Nutrition, Metabolic Diseases and Immunity in Dairy Cows

G.H. Wentink[1,2], V.P.M.G. Rutten[3], Th. Wensing[2]
[1]Holland Genetics, P.O. Box 5073, 6802 EB Arnhem, The Netherlands
[2]Department of Large Animal Medicine, Veterinary Faculty Utrecht, The Netherlands
[3]Department of Infectious Diseases and Immunology, Veterinary Faculty Utrecht, The Netherlands

Abstract

In this short review attention is focused on the occurrence of metabolic diseases in combination with disturbances of the immunologic response. Epidemiological surveys in cows suffering from hepatic lipidosis indicate an increased percentage of aspecific infectious diseases. Few experiments have been described in which immunoreactivity in cows with spontaneous or induced metabolic diseases were studied.

The results reported in these studies indeed strongly suggest impairment of the immune response in metabolic diseases, but do not indicate a causative relationship between metabolism and immunity.

Introduction

Nowadays daily milk production levels of about 45 liters during 50 consecutive days are no exception. In the Netherlands top class heifers produce 35 liters of milk a day in the first 100 days of lactation. Energy demands are enormous for these animals.

For a marathon runner the energy demand is about 3 times the maintenance level but the energy requirement for a cow producing 45 liters of milk daily is about 4 times maintenance level. And a cow maintains this level of milk production during at least 50 days. **The modern cow should be considered as a top athlete.**

The increased milk production increases the risk for metabolic disturbances when energy demands and energy supply do not fit.[4,24,26]

Clinical or subclinical metabolic disturbances frequently are associated with infections caused by common pathogens suggesting increased susceptibility or impaired aspecific or specific defense mechanisms.[6,8,15,16,23] These data are mainly derived from epidemiological surveys. Only a few experiments have been done.

Metabolic disturbances may affect the immune response either directly by altering the metabolism of immunocompetent cells or indirectly by the influence of metabolic substances on these cells. Alterations of the stability or integrity of cell membranes, of the expression of cell receptors and adhesion molecules, or even of lymphocyte subpopulations in the peripheral blood can be provoked.[1,20,21]

In this short review attention will be focused on the relation between metabolic imbalances during the first few weeks after parturition on the one side and the immune response on the other.

Immune system

In figure 1 a short outline of the immune system is presented.[22]

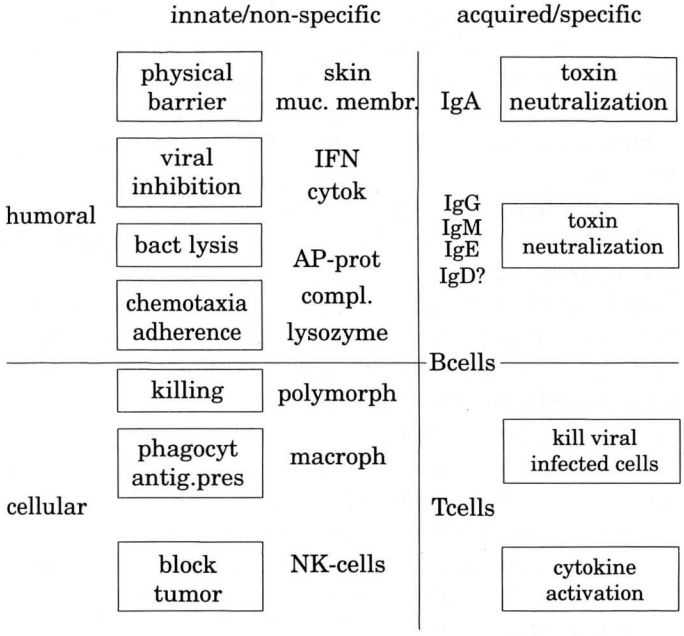
Probably the most important protection of the body against pathogenic intruders are skin and mucous membranes.

Whenever pathogens intrude the body, they first meet molecules and factors which prevent multiplication of these pathogens. These factors are nominated the innate (non-specific) immune system and become active irrespective of the kind of pathogen.

This innate immune system can be subdivided into humoral (complement, lysozyme, proinflammatory cytokines, acute phase proteins, interferons), and into cellular components (polymorphonuclear cells, macrophages, natural killer cells), all of which have their specific methods to inactivate or kill intruders or malignant cells. The innate immunocompetent cells migrate to the site of infection, engulf and kill the intruders. Parts of the ingested pathogens are presented in Major Histocompatibility Complexes (MHC) on the surface of these cells to stimulate specific immunocompetent cells

Presented at the XIX World Buiatrics Congress, Edinburgh, Scotland, July 8 12, 1996.

Figure 1.



A short outline of the immune system subdivided into innate and acquired, and humoral and cellular fields. The first line of defense is made up by the skin and mucous membranes which prevent intruding of pathogens into the body by forming a physical barrier, by enzymes, acidic environment, prevention of adhesion by the normal bacterial flora, and by movements of cilia in the mucous membranes in the respiratory tract.

Once penetrated into the body, pathogens meet the effects of proinflammatory cytokines and interferons produced by various cell types, acute phase (AP-) proteins mainly produced in the liver, complement and lysozyme, and phagocytic cells and natural killer cells. These factors bring about inhibition of virus multiplication, tumor growth, chemotaxis, adherence and bacterial lysis, either directly or by stimulation of influx and activation of various types of cells (inflammation). Cell-cell contacts by upregulation of adhesion molecules and the production of cytokines regulate a comprehensive coherence between the different branches of the immune system.

Innate phagocytic antigen presenting cells present the processed pathogen T-cells which produce a defense specific for that particular antigen. T-cells perform helper functions or may kill virus infected cells. Specific antibodies for neutralization and stimulation of phagocytosis are produced by B-cells.

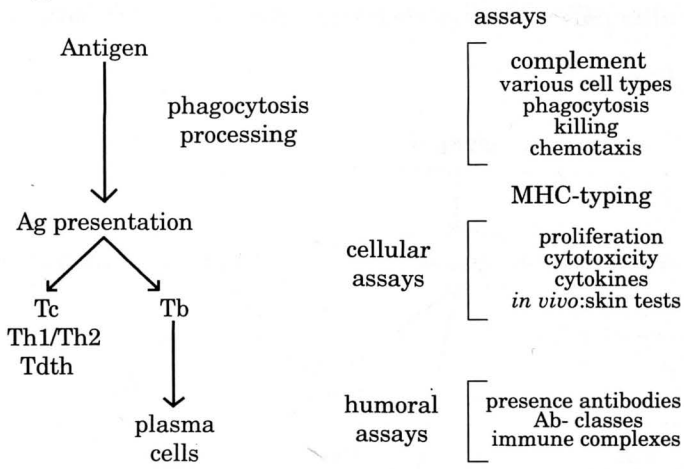
for the development of acquired specific immunity.

The specific immune system is stimulated and its action is concentrated on the particular pathogen. It is as the innate immune system subdivided into humoral (immunoglobulins produced by B-cells) and a cellular components (T-cells).

The innate and acquired immune systems activate and stimulate each other by comprehensive interactions. These interactions may be initiated by soluble factors secreted by damaged cells (products of arachidonic acid) or infected cells (cytokines), and by subsequent cell-cell interactions in which adhesion molecules play a role.[22]

The function of the immune system is evaluated by measuring the amount of particular molecules in the peripheral blood involved in the immune response (TNF, cytokines, the amount of globulins and their subclasses against specific pathogens) or by measuring activities of immunocompetent cells *in vitro* (Figure 2). These methods surpass the ensemble acting of immune mediators of the local reaction, the production of proinflammatory cytokines, and subsequent effector mechanisms. Furthermore, laboratory methods only can provide one read out and activity at one time point. *In vitro* tests very often are performed by using cell stimulating factors (PHA, PWM, ConA, LPS) which do not necessarily reflect efficacy *in vivo*.[22]

Figure 2.



A short outline of the sequential activity of the immune system and the relationship with laboratory methods to demonstrate activity or activation.

Metabolic diseases

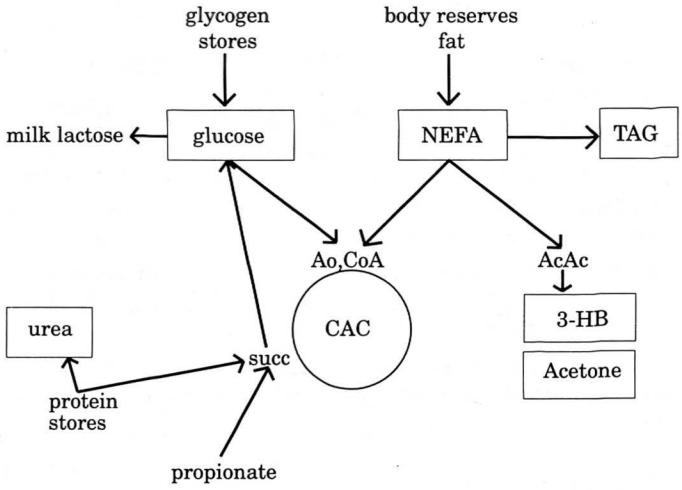
These disturbances are the consequence of the imbalance between the rates of input of energy and the output of production.[4,24] The diseases comprise milk fever, ketonaemia and hepatic lipidosis, the latter two of which are associated with the frequent occurrence of aspecific infections.[5,6,8,15,16,20] A short metabolic pathway is presented in figure 3.[24] The most important metabolites that are present above the normal level or are deficient in the peripheral blood, and are suspected to interfere with the activity of immunocompetent cells are glucose, ketone bodies, non esterified fatty acids (NEFA) liberated from the fat deposits, and urea, presented in boxes in figure 3.[3,4,26,28]

Bovine ketosis is a syndrome that occurs in the first few weeks after parturition and is the result of an imbalance between energy intake and output.[4,24] It may be caused by low food quality or by reduced food intake. As a result elevated levels of 3-hydroxybutyrate (3-HB) and low levels of glucose are found in the peripheral blood. Elevated levels of 3-HB may also originate from spoiled silage (alimentary ketosis).[4]

Hepatic lipidosis occurs in recently calved cows, which have a reduced feed intake during the last week

of gestation or the first few days after delivery and therefore mobilize during the first few days after parturition fatty acids in exacerbated amounts from the body reserves.[2,4,26] NEFA's are transported to the liver which can not deal with such an amount of NEFA's either by overflux or caused by reduced capacity to export lipoproteins from the liver by shortage of apolipoproteins.[3,4] The fatty liver produces haptoglobins in increased amounts thereby influencing the immune response.[29] Obesity during the last part of the dry period is a predisposing factor for the development of hepatic lipidosis, but actually it is the rate of lipolysis.[7,8,15,16,18,21,24,26] A very fast loss of body condition score during the first week after parturition is a clear indication of hepatic lipidosis.

Figure 3.



A short outline of the metabolic pathways involved in fat and carbohydrate metabolism.

In the rumen the succinate is formed which is absorbed and utilized for the production of glucose. Glucose is the precursor for lactose, the main driving force for milk volume.

In situations of energy imbalances lipolysis from the fat deposits occurs and non esterified fatty acids (NEFA) are transported to the liver cells. In the liver cells the fatty acids maybe oxidized in the critic acid cycle or may be converted into ketone bodies which are exported to other parts of the body for energy supply. In the case of serious energy shortage proteins may be utilized for energy production and urea is left over as a waste product. In extreme situations NEFA's are esterified and stored as tricylglycorol (TG) in the cytosol in the liver cells.

Substances that can be determined in routine laboratories are given in boxes.

This syndrome may occur in dairy cows during the dry period (**pregnancy toxaemia**).[4] A prerequisite for this syndrome to develop is a sudden reduction of energy intake combined with twin pregnancy. In beef cows the syndrome of pregnancy toxaemia is mentioned more often.[4]

Bovine ketosis and hepatic lipidosis very often occur clinically unnoticed, but with elevated 3-HB levels in the blood.[4]

Discussion

In some experiments conducted to study immunoreactivity during metabolic disturbances immunocompetent cells were isolated from normal individuals and cultured *in vitro* in the presence of metabolic substances which are present in increased or decreased amounts in the blood.[11,12,13]

Furthermore, the activity of immunocompetent cells is studied using cells collected from animals suffering from spontaneous or experimentally induced metabolic disturbances.[10,25] In these experiments too the activity of the immune system is evaluated in laboratory conditions. Mononuclear cells collected from cows with experimental ketosis showed a reduced migration capacity under agarose.[14]

The results obtained in *in vitro* experiments depict the activity of isolated humoral substances or immunocompetent cells in laboratory conditions, at one time point with one read out of the immune response in the surpassing of alternative methods which maybe active in *in vivo* conditions.

Therefore, challenge experiments using animals experimentally brought into conditions which reflect naturally occurring metabolic diseases probably are the best model for the evaluation on of deleterious effects of metabolic products on the function of the immune system. However, experiments like these are expensive, time consuming and harmful for the experimental cows.

Only few *in vivo* immunologic experiments have been reported using animals suffering from experimental metabolic diseases.[9,20,27] These experiments indeed strongly suggest impaired immunoreactivity in cows suffering from hepatic lipidosis. Hill, *et al*[9] found an increased severity and prolonged duration of mastitis after an experimental intramammary *E.Coli* infection in cows with increased levels of hepatic TAG. Reid, *et al*[20] described reduced influx of polymorphonuclear cells into the milk in cows with elevated hepatic TAG levels, while phagocytosis and killing of bacteria by polymorphs were unaffected. Wentink, *et al*[27] found after vaccination with Tetanus Toxoid (TT) vaccine on day 3 after parturition a reduction of specific blastogenic responses for TT in cows with elevated hepatic triacylglycerol (TAG). These animals also had a reduced lymphocyte accumulation associated with skin allotransplants performed at day 3 after parturition compared to animals with low levels of hepatic TAG.

Conclusion

The results obtained in the *in vivo* experiments support the suggestion of impaired immunoreactivity in animals suffering from hepatic lipidosis, but fail to provide insight into immunologic mechanisms that may be impaired.

References

1. Alderson, JCE and C Green. Febs Letters 52:208 (1975). 2. Bertics, SJ, RR Grummer, C Cadorniga-Valino, EE Stoddard, *J Dairy Sci.* 75:1914 (1992). 3. Bogin, E, Y Avidar, M Merom, S Soback, G Brenner, *J Comp Path* 98:337 (1988). 4. Bruss, ML *Adv Vet Sci Comp Med* 37:417 (1993). 5. Burkholder, WJ and WS Swecker Jr. Seminars in *Vet Med Surg* 5:154 (1990). 6. Fronk, TJ, LH Schultz, AR Hardie *J Dairy Sci* 63:1080 (1980). 7. Gaal, T, CJ Roberts, IM Reid, AM Dew, CM Copp. *Vet Rec* 113:53 (1983). 8. Gerloff, BJ, TH Herdt, RS Emery. *JAVMA* 188:845 (1986). 9. Hill, AW, IM Reid, RA Collins. *Vet Rec* 117:549 (1985). 10. Kandefer-Szerszen M, J Filar, A Szuster-Ciesielska, W Rzeski Dtsch tierärtl Wschr 99:440 (1992). 11. Klucinski W, P Ostaszewski, A Winnicka, S Targowski, B Szeleszczuk. *J Vet Med* A 35:626 (1988). 12. Klucinski W, E Miernik-Degórska, A Degórsk, S Targowski, A Winnicka. *J Vet Med.* A 35:626 (1988) 13. Klucinski W, A Degórski, E Miernik-Degórska, S Targowski, A Winnicka. *J Vet Med* A 35:632 (1988). 14. Kremer WDJ, EN Noorhuizen-Stassen, FJ Grommers, YH Schukken, R Heeringa, A Brand, C Burvenich. *J Dairy Sci* 76:3428 (1993). 15. Morrow DA. *J Dairy Sci* 59:1926 (1976). 16. Morrow DA, D Hillman, AW Dade, H Kitchen. *JAVMA* 174 161 (1979) 17. Reddy, PG and RA Frey, *Adv Vet Sci Comp Med* 35:255 (1990). 18. Reid IM and RA Collins. *Invest Pathol* 3:237 (1980). 19. Reid IM, RA Collins, AM Dew, AW Hill, MR Williams. 5th Int. Conf Prod Dis, Stockholm, p191 (1983). 20. Reid IM, AM Dew, LA Williams *Res Vet Sci* 37:63 (1984) 21. Roitt IM. Essential Immunology 7th ed Blackwell (1991). 22. Roberts, CJ, IM Reid, GJ Rowlands, A Patterson. *Vet Rec* 108:7 (1981). 23. Stöber M, and D Dirksen. *Prakt Tierarzt* 63:79 (1982). 24. Targowski, SP, W Klucinski, ET Littledike, DA Hoy, *Amer J Vet Res* 46:1378 (1985). 25. Van den Top, AM, MJH Geelen, Th Wensing, GH Wentink, A Th van't Klooster, AC Beijnen. *J Dairy Sci* 78:2208 (1995). 26. Wentink, GH, VPMG Rutten, TSGAM van den Ingh, A Hock, KE Müller, T Wensing, submitted. 27. West, HJ *Res Vet Sci* 48:221 (1990) 28. Yoshino, K, N Katoh, K Tagahashi, A Yuasa. *Am J Vet Res* 53:951 (1992).

Abstract

Effects of parenteral administration of vitamin E on health of periparturient dairy cows

R. J. Erskine, *et al*

J. Am. Vet. Med. Assoc., 1997; 211:466-469

Two hundred four Holstein cows were given 3,000 mg of vitamin E, IM, once, 8 to 14 days before expected parturition, and 216 control cows were not treated. Serum concentrations of tocopherol, the tocopherol: cholesterol ratio, and glutathione peroxidase activity in blood were determined for 36 treated and 36 control cattle from samples obtained immediately prior to injection of vitamin E, at 7 and 14 days after administration, and at 30 days after parturition. The incidence of retained placenta and metritis (13/204[6.4%] and 8/204 [3.9%], respectively) was significantly less for the group treated with vitamin E than for the control group (27/216 [12.5%] and 19/216 [8.8%], respectively). The incidence of clinical mastitis during the 30-day period after parturition did not differ between treatment groups. Serum vitamin E concentration was significantly higher in vitamin E-treated cattle than in control cattle 7 and 14 days after administration. However, the serum tocopherol: cholesterol ratio was significantly higher for vitamin E-treated cattle than for control cattle only at 7 days after administration. Parenteral administration of vitamin E before parturition may decrease the incidence of retained placenta and metritis in dairy cattle.