario incluir en la alimentación suplementos de elevado contenido en carbohidratos no estructurales. Sin embargo, el uso de estas dietas puede provocar cambios sustanciales en el ecosistema ruminal, disminuyendo el pH y promoviendo el desarrollo de acidosis ruminal subaguda. Esto genera la lisis celular de las bacterias gram negativas, la liberación de lipopolisacáridos, la ruptura de la tolerancia inmunológica y la activación de una cascada de mediadores inflamatorios que tienen consecuencias sistémicas y afectan el rendimiento productivo del animal y la calidad composicional de la leche. El tracto gastrointestinal es el lugar más importante donde se producen los lipopolisacáridos, pero el mecanismo de translocación del rumen a la circulación periférica es aún controversial. En esta revisión de literatura se propone un modelo biológico que integra aspectos nutricionales e inmunológicos relacionados con la producción, absorción y mecanismos de acción de los lipopolisacáridos y los efectos sobre la producción y la calidad composicional de la leche.

Palabras clave

Carbohidratos no estructurales, inmunógenos, inmunología nutricional, lipopolisacáridos, SARA.

Resumo

A imunologia nutricional combina duas áreas de conhecimento que não interagem até alguns anos atrás. Um dos melhores exemplos estudados até o presente consiste no rúmen bovino. A relação simbiótica entre hospedeiro e microrganismos do rúmen pode ser alterada causando uma quebra da tolerância imune e um desequilíbrio na homeostase do animal. Para satisfazer as necessidades energéticas de vacas de alta produção leiteira é necessário fornecer suplementos alimentares de elevado conteúdo em carboidratos não estruturais. No entanto, o uso dessas dietas pode provocar alterações importantes no ecossistema ruminal, reduzindo o pH e promovendo o desenvolvimento de acidose ruminal subaguda. Isto gera a lise de bactérias gram-negativas, a liberação de lipopolissacarídeos, a quebra da tolerância imune e a ativação de uma cascata de mediadores inflamatórios que têm efeitos sistêmicos e afetam o desempenho produtivo do animal e a composição do leite. O trato gastrointestinal é o lugar mais importante na produção dos lipopolissacarídeos, mas o mecanismo de translocação do rúmen para a circulação periférica é ainda controversa. Nesta revisão de literatura se propõe um modelo biológico que integra aspectos nutricionais e imunológicos relacionados com a produção, absorção e mecanismos de ação de os lipopolissacarídeos e os efeitos sobre a produção e composição do leite.

Palavras-chave

Dieta das aves domestica, galinhas especializadas na produção de ovos, fosforo, vitamina D.

Introduction

The study of the interactions between nutrition and immunology provides a new perspective beyond the maximum performance, especially from the point of view of animal health and its consequences in longevity. In dairy cattle, there is a well-known example of this (relationship between non-structural carbohydrate and sub-acute ruminal acidosis) which can break the homeostasis with underlying economic consequences affecting the net profit. According to this, the study of the mechanisms by which nutrition components affects immune status, provide new insight into the nutritional management of dairy cow due to the immune system requires higher amounts of energy for its functioning that could be rechanneled into milk yield.

Nutritional immunology is an interdisciplinary field that has made possible the interaction of different specialties which traditionally do research independently. Such science focuses on the study of underlying mechanisms of the immune response modulation by active components supplied through the feedstuff. Thanks to this new discipline, new mechanisms of action, different from nutritional ones, have been discovered, such as the conjugated linoleic acid (CLA), linolenic acid, resveratrol and E, A, and D vitamins³⁷. Besides, new explanations have been found to modulate the immune response and therefore the health status of animals with diet-derived compounds²⁶.

The bovine rumen is a representative example of the host-microorganism symbiosis that might be altered causing a breakdown in immunological tolerance, leading to imbalance in homeostasis. Therefore, there is an interest in the study of such interaction to understand the immune-pathological mechanisms by which the host takes effective action against some immunogens generated after the feedstuff with high amounts of NSC, causing substantial changes in the ruminal ecosystem by decreasing rumen pH and developing Sub-Acute Ruminant Acidosis (SARA)^{17,27}.

SARA is characterized by favoring proliferation of negative gram bacteria (i.e *Escherichia coli*) over positive gram bacteria which, once dead in the gastrointestinal tract, releases endotoxin such as lipopolysaccharides (LPS)³⁸. However, the translocation mechanism of the LPS from the rumen to the peripheral circulation is still controversial and it seems that it would not be through the ruminal papillae but through the gut. LPS are immunogens classified as pathogen associated molecular patterns (PAMPs) which are able to stimulate pattern recognition receptors (PRR) of the innate immune system. Once the interaction PAMPs-PRR takes place, immunological tolerance is broken and molecular production is started with important local and systemic implications¹.

Non-structural carbohydrates (NSC) and sub-acute ruminal acidosis (SARA)

70% to 80% of dairy cows' diet are Carbohydrates⁴²; from which NSC (compounds of plants containing simple sugar or those more complex like starch) are the most used in Livestock. The main source of supplement in dairy cows is grains, as they are an effective-cost option of digestive energy to fulfill the high requirements of dairy cows that forages cannot meet⁴⁴. Feedstuffs with nutritionally dense diets increase the amount of volatile fatty acids and lactic acid in the rumen, which exceeds its absorption capacity and therefore the buffer power of the animal organism^{30,51}. The combination of these factors creates a decrease in the ruminal pH for long periods during the day (pH <5,6 for more than 3 hours) creating SARA. This sub-clinic acidosis affects dry matter intake, milk yield, ruminal microflora, and digestion; it may cause diarrhea, damage in the mucosa of the gastrointestinal tract, laminitis and liver abscesses in dairy cows^{30,41,51}.

Production and translocation of endotoxin in dairy cows

There are three theories about the translocation of endotoxins to the circulation. The first is directly through the rumen mucosa; the second is in the gut; and the third by specific transporters. The ruminal epithelium is a stratified squamous type with four strata: basale, spinosum, granulosum, and corneum⁵⁰. The stratum basale is the cell layer adjacent to the basale lamina (that is in contact with the circulation) with a substantial amount of mitochondria and other organelles. The next strata are the spinosum and granulosum which do not have a clearly defined division. The epithelium loses mitochondria and evenness as stratum advances. Strata spinosum and granulosum contribute to most metabolic functions of tissues (i.e ketogenesis) and they are the reservoir of cells with the highest participation in energetic metabolism of the animal⁷.

In the stratum granulosum, cells have tight junctions mediated by desmosomes (cell structures remaining attached to neighboring cells) that act as a diffusion barrier in the rumen wall. The cells in the stratum corneum, the outermost, are characterized because they have lost most of the organelles, although the presence of keratin is increased, allowing it to work as a natural barrier and becoming an innate defense mechanism in the rumen. The number of cells of the stratum corneum is highly dependent on the composition of the diet²⁰. Animals fed with diets high in concentrated reduce the ruminal pH and increase rate propionate-acetate and the molar proportions of butyrate, which results in a thick corneal layer with more than 15 cell layers. In the case of animals fed with diets high in forage, the stratum corneum consists of just 4 cell layers²⁰. Therefore, as stratum corneum layers advance from the outside inward, the integrity of desmosomes is missing and cells without such joints are seen. Tight junctions or occludens areas, which form an impermeable barrier, are located in the middle layers (strata granulosum and spinosum) and not in the outer layers or corneal layers²⁴.

The major source of endotoxin in dairy cows is the gastrointestinal tract, which contains a high amount of gram negative bacteria, especially when diets include high amounts of NSC, resulting in a potential source of LPS when entering to the organism through the

gastrointestinal tract³⁸. Accordingly, the most important factor that increases the concentration of LPS in the rumen fluid, in the first third of lactation, is the abrupt shift to energetically denser diets at the beginning of lactation^{2, 17, 27}. LPS are subsequently released to the rumen fluid during lysis of gram negative bacteria. Several studies have shown that when the concentration of LPS in the lumen of the gastrointestinal tract increases after a diet rich in NSC or by oral administration⁶ these are translocated into the systemic circulation^{17, 27} (Figure 1). Such translocation leads to a failure in the permeability of the ruminal epithelium caused by high osmolality (the total number of particles of solute in a solvent kg) creating inflammation and rupture of the ruminal papillae³⁰.

Other studies have shown that the translocation of LPS from the gut to the peripheral circulation increases due to the inflammation of the intestinal epithelium, together with an excessive production of cytokines and tissue destruction, causing an increase in the enteric permeability^{6, 14}.

In vitro experiments have shown that endotoxins are transported from the gastrointestinal tract into the peripheral circulation, in particular through the ruminal wall at a greater speed than in the colon wall but at pH acids, increasing 5 to 6 times permeability through the colon and ruminal tissues and allowing the passage of large molecules¹⁶.

Despite the evidence of LPS passing from the rumen and gut into the blood, the precise place of translocation is still controversial. There is no direct evidence that the LPS free from rumen and subsequent to SARA move through the ruminal walls into the bloodstream. It is also difficult to explain from the anatomical point of view because of the multilayer structure of the ruminal epithelium⁷. In the study *in vitro* of Emmanuel *et al.*¹⁶ it was demonstrated LPS pass through the rumen wall at pH 5.5. However, the LPS concentrations added to mucosal tissues were 500 µg/ml, one dose 50 times greater than the free LPS in the rumen when it is induced with SARA grain-based diet^{17, 27}. This could have caused a disruption in the structure and a failure in the barrier of the rumen epithelium, which is unlikely to happen with concentrations close to the physiological state³⁴.

In order to know the site of ruminal endotoxin absorption, a study was carried out in steers and *Escherichia coli*

endotoxin were administered directly into their rumen labeled with ^{51}Cr ^{4, 33}. These studies showed that none of the steers experienced absorption through the lymph (thoracic duct) or blood (portal vein) or forage based-diets or diets with high inclusion of grains or acidosis itself. Khafipour *et al.* ²⁸ showed that there was no correlation between the concentration of LPS in the rumen, the

severity of SARA and the degree of inflammation in lactating Holstein dairy cattle. According to the above evidence, the rumen may be impermeable to endotoxins in physiological conditions, unless it suffers a considerable injury in the tissue integrity. Therefore, it is possible that the translocation of LPS occurs primarily from the gut.

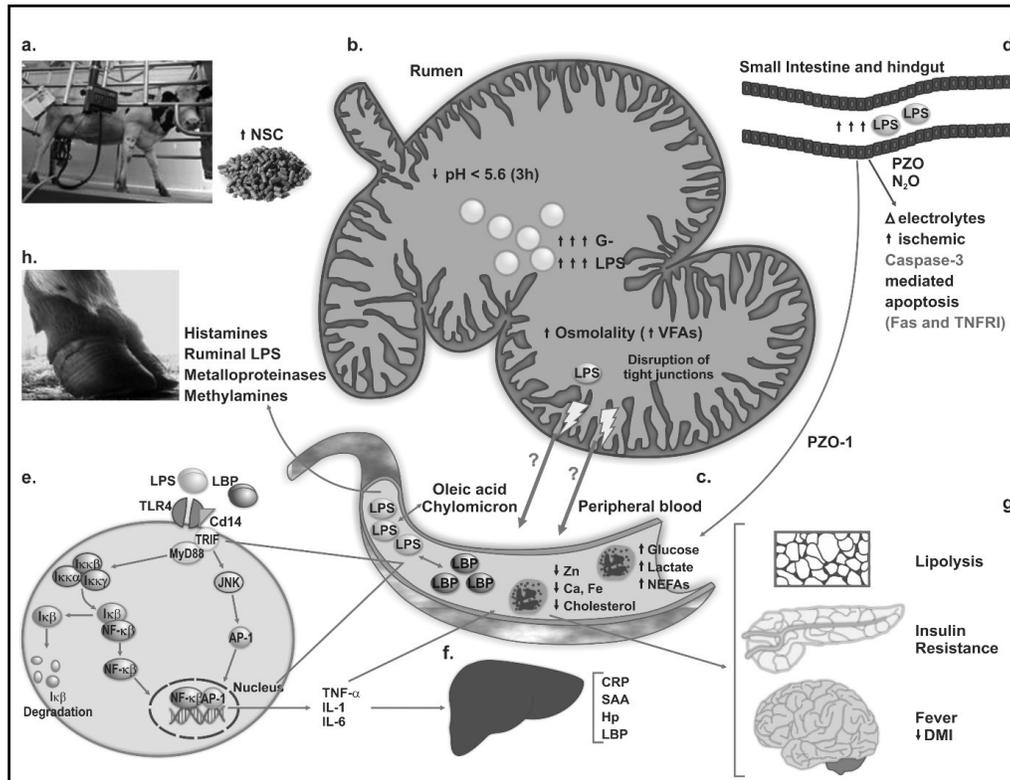


Figure 1. SARA Effects on rumen health and its systemic effects. **a.** SARA is preceded by consumption of a high amount of non-structural carbohydrates (NSCs) at specific times of day (during the milking). **b.** Once NSCs are fermented in the rumen, they are transformed into volatile fatty acids (VFA) which cause a decrease in pH to 5.6 levels for at least 3 continuous hours (SARA diagnostic criteria). This stimulates the production of gram negative bacteria, which die and release their cell wall components such as endotoxin, being lipopolysaccharides (LPS) the most representative. **c.** So far it is controversial whether the permanent effect of low pH and high osmolality may cause the breakdown of proteins of tight junctions (PZO) of ruminal epithelium which has a complex histological structure. **d.** In the intestine, in addition to LPS coming from the rumen, new LPS are also produced with effects over intestinal epithelial cells. These in turn respond with the release of nitric oxide, promoting the permeability and absorption of LPS to the periphery. Furthermore, the apoptosis of these cells is activated by caspase-3. **e.** Once in circulation, either through the rumen or intestinal, LPS are attached to acute phase reactants (APR) as the binding protein of LPS which are transported to the liver where the macrophage hepatic or cell Kupfer are detected by the Toll like receptor 4 (TLR-4) and co-receptor CD14. This union creates a cascade of signals which ends in the activation of the transcription factor NFκB, traveling from cytoplasm to promoting zones of genes encoding for pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6. **f.** Cytokines stimulate hepatocyte to produce APR as haptoglobin, serum amyloid A, C reactive protein, among others. **g.** APR have systemic effects such as lipolysis in adipose tissue, insensitivity to insulin in pancreas, fever and decrease of dry matter intake. **h.** Laminitis may come as a result of SARA, for which four major causes have been proposed: production of histamines, LPS in rumen, matrix Metalloproteinases, and methylamines.

The theory on which LPS pass through the gut is based on the fact that the intestinal epithelial of the bovine is a monolayer structure with tight junctions at the apical pole of the cell⁴⁷. Chin *et al.*¹³ showed that an abnormal concentration of endotoxin in the intestinal lumen induced cell apoptosis, as a result, disruption of the tight junctions, specifically in the ZO-1 protein was initiated; the production of nitric oxide was increased, causing increased mucosal permeability and blood flow with influx of inflammatory cells into the area. Another study showed that the enterocyte regulatory system was altered in presence of LPS through the inhibition of proton pump under extracellular acidotic conditions, which resulted in a cytoplasmic acidification and alteration in cellular function¹².

The rumen is an immense source of LPS, when present in the gut, many of them are excreted through the bile salts¹⁰; the remaining ones are displaced into the circulation. A small proportion of LPS consistently occurs in the gut for which immune tolerance in the host is developed, alleviating some of the responses resulting from the acute phase of inflammation². In this case the production of LPS is independent from pH but dependent on starches that are not degraded in the rumen. The overshoot of starches that reach the ileum and large intestine causes a change in the populations of micro-organisms and consequently an increase in the release occurs in the posterior tract of LPS⁵³. Finally, SARA is an entity which triggers the production of LPS because of the death of gram negative bacteria (due to the decrease in ruminal pH for three or more hours) subsequent to a diet rich in NSC, even though the translocation mechanism of LPS from either the rumen or the gut into the circulation is controversial³.

The latest theory is that the LPS use transcellular and paracellular mechanisms by Toll- receptor 4 type (TLR-4)⁴⁰. Furthermore, Goshal *et al.*²² showed that LPS can be transported into the blood by mechanisms provided by long chain fatty acids like oleic acid and formation of chylomicron from intestinal epithelial cells. The arrival of LPS into the systemic circulation, triggers the production of acute phase reactants (APR) of inflammation, such as the lipopolysaccharide binding protein (LBP), serum amyloid A (SAA), the C-reactive protein (CRP), and the haptoglobin (Hp), which stimulate the macrophages or hepatic Kupffer cells and other phagocytic cells mediated by the TLR-4 the release of pro-inflammatory cytokines such as the tumor necrosis factor alpha (TNF- α), the interleukin 1 (IL-1 β) and IL-6¹⁷. The APRs are generated as response

of the animal to disturbances in the homeostasis caused by infection, tissue injury, neoplastic growth or immunological disorders¹⁹. The APR are responsible for carrying out the functions of systemic response, providing energy and substrates for defense against pathogens, preventing the transfer of metabolites needed for them and limiting and helping repair the damage of the infected tissue¹⁹.

LBP function is to facilitate the removal of endotoxins from blood, either by carrying them to the macrophages when they are in low concentration or transporting with lipoprotein of high density²¹. The Hp is macromolecular protein binding hemoglobin which occurs during acute inflammation⁵⁴. SAA is an apolipoprotein which is associated with high density lipoproteins during the acute response. Both HP and SAA are highly sensitive in bovine³⁶. The CRP is part of the innate immune system and belongs to the family of pentraxins. Its main function is to bind to phosphocholine, allowing the recognition of pathogens or phospholipid constituents of damaged cells after an inflammatory process. It also can activate the complement system and phagocytic cells⁵⁶.

During the acute phase response, the pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6 lead to changes in the stability of the mitochondria in various tissues, thereby affecting the animal metabolic profiles¹⁵. One example is the important relationship between the glucose levels in blood and liver, which are regulated according to the needs of the immune system cells. In moderate inflammation, there is an increase in the uptake of glucose into these cells, generating a stimulus for hepatic glucose production and a corresponding increase in blood glucose. However, with a more intense acute response, there is a marked increase in plasma glucose levels¹⁵.

Changes have also been described in the profile of minerals and other metabolites in dairy cows during inflammatory states such as SARA. Zebeli *et al.*⁵⁷ demonstrated an inverse association between plasma levels of Ca, Fe, cholesterol and consumption of barley diet beyond 45% dry matter. This study showed a positive relationship with lactate. Such alterations generate clues about the effects endotoxins may be generating in the host. For example, cholesterol is the main precursor for the synthesis of bile acids; thus the decrease at high grain diets could be associated with the need to increase bile secretions to detoxify high amounts of endotoxins

present in the gastrointestinal tract¹¹. Plasma Ca has been involved in the detoxifying capability of endotoxin in the host, decreasing their detoxifying capacity when there are high concentrations of the mineral⁴⁶. Fe is an important mineral for the growing of microorganisms which is transferred from the peripheral blood to the reticular endothelial system, limiting both its availability and growth. Lactatemia is reported to be caused by an enhanced glycogenolysis and a reduced capacity of the extrahepatic tissues to utilize lactate⁴⁹.

Laminitis has a strong relationship with SARA and immunogens generated by the ingestion of high grain diets. Four key molecules have been involved in the development of laminitis. The first is histamine, the second are endotoxins, the third are metalloproteinases and the fourth are methylamines. One of the most controversial is histamine because Goth²³ injected histamine in cows and they did not develop any type of laminitis. One of the reasons for this result is the rapid degradation of histamine in the gastrointestinal tract, which do not occur with endotoxin or metalloproteinases. It is important to note that the metalloproteinases are enzymes activated by cell wall components of gram positive bacteria such as lipoteichoic acid (LTA). In a study in dairy cows, a vaccine was designed for oral administration only against *Escherichia coli* LPS or concomitantly with the blocking of LTA. When it was administered only against LPS, there was a decrease in the incidence of laminitis, and when blockers LPS and LTA were mixed, a greater decrease in incidence of laminitis was demonstrated². A diet based on high percentages of grain increases in number concentration of methylamine in rumen²; when passing from the rumen to circulation it may cause damage in blood vessels in the hoof of cow through free radicals such as formaldehyde, hydrogen peroxide, and ammonia via amino oxidase sensitive to semi-carbazide⁵⁵.

Endotoxins and mammary gland

Although there are no exact details on how LPS and mediators of the inflammation of fat production affect milk, it is speculated that this effect may be explained by the release of cytokines such as TNF- α and IL-1 β , produced by the macrophage and released into the circulation of the blood⁵². Based on the analysis of the literature the following model was built (Figure 2).

Several studies have suggested that intraperitoneal infusion of LPS or the administration of TNF- α or IL-1 β

in peripheral blood reduces lipogenesis in mammary gland of lactating rats^{5,35}. Also, it has shown that TNF- α inhibit the activity of lipoprotein lipase (LPL), a key enzyme in the release of glycerol and non-esterified fatty acids (NEFAs), limiting the supply of circulating lipids available for its metabolism in mammary gland⁵.

Additionally it has been reported that some mediators generated by LPS inhibit the activity of key enzymes involved in de novo synthesis of fatty acids such as fatty acid synthase and acetyl-CoA carboxylase^{35, 43}. In this sense, some APR as CRP, are involved in lipid metabolism²⁹. Several studies have shown that administration of LPS affects the VLDL secretion with a marked dose-dependent effect. That is, at low doses of LPS the VLDL increases, whereas at higher doses, the removal rate of VLDL decreases¹⁸. CRP is increased because of the presence of LPS from the rumen, which is also associated with VLDL (Figure 2). In cows, VLDL is the primary source of triglycerides which are then transferred to the mammary gland cells⁹. Approximately 50% of fatty acids in ruminant milk are derived from blood triglycerides⁹.

During lactation there is an increase in LPL activity of mammary tissue with a decrease in LPL of adipose tissue²⁵. The association between CRP and VLDL is a defense mechanism of the host to prevent activation of LPL by apoC-II during inflammatory states and reduce the removal of triglyceride-rich lipoproteins such as VLDL. In other words, the host keeps fat synthesis in the mammary gland to have it available to defend itself against an attack. This is evidenced by Barcia and Harris⁸, who showed that triglyceride-rich lipoproteins are attached to LPS, promoting a protective response against LPS-induced toxicity and modulating the response of the host against bacterial toxins.

The effect of SARA on parameters like the milk protein is not yet clear, however, some changes occurring therein are due to an increase in digestible organic matter in the rumen that enhance the synthesis of microbial protein³⁹. Few studies have demonstrated a decrease in protein of milk in cows with SARA. Stone⁵¹ evaluated 500 cows that had suffered SARA and whose rumen pH increased through diet. In response to an apparent pH recovery, milk production increased by 2.7 kg/day; fat, and protein in 0.3 and 0.1 percentage points. Another study in dairy cows showed that both the production and the fat content decreased in response to an increase in

the amount of grains in the diet and their corresponding activation of the inflammatory response²⁷. According to some authors, there is a negative correlation between the content, production and production adjusted at 3.5% fat in milk and CRP levels in cows fed with incremental levels of barley grains (0%, 15%, 30% and 45%)⁵⁶. This same study reported a positive relationship between

milk production and incremental levels of barley. While incremental levels of barley were associated with milk production, the energy efficiency of the same (calculated as the amount of milk fat per kg of dry matter intake) decreased 26% compared to cows that received 0% of barley.

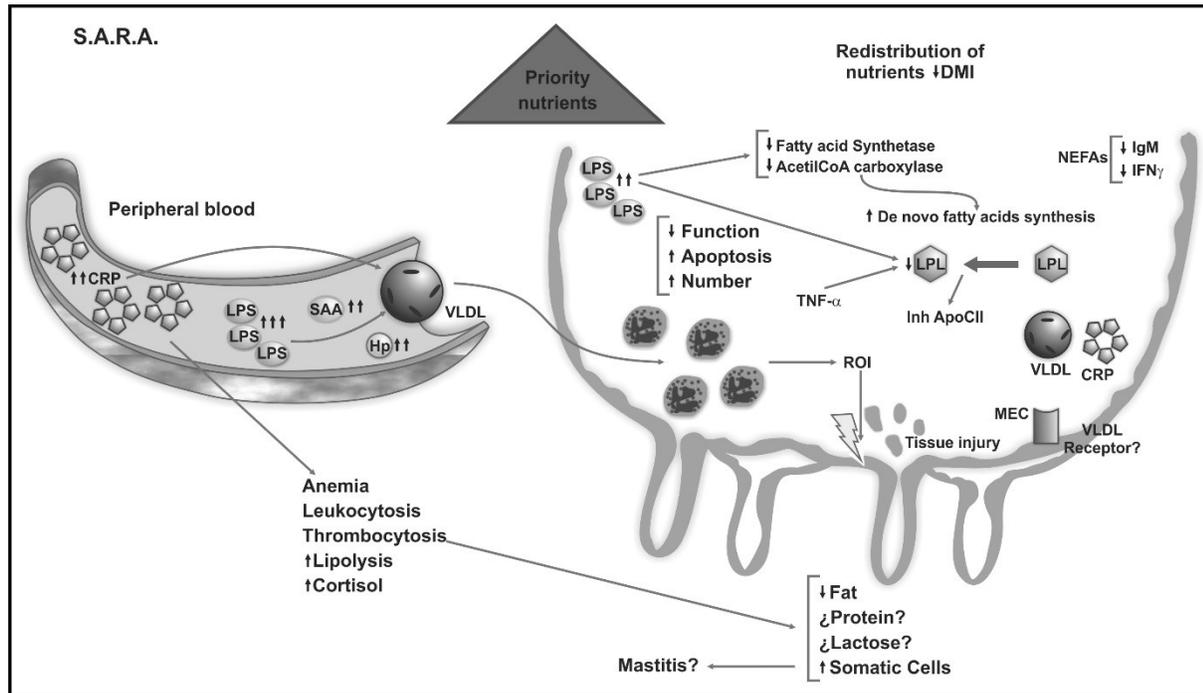


Figure 2. Effects of SARA in mammary gland. Once the LPS are located in periphery, they generate the production of APR with local and systemic effects (i.e., mammary gland). Systemic effects include anemia, leukocytosis, thrombocytosis, increased lipolysis and cortisol. Mammary gland immediately changes its synthesis priorities of milk components (fat, protein and lactose) to nutrients reserve so that the immune system defends itself from the stimulus that is attacking it. LPS are transported by VLDL which have direct effect on some enzymes (synthase of fatty acids, acetylCoA, carboxylase and LPL) synthesizing de novo fatty acids of milk, which would explain, in part, the fat reduction in animals with SARA. Non-esterified fatty acids (NEFAs) modulate the activity of polymorphonuclears (PMNs) and cause a decrease in the production of IgM and IFN γ . The PMNs begin phagocytic activity with subsequent generation of oxygen free radicals causing tissue damage in mammary epithelial cells, which may explain in part an increase in somatic cell counts of milk. However, its effect is confused because the association of diseases such as SARA and Mastitis is frequent. APR and pro-inflammatory cytokines within the mammary gland are responsible for the hipofagia and tissue lipolysis at the central level.

A study in France in cows with SARA showed an association with both somatic cell counts and indicators of the negative energy balance (i.e. NEFAs). That relationship grew twice when comparing cows at risk of SARA from moderate to high (based on the protein fat ratio)⁴⁵. The explanation could be that the NEFAs have been associated with the regulation of some functions of the bovine PMNs, in particular with an increase in the respiratory burst associated with phagocytosis, reduction in cell viability and a marked increase in necrosis. Paradoxically, the NEFAs showed no effect on apoptosis^{32, 48}. It is clear that a relationship exists between lipomobilization, levels in plasma NEFAs and modulation of the bovine PMNs functions. However, more studies are needed to help understand the mechanisms by which this relationship occurs because it is not clear so far.

Concluding remarks

The intake of diets high in NSCs and development of SARA in dairy cows are well known from the perspective of animal nutrition. However, during this condition PAMPs molecules type are generated (e.g. LPS) which have the ability to activate the immune system generating impacts both locally and systemically. Recently, a new discipline has been growing, known as nutritional immunology, which has allowed understanding the cause and effect relationship between nutrients and the production of immune system molecules capable of altering homeostasis, animal welfare and the productive performance. The gastrointestinal tract is the most important source of PAMPs production in ruminants. However, the anatomical site in which the translocation occurs, for subsequently joining their respective receptors (receptors of the immune system such as TLRs) and then generating bioactive molecules (APRs and cytokines), is a fundamental and also controversial issue. So far, there is a greater biological plausibility (including histological structure) in which this translocation occurs from the gut and not from the rumen. The binding of PAMPs with their respective receptors triggers a number of responses mediated by APR in the host that explain, at least in part, SARA symptomatology such as the decline in dry matter intake, alteration in compositional quality of milk, the decrease in digestibility of the fiber, among others.

During the acute phase of inflammation, proinflammatory cytokines with systemic effect are also generated, which

causes a greater energetic consumption by limiting the amount of energy available for production and maintenance functions. Locally, vaso-active molecules with inflammatory capacity are produced, generating other symptomatology like laminitis. In the mammary gland there are alterations in nutrient availability, causing several changes, among them, the compositional quality of milk. The study of the immunological basis of SARA pathophysiology, together with a deep nutritional knowledge, will make possible to understand more integrally the role of each of its molecules and the impact on both the severity and prognosis of the disease. It will also allow developing new feedstuff strategies to improve host's homeostasis, animal welfare, and performance.

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