Genomics of subacute ruminal acidosis

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SUMMARY

The present review will present the most recent development in sub-acute ruminal acidosis (SARA) regarding high concentrate diet and its interaction on gene expression. The SARA is a common disorder in high producing ruminants. In addition SARA is a big challenge for ruminant nutritionists, therefore, the subject has been extensively studied in recent decades. In current decade nutrigenomic has been used to understand the cellular response influenced by high concentrate diet in ruminants. For sustainability of higher growth and production, animals are forced to feed on high concentrate and low fiber in diet. High concentrate diet leads to accumulation of higher concentration of VFA consequently ruminal pH decreases. Depression in pH for longer duration impairs ruminal epithelium tight junctions and hyperkeratosis. SARA is characterized by fewer tight junctions between cells, thinner cell layers, and an increased sloughing of the stratum corneum leading to a weakened permeability barrier. Ruminal epithelium serves as barrier for microbes, damages to ruminal epithelium leads to translocation of lipopolysaccharides (LPS) from compromised ruminal epithelium to blood circulation and different organs of the body. The LPS induce immunogenic response in ruminal papillae, epithelium, liver, and other organs. LPS induce a cascade mechanism of gene expression by binding with Toll-like receptor 4 (TLR4) a receptor for LPS, binding of LPS with TLR4 activate nuclear factor kappa B (NF-κB) consequently genes for interleukin 6 (IL), IL-8, tumor necrosis factor (TNF)-α and many more genes were up regulated or down regulated in rumen epithelium and other organs. In conclusion feeding high concentrate diets to ruminants' triggered local and systemic inflammation response at molecular level. By exploring the mechanism of SARA and its effects on gene up regulation or down regulation can be a value able tools for understanding the SARA and its adverse effects on animal health and production performance.

KEY WORDS

Gene expression, High concentrate, rumen epithelium, SARA, TLR-4.

INTRODUCTION

Nutrigenomics is an emerging science that is based on combination of two major sciences, nutrition and genomics. The study of the interaction of nutrients or other dietary bioactive substances at molecular level or gene expression[1,2]. Nutrition or nutrients have direct influence on organism at molecular level. The science of nutrigenomics tells us which type of nutrients we have consumed in past, by changing the gene expression level of certain genes. What we eat or feed to animals it is a message to an organism's body. By learning the language or message that is given by nutrients we can control the genetic expression of desirable genes[3]. Nutrigenomics is an emerging field of research in animals and holds great potential to improve health and productivity[4,5]. In current decades animal nutritionists are trying to find alternative ways to explore the potential of diets and animals by evaluating the gene expression in response to various diets. To the best of author knowledge there is not a single review paper published in this area. The purpose of this review is to summarize the high concentrate diet and its effects on gene expression in rumen epithelium, liver, uterus and mammary gland.

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SUBACUTE RUMINAL ACIDOSIS

In intensive ruminant production system for the sustainability of high production provision of highly fermentable carbohydrates in the form of cereal grains is common practice[6]. Due to highly fermentable diets, production of SCFA increases, absorption and lower buffering capacity lead to accumulation of SCFA, consequently lower ruminal pH. Ruminal pH <5.6 for 180 m/days is considered as a threshold level for SARA[7,8]. The rumen is the first organ that is influenced by low ruminal pH. Depression in ruminal pH leads to induction of certain changes in the ruminal epithelium and compromises the epithelium integrity[9]. Additionally, depression in pH for long-term induces parakeratosis and hyperkeratosis[10], consequently invasion of pathogenic microbes into portal vein drainage results into liver abscess and other diseases[11]. Lower ruminal pH or in case of SARA, lysis of gram-negative bacteria increases, consequently lipopolysaccharide (LPS) an endotoxin are free to translocate through damaged ruminal wall[12,13]. Lipopolysaccharide is a strong inflammatory inducer that can elicit inflammatory responses[14]. There is certain inflammatory response are induced during inflammation e.g Toll-like receptor 4 (TLR4) a receptor for LPS, binding of LPS with TLR4 activate nuclear factor kappa B (NF-kB) consequently genes for interleukin 6 (IL), IL-8, tumor necrosis factor (TNF)-α up regulated at inflammation site[15]. In current decade it is well established that SCFA has direct effects on gene expression in intestinal tissue[16].

BUTYRIC ACID AS NUTRIGENOMIC

In ruminants, butyrate is the preferred energy source for stomach wall and plays a major role in energy metabolism. Ruminants utilize 70% of butyrate as energy sources for stomach wall, monogastric hindgut also utilizes butyrate as a major energy source[17]. In dairy cows, butyrate is one of the short-chain fatty acids which is extensively studied as nutrigenomics. Butyrate upregulates a large number of gene expression involved in rumen development, cell cycle arrest and immune response[18]. Butyrate is also considered as histone deacetylase inhibitor drug that can inhibit cell proliferation and cell apoptosis[19] and play a role as antitumorigenic[20]. In a recent study, it is reported that relative expression of IL-1β, IL-8, IL-10 up-regulated in high concentrate (HC) diet in goats fed concentrate to forage ratio 60:40, whereas those supplemented with sodium butyrate IL-1β, IL-8, IL-10 were similar to those fed low concentrate (LC). Toll-like receptor-4 were similar in LC and those supplements with sodium butyrate with HC. Relative gene expression of matrix metalloproteinase-2 (MMP) and MMP-9 tight junction degrading enzymes were also higher in HC as compared to LC and those supplemented with sodium butyrate with HC. Down-regulation of MMP-2, MMP-9, IL-1β, IL-8, and IL-10 by supplementation of sodium butyrate can be helpful to ameliorate the adverse effects of the HC diet in ruminant[21]. In another experiment rumen gene expression was evaluated in dairy cow in which butyric acid was supplemented 2.5% of DM. In this experiment differential expression of 1191 genes were indicated by microarray, forty-nine of 1191 were differentially expressed (Table 1) by qRT-PCR. Out of 49, nine genes were up-regulated, 20 down regulated and 20 were unaffected by supplementation of butyrate[22].

HIGH CONCENTRATE, SARA AND ITS EFFECTS ON RUMEN EPITHELIUM AND GENE EXPRESSION

Rumen epithelium is stratified squamous epithelium, which is further divided into four distinct strata. From the luminal surface the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale. Each stratified layer performs a specific function and serves as syncytium[23]. After stratified corneum and stratified granulosum cells are connected with each other with the help of tight junctions. Tight junction proteins are multifunctional protein complex, there are more than 40 tight junction proteins, and the principal function of these proteins is to prevent leakage[24]. Claudin-1 and zonula occluden-1 are the two principle tight junction proteins[23]. In ruminal epithelium these two tight cell junction proteins form a barrier that prevents the translocation of larger molecules, pathogenic microbes[25] and LPS[26]. Expression of tight cell junction proteins were evaluated in goats fed HC diet, Expression of mRNA for claudin-4, occludin, ZO-1 were down regulated in HC fed goats. However, the expression of claudin-1 gene was up regulated. Results revealed that the HC diet has profound effects on the ruminal epithelium. Expression of IL-1, IL-6, and IL-10 were similar in HC and hay fed goats, while TNF-α and IFN-γ were up regulated in HC fed goats. There is a positive correlation in mRNA expression between claudin-1 and IFN-γ. While claudin-4 negatively correlated with TNF-γ[27].

Highly fermentable carbohydrates have an influence on rumen papillae size, consequently more surface area for absorption of SCFA[28]. The molecular signaling mechanism is not completely understood. However, IGF-1 is thought to be the candidate gene responsible for rumen epithelium growth proliferation[29]. Cascade mechanisms of IGF-1 can be modulated by IGF-binding proteins[30]. Modulation of IGF-1 mechanism also observed in transition cows fed the HC diet. In this experiment expression of mRNA for IGFBP5 up-regulated, whereas, IGFBP3 and IGFBP6 were downregulated[9].

Toll-like receptors are a group of receptors identified in monogastric gut tissue[31]. However, the presence of TLR-1-10 also confirmed in dairy calves, TLR recognizes the differential pathogenic-host immune interaction and trigger the immunogenic response[32]. A recent experiment in goats fed HC diet mRNA expression of TLR2, TLR3 and TLR5 were up regulated in rumen epithelial tissue. However, the relative expression of TLR4 was not affected by diet or low ruminal pH[33]. On the contrary, several other studies reported the up regulation of TLR-4 mRNA expression[21,34,37]. Variation in the relative expression of TRL-4 may be associated with different location of sample collection or change in diet, because diet causes a shift in the bacterial population, shifting of the bacterial population may induce differential expression of TLR in different studies[33].

SARA AND LIVER GENE EXPRESSION

Translocation of LPS from ruminal fluid to the bloodstream during SARA[38] activates the immune response which is stimulated by recognition of LPS from TLR-4 receptor[39]. TLR-4 is a receptor for LPS, expression of TLR-4 was higher in those fed HC[21,36]. TLR4 is known to initiate a signal transduction mechanism consequently NF-kB activated[15] and orchestrates of a pool of acute-phase proteins synthesis initiated[40]. Nuclear factor-kappa B is the most important transcription factor which is responsible for the production of pro-inflammatory cytokines and chemokines, such as TNFα, IL-1, and IL-6. These chemokines and cytokines travel to the liver through bloodstream induce pathological changes in the liver[41] and up regulate the expression of acute-phase protein (AAP) mRNA[36] consequently the production of APP increase[41].

In a recent study expression of IL-10, IL-8, CCL5 and CCL20 in the liver were higher by 5, 11, 21 and 3 fold respectively in HC fed goats as compared to those fed LC. Expression of liver protein for primary pro inflammatory cytokines IL-1β, IL-6, TNFα was also higher in HC as compared to those fed LC diet. Expression of mRNA for APP, serum amyloid A3 (SAA), haptoglobin and lipopolysaccharide-binding protein was up regulated by 44, 29 and 8 fold respectively in HC fed goats as compared to those fed LC[36].

The expression of immune genes in the liver in response to SARA is strengthened by a recent study. In this experiment mRNA expression of inflammatory mediators IL-1α, IL-1β, and TNF-α higher in HC fed dairy cow by 3 folds, IL-6 expression was higher by 47 fold. Acute-phase proteins such as LBP, SAA3, and HP expression were higher by 10.32, 8.64, and 3.97-fold respectively[37]. Serum amyloid A is a high-den-

Table 1 - Expression of genes in various studies during subacute ruminal acidosis.

Observations	Rumen pH	Gene	Reference
Up regulation in those fed HC		IL-1β, IL-8, IL-10, TNF-α, TLR-4, MMP-2, MMP-9, MPO, CD68	Dai et al., 2017
Down regulation in those treated with sodium butyrate with HC		IL-1β, IL-8, IL-10, TNF-α, MMP-2, MMP-9, MPO	Dai et al., 2017
Up regulation HC diet (40:60 Concentrate: Forage)	pH <5.6 for >180 m/day	TRAF6, NF-κB, p38, MAPK, extracellular regulated protein kinases MAPK, IL-1 and SAA	Guo et al., 2017
Not influenced by experimental diet	pH <5.6 for >180 m/day	TLR-4	Guo et al., 2017
Up regulation in histamine treated	5.5	TNF-α, IL-6, and IL-1β	Sun et al., 2017
Up regulation in HC	<5.8 for >3 h	TLR4, IL6, 1β, MyD88, TRAF6 and NF-κB	Bilal et al., 2017
Down regulation in HC supplemented with sodium butyrate	<5.8 for >3 h	TLR4, MyD88, TRAF-6, NF-κB, IL-1β and IL-6	Bilal et al., 2017
Up regulation in HC		IL-1β, IL-2, IL-22, CCL19, CCL8, CX3CR1, CXCL6, INHBE, LEPR, PRL, and TNFRSF9	Zhang et al., 2016
Up regulation in HC	<5.6 for 223 min/day	TLR4, MyD88, TRAF-6, NF-κB, TNF-α, IL-8, IL-1β and LBP	Bilal et al., 2016
Up regulated in HC		TLR4, LBP, IL-1A, IL-1B, IL-6, TNF-α, IL-8, IL-10, CCL5, CCL20, SAA3	Chang et al., 2015
Up regulated in HC fed goats	5.33	Claudin-1, TNF-α, IFN-γ	Liu et., 2013
Down regulated in HC fed goats	5.33	Claudin-4, occludin, ZO-1	Liu et., 2013
Not influenced by HC or LC	5.33	IL-1, IL-6, and IL-10	Liu et., 2013
Up regulated in HC	<5.8 from 2 to 6 h	P45017α, 3β-HSD, HP and SAA	Jia et., al 2014
Up regulated in butyrate (2.5% DM) supplemented	5.67	LCN2, MMP1, MUC16, GPX2, CSTA, FUT1 SERPINE2, BCAM, RAC3	Dionissopoulos et al., 2013
Down regulated in butyrate (2.5% DM) supplemented	5.67	MTOR, AKIRIN2, NFKBIZ, ACVR2A, LAMB1, FRS2, PPARD NFKB2, LBP, NEDD4L, SGK1, DEDD2, MAP3K8, PARD6B, PLIN2, ADA, HPGD, FMO5, BMP6, TCHH	Dionissopoulos et al., 2013
Unaffected in butyrate (2.5% DM) supplemented and control treatment	5.67	CD14/TLR4/LY96, EGF, EGFR, ERK1/2, Fgf, Fgfr, FN1, IGFBP7, IL10, LY96, MIF, MLST8, NFKB1, PTGS1, PTGS2, SMAD1, STAT6, TGFB1I1, TLR4, TNFRSF6B	Dionissopoulos et al., 2013
Up regulation in HC fed goats	pH <5.6 for >180 m/day	TLR-4, IL-8, IL-10, CCL5, CCL20, HP, SAA3, LBP, IL-1β, IL-6, TNFα	Chang et al., 2015
Up regulation in HC fed dairy cow	pH <5.6 for >180 m/day	LAP, TNF-α, IL-8, IL-1β and IL-6	Jin et al., 2016
Up regulation in HC fed goats		TLR-2,TLR-3, TLR-5	Liu et al., 2015

sity lipoprotein which is responsible for migration of neutrophils and monocytes at the site of inflammation, HP binds with free hemoglobin released from damaged erythrocytes and serves as anti-inflammatory agent, while LBP form complex with LPS in blood or extracellular fluid facilitate the neutralization of LPS consequently initiate the release of inflammatory mediators, Such as TNF-α, IL-6 and IL-1β[42,43]. Relative expression of TLR-4 was not influenced by HC diet (40:60 Concentrate: Forage), In this experiment expression of TLR-4 was slightly lower in HC fed dairy cows as compared to those fed LC diet[34]. On the contrary several studies reported higher mRNA expression for TLR-4[21,35,36], lower expression of mRNA for TLR-4 may be associated with clearance of LPS from the liver into intestine along with bile secretion, subsequently, hypo responsiveness of liver cells to LPS makes it possible lower level of expression of TLR-4[44]. However, mRNA expression TNF receptor-associated factor 6 (TRAF6), NF-κB, p38, mitogen activated protein kinase (MAPK), extracellular regulated protein kinases (ERK) MAPK was higher in HC treatment. Similarly, the relative ge-

ne expression of IL-1 and SARA was higher in HC fed cows. By keeping in view the above-mentioned studies, it can be concluded that translocation of LPS during SARA induce pathological damages to liver cells, impairment of certain liver function, up regulation or down regulation of hepatic immune genes expression and activation of inflammatory signaling pathways[34].

SARA AND ITS EFFECTS ON OTHER ORGANS

Mammary gland

Translocation of LPS induces a systematic inflammatory response and a cascade of gene expression activated in different organs of the body[41]. In a recent study, mammary gene expression was evaluated in dairy cow fed HC and LC with concentrate to forage ratio (60:40, 40:60) respectively. Expression of mRNA showed that lingual antimicrobial peptide (LAP), TNF-α, IL-8, IL-1β and IL-6 were up regulated in HC as compared to those fed LC. In this experiment, NF-κB was not affected by the HC diet. So, provision of HC for long-term not only has adverse effects on rumen epithelium, instead of translocation of rumen derived LPS from the rumen to bloodstream also initiate the synthesis of LAP synthesis via the NF-kB signaling pathway in mammary glands of lactating cows[45].

Histone 3 acetylation is involved in DNA replication, transcription, repair, and various cellular functions, cell proliferation is also facilitated by histone acetylation[46,47]. A high concentrate diet induces epigenetic changes in mammary tissue. Histone 3 acetylation was lower in dairy cows fed HC as compared to those fed LC. Lower concentration of histone 3 acetylation in mammary tissue may be associated with a higher concentration of LPS, However, the exact mechanism is not completely explored further research is warranted to identify the LPS mediated depression of histone acetylation[48].

Uterus

Similarly, in a recent study, it is evaluated that SARA had adverse effects on uterus gene expression. In this experiment TLR4, MyD88, TRAF-6, NF-κB, TNF-α, IL-8, IL-1β and LBP were up regulated in HC (40:60, Forage: Concentrate respectively). In conclusion, the authors stated that long-term provision of the HC diet causes a uterine inflammatory response in mid lactating dairy cows[35]. Similarly, expression of the uterine genes were also observed in goats fed HC. In this experiment TLR4, IL6, 1β, MyD88, TRAF-6 and NF-κB were up regulated in the HC group[49]. Adverse effects of SARA on rumen pH and uterine gene expression ameliorated by supplementation of sodium butyrate in lactating goat by similar authors in another work. Expression of mRNA of TLR4, MyD88, TRAF-6, NF-κB, IL-1β and IL-6 were lower in those supplemented sodium butyrate with HC as compared to those fed HC only[50]. Lower expression of mRNA for proinflammatory cytokines were associated with anti-inflammatory properties of sodium butyrate[51]. Another possible explanation is that sodium butyrate plays a role as a buffering agent in the rumen and increases ruminal pH[52]. Inflammatory response from uterine tissue may be associated with higher concentration LPS in the bloodstream of HC fed animals as compared to those fed LC[45].

Adrenal gland

It is a proven fact that there is a strong relationship between immune response and stress. Studies have shown that LPS activates the hypothalamic pituitary adrenal axis (HPA) in dairy cows[53]. Similarly, sheep injected with IL-6 stimulated secretion of cortisol and corticotropin hormone into peripheral circulating system. Secretion of cortisol and corticotropin indicating a cross-talk of the immune system and the HPA axis[54]. Relative gene expression of P45017α and 3β-HSD in the adrenal cortex were up regulated in SARA goats fed HC (60:40, Concentrate: Forage) as compared to those fed LC[43]. For the synthesis of cortisol, cytochrome P450 catalyzes the conversion of cholesterol to form pregnenolone[55]. Another key regulatory step for cortisol synthesis is the conversion of pregnenolone to form progesterone and catalyzing the conversion of 17-hydroxypregnenolone to 17-hydroxyprogesterone, which is catalyzed by 3β-HSD[56].

HISTAMINE AS A SIGNALING MOLECULE

Depression in ruminal pH induces a lytic process of bacteria which produce LPS and histamine, histamine is considered to be a potent inducer of rumenitis in SARA. A high concentration of histamine in ruminal fluid during SARA induce pathophysiological changes in the ruminal wall, therefore availability of energy becomes limited to animals[57]. Histamine is a potent inflammatory mediator, by doing so it works as a signaling molecule for up regulation of inflammatory cytokines[58]. The nuclear factor-κB (NF-κB) plays an important role in the regulation of inflammatory pro mediator gene expression[59]. Recently a study conducted to evaluate the relative gene expression in female Holstein cow for TNF-α, IL-6, and IL-1β, histamine treated group showed a higher level of mRNA expression for these inflammatory mediators as compare to control bovine ruminal epithelial cells[60].

SARA AND ITS RELATION WITH LAMINITIS

Laminitis, an aseptic inflammation of the dermal layers inside the hoof, one of the leading causes of lameness in dairy cows at commercial dairy farms[62]. Laminitis has been associated with many factors like traumatic, floor, bedding[63], diet and feeding management specifically with acute and subacute ruminal acidosis[64]. However, the pathophysiological relationship between SARA and laminitis is still unclear[65]. Subacute ruminal acidosis could be one of the reasons for the onset of laminitis in high producing animals[66,67]. One of the proposed relationships is damaged epithelium may permit the absorption of various vasoactive substances such as histamine, biogenic amines and LPS. Translocation of vasoactive substances damages to the capillaries of the lamellae in the foot and causing hemorrhage, inflammation and lameness[65,68]. On the contrary, in dairy cattle LPS increased in rumen rather than peripheral blood circulation in grain induced SARA[69], which disagrees with[65,68]. Another hypothesis has found that matrix metalloproteinase could break the junction of corium and horn in equine[70]. So far, this hypothesis has not been reproduced in dairy cows.

CONCLUSIONS

Keeping in view the above-mentioned studies it can be concluded that a high concentrate diet induces SARA. Depression in pH impairs the epithelial tight junctions consequently translocation of LPS occurs. Lipopolysaccharide activates the cascade mechanism and immunogenic expression of genes involved in the inflammatory process. The rumen is the first organ affected by low ruminal pH, however, liver, uterus, mammary gland and adrenal gland also affected by SARA. Relative gene expression in the rumen or other organs helps to understand the molecular mechanism responsible for SARA.

DECLARATION OF INTEREST

Author declare no conflict of interest.

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