Article 120

Acute Phase Proteins - a Potent Biomarker for Mastitis

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Acute-phase proteins (APPs) are serum molecules synthesized by many cell categories, especially hepatocytes. Usually, the structure of APPs and acute-phase responses are similar in all species, having universal character in animal kingdom. The concentration of APPs in blood plasma varies in response to infection or inflammation. In recent investigations, it was discovered that some APPs were secreted in bovine milk during clinical mastitis which can be used as a bio marker for early detection of mastitis. The objective of this review is to get an over view about APPs with its role in mastitis.

KEY WORDS
Acute phase proteins, mastitis, cytokine, haptoglobin (Hp).

INTRODUCTION

The APR was defined for the first time in 1941 by Abernethy and Avery (1941). It describes the organism's response to injury, infection or trauma of a tissue as well as to immunological disorders e.g. rheumatoid arthritis. It comprises a complex cascade of reactions to prevent further tissue damage, eliminate any infective organisms and enhance the healing process in order to restore homeostasis. It is initiated by macrophages of the affected tissue or by blood monocytes which release a wide range of mediators including cytokines. These cytokines act on fibroblasts and endothelial cells in the near vicinity causing a second release of cytokines. Only this second wave of cytokines triggers the actual cascade of complex reactions as part of the APR occurring locally and systemically. Locally, cytokines mediate leukocyte recruitment, in particular neutrophils and mononuclear cells, to the sites of inflammation. Systemically, they act on the immune system, bone marrow, brain and liver, and the reaction comprises the generation of a febrile response, an increase in adrenocorticotropic hormone (ACTH) secretion, leukocytosis and alteration of the hepatic APP gene expression. This change of hepatic APP expression leads to increases as well as decreases of APP plasma concentrations dividing them into positive and negative APPs, respectively (Heinrich et al. (1990) and Baumann and Gauldie (1994). Since Hp is produced at elevated levels during the APR, it is categorized as a positive APP (Skinner et al., 1991; Dobryszycka, 1997).

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SPECIES SPECIFIC APP RESPONSE DURING APR

Several plasma proteins are known as APPs, however, depending on the species the protein pattern of each single APP during the APR is highly variable. In cattle, Hp and serum amyloid A (SAA) are considered as the most prominent APPs, whereas C-reactive protein (CRP) is normally present in circulation and its concentration remains unchanged during an acute phase (Eckersall and Conner, 1988; Gronlund et al., 2003; Pedersen et al., 2003). In contrast, CRP is recognized as a major reactant in the pig together with pig-Map (pig major acute phase protein) and also Hp (Lampreave et al., 1994; Gonzalez-Ramon et al., 2000). In man, CRP besides SAA shows the highest increases during an APR, whereas Hp increases only moderately (Heinrich et al., 1990). Similarly in the dog, CRP is classified as a major APP, whereas in the rat, α2-

macroglobulin and α1-acid glycoprotein are the APPs with the greatest increase of concentration during the APR (Eckersall and Conner, 1988; Heinrich et al., 1990).

CYTOKINE CONTROL OF APP SYNTHESIS

Cytokines act directly upon specific receptors of hepatocytes prompting APP production (Peters et al., 1997). APPs can be divided into two major categories according to their regulators: type 1 APP production is induced by interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α), whereas type 2 APP synthesis is elicited by IL-6 (Baumann and Gauldie, 1994). IL-6 is believed to be the primary stimulator of most APP genes; however, there is evidence that IL-1 and TNF-α can amplify the effects of IL-6 (Heinrich et al., 1990). In cattle, IL-6 could be established as the principal regulator of Hp production in hepatocytes (Yoshioka et al., 2002); hence, it can be classified as type 2 APP in this species. Similarly, Hp is ranked as type 2 APP in man, however, as type 1 in the rat (Baumann and Gauldie, 1994). Induced by IL-6, the actual Hp gene transcription within a cell is mediated by signal transducers and activators of transcription proteins (STAT) of which STAT3 has been described as the main signaling protein in mice hepatocytes in vitro (Kim and Baumann, 1997). After binding of IL-6 to its receptor, STAT3 is activated at the cytoplasmic side of the IL-6 receptor by phosphorylation. Once activated it translocates to the nucleus. In mice, the three main regulatory elements of the Hp gene promoter are two recognition sites for the transcription factor CCAAT/enhancer binding protein beta (C/EBPβ) flanking a STAT interaction site. Binding of STAT3 to this interaction site has been identified as the key up-regulator of murine Hp gene transcription induced by IL-6, whereas binding of other STAT proteins, e.g. STAT5, exerts inhibitory effects (Kim and Baumann, 1997; Wang et al., 2001). Besides their direct regulatory effect, cytokines can also act via the pituitary-adrenal axis on APP production. They mediate an increased release of glucocorticoids by causing a higher secretion of ACTH during the APR. Glucocorticoids, in turn, enhance the APP production in hepatocytes on the one hand, and reduce the release of cytokines from monocytes and macrophages on the other hand (Heinrich et al., 1990). However, the effect on Hp expression in hepatocytes via this route appears low compared to the direct route (Marinkovic and Baumann, 1990). The signaling pathway of ACTH on the Hp promoter has yet to be fully characterized; a direct glucocorticoid receptor binding site in the murine Hp promoter is suspected (Pajovic et al., 1994).

APP IN MASTITIS

Mastitis, a prevalent condition of lactating dairy cattle, is caused by bacterial infection of the mammary glands by a variety of gram-positive and gram-negative bacteria (Cullor and Tyler, 1996). Mastitis has been shown previously to induce a major increase in the plasma concentrations of Hp, SAA and α1 acid glycoprotein (Eckersall et al., 2001). In recent investigations, it was discovered that Hp and SAA were secreted in bovine milk during clinical mastitis (Eckersall et al., 2001). It has also been shown that experimentally induced mastitis can stimulate expression of these proteins in milk (Eckersall et al., 2001; Gronlund et al., 2003). Others have shown that the form of SAA present in milk during mastitis is the bovine equivalent of the human SAA3 isoform, which has been called mammary-associated SAA3 (M-SAA3) and that this isoform is present in bovine colostrum (McDonald et al., 2001). There are 2 likely sites of production of Hp and M-SAA3 secreted in milk. The APP could be synthesized in the liver and exported to the mammary gland during infection by leakage from the systemic circulation or there could be de novo synthesis of the APP within mammary gland tissues. Extra-hepatic synthesis of APP has been observed previously. Extra-hepatic production of M-SAA3 and Hp has been reported in intestine, lung, and adipose tissue in humans and laboratory animals (Friedrichs et al., 1995; Yang et al., 1995, 2000; Urieli-Shoval et al., 1998, 2000; Vreugdenhil et al., 1999), and it is therefore possible that synthesis of APP may also take place in mammary tissue. Recent data from investigations of the expression of mRNA for M-SAA3 and Hp suggest that mammary

tissue can be a source of the APP in bovine milk (Molenaar et al., 2002; Hiss et al., 2004). The secretion of APP in milk during IMI is presumably related to their roles in innate immunity in resisting the invasion and establishment of pathogens. Haptoglobin acts in plasma as a scavenger molecule for free hemoglobin, but also has antioxidant activities (Lim et al., 2000) and this may be an important function in milk. Serum amyloid A also has scavenging roles in the circulation, being involved in lipid transport, and has recently been identified as possessing direct antibacterial activity (Hari-Dass et al., 2005). Furthermore, a potential role for M-SAA3 in milk is suggested by its ability to stimulate the secretion of mucin from intestinal epithelial cells and in this process, act as an indirect antibacterial agent in the neonate (Larson et al., 2003), especially as a component of colostrum.

HAPTOGLOBIN (Hp)

It's a protein found in blood plasma, Hp binds free hemoglobin (Hb) released from erythrocytes with high affinity and thereby inhibit its oxidative activity. The Hp-Hb complex will then be removed by the reticulo-endothelial system. Hp is produced primarily by liver but skin, lung and kidney can also produce. In Intravascular hemolysis, free Hp will be released into circulation and hence Hp will bind the Hb. This causes decline in Hp levels. In contrast, Extravascular hemolysis the reticulo-endothelial system, especially splenic monocytes phagocytose the erythrocytes and Hb is not released into circulation, Serum Hp levels are normal. The occurrence of Hp in bovine plasma was noted by Liany (1957) and by Neuhaus and Sogoian (1961) but Bremner (1964) reported that plasma samples from healthy calves contained very little level of Hp. Richter (1974) found very low levels of Hp in the plasma of normal cattle, with physiological levels being below 0.1 mg/ml, as determined by hemoglobin binding capacity (HbBC). In all species, Hp is an acute phase reactant with a variety of inflammatory conditions. In pathological conditions, increased level of Hp has been reported in mastitis of cattle (Spooner & Miller, 1971; Conner et al., 1989). Bovine Hp shared antigenic determinants with Hp from goats, sheep, deer, elk and bison which all cross-reacted with an antiserum to goat Hp, while the Hp from species such as rat, rabbit, cat, dog, horse and pigs did not react Travis & Sanders, 1972.

CONCLUSION

The acute phase reaction is a natural response to tissue injury and includes a range of metabolic activities which include alterations in the rate of synthesis of several proteins produced by the liver. It is established that the cytokines play a key role in mediating this response. Measurement of the proteins in serum is of considerable value in the diagnosis, management and prognosis of many diseases that exhibit an acute phase response such as mastitis. Though little information is available about the APP in relation to mastitis, A detailed study may be needed to establish a strong correlation between the two.

REFERENCES

1. A Abernethy TJ. and Avery OT: The occurrence during acute infections of a protein not normally present in the blood. J Exp Med 1941, 73:173-182.
2. Heinrich PC, Castell JV and Andus T. Interleukin-6 and the acute phase response. Biochem J 1990, 265:621-636.
3. Baumann H and Gauldie J. The acute phase response. Immunol Today 1994, 15:74-80.
4. Skinner JG, Brown RA and Roberts L. Bovine haptoglobin response in clinically defined field conditions. Vet Rec 1991, 128:147-149.
5. Dobryszycka W. Biological functions of haptoglobin – new pieces to an old puzzle. Eur J Clin Chem Clin Biochem 1997, 35:647-654.
6. Eckersall PD and Conner JG. Bovine and canine acute phase proteins. Vet Res Commun 1988, 12:169-178.
7. Gronlund U, Hulten C, Eckersall PD, Hogarth C and Persson Waller K. Haptoglobin and serum amyloid in milk and serum during acute and chronic experimentally induced Staphylococcus aureus mastitis. J Dairy Res 2003, 70:379-386.

8. Pedersen LH, Aalbaek B, Rontved CM, Ingvartsen KL, Sorensen NS, Heegaard PM and Jensen HE. Early pathogenesis and inflammatory response in experimental bovine mastitis due to Streptococcus uberis. J Comp Pathol 2003, 128:156-164.
9. Lampreave F, Gonzalez-Ramon N, Martinez-Ayensa S, Hernandez MA, Lorenzo HK, Garcia-Gil A and Pineiro A. Characterization of the acute phase serum protein response in pigs. Electrophoresis 1994, 15:672-676.
10. Gonzalez-Ramon N, Hoebe K, Alava MA, Van Leengoed L, Pineiro M, Carmona S, Iturralde M, Lampreave F and Pineiro A. Pig MAP/ITIH4 and haptoglobin are interleukin-6-dependent acute-phase plasma proteins in porcine primary cultured hepatocytes. Eur J Biochem 2000, 267:1878-1885.
11. Peters M, Odenthal M, Schirmacher P, Blessing M, Fattori E, Ciliberto G, Meyer zum Buschenfelde KH and Rose-John S. Soluble IL-6 receptor leads to a paracrine modulation of the IL-6-induced hepatic acute phase response in double transgenic mice. J Immunol 1997, 159:1474-1481.
12. Yoshioka M, Watanabe A, Shimada N, Murata H, Yokomizo Y and Nakajima Y. Regulation of haptoglobin secretion by recombinant bovine cytokines in primary cultured bovine hepatocytes. Domest Anim Endocrinol 2002, 23:425-433.
13. Kim H and Baumann H. The carboxyl-terminal region of STAT3 controls gene induction by the mouse haptoglobin promoter. J Biol Chem 1997, 272:14571-14579.
14. Wang Y, Kinzie E, Berger FG, Lim SK and Baumann H. Haptoglobin, an inflammation-inducible plasma protein. Redox Rep 2001, 6:379-385.
15. Marinkovic S and Baumann H. Structure, hormonal regulation, and identification of the interleukin-6- and dexamethasone-responsive element of the rat haptoglobin gene. Mol Cell Biol 1990, 10:1573-1583.
16. Pajovic S, Jones VE, Prowse KR, Berger FG and Baumann H. Species-specific changes in regulatory elements of mouse haptoglobin genes. J Biol Chem 1994, 269:2215-2224.
17. Cullor JS, and JW Tyler. Mammary gland health and disorders. Pages 1178 1193 in Large Animal Internal Medicine. BP Smith, ed. Mosby, St. Louis, MO. 1996.
18. Eckersall PD, FJ Young, C McComb, CJ Hogarth, S Safi, A Weber, T McDonald, AM Nolan, and JL Fitzpatrick. Acute phase proteins in serum and milk from dairy cows with clinical mastitis. Vet. Rec. 2001, 148:35–41.
19. Gronlund U, C Hulten, PD Eckersall, C Hogarth and KP Waller. Haptoglobin and serum amyloid A in milk and serum during acute and chronic experimentally induced Staphylococcus aureus mastitis. J. Dairy Res. 2003, 70:379–386.
20. McDonald TL, MA Larson, DR Mack, and A Weber. Elevated extrahepatic expression and secretion of mammaryassociated serum amyloid A 3 (M-SAA3) into colostrum. Vet. Immunol. Immunopathol. 2001, 83:203–211.
21. Friedrichs WE, AL Navarijoashbaugh, BH Bowman, and F Yang. Expression and inflammatory regulation of haptoglobin gene in adipocytes. Biochem. Biophys. Res. Commun. 1995, 209:250–256.
22. Yang FM, WE Friedrichs, AL Navarijoashbaugh, LA DeGraffenried, BH Bowman, and JJ Coalson. Cell-type-specific and inflammatory-induced expression of haptoglobin gene in lung. Lab. Invest. 1995, 73:433–440.
23. Urieli-Shoval S, P Cohen, S Eisenberg, and Y Matzner. Widespread expression of serum amyloid A in histologically normal human tissues: Predominant localization to the epithelium. J. Histochem. Cytochem. 1998, 46:1377–1384.
24. Urieli-Shoval S, RP LiAbernethy TJ. and Avery OT: The occurrence during acute infections of a protein not normally present in the blood. J Exp Med 1941, 73:173-182.
25. Heinrich PC, Castell JV and Andus T. Interleukin-6 and the acute phase response. Biochem J 1990, 265:621-636.
26. Baumann H and Gauldie J. The acute phase response. Immunol Today 1994, 15:74-80.
27. Skinner JG, Brown RA and Roberts L. Bovine haptoglobin response in clinically defined field conditions. Vet Rec 1991, 128:147-149.
28. Dobryszycka W. Biological functions of haptoglobin – new pieces to an old puzzle. Eur J Clin Chem Clin Biochem 1997, 35:647-654.

29. Eckersall PD and Conner JG. Bovine and canine acute phase proteins. Vet Res Commun 1988, 12:169-178.

30. Gronlund U, Hulten C, Eckersall PD, Hogarth C and Persson Waller K. Haptoglobin and serum amyloid in milk and serum during acute and chronic experimentally induced Staphylococcus aureus mastitis. J Dairy Res 2003, 70:379-386.

31. Pedersen LH, Aalbaek B, Rontved CM, Ingvartsen KL, Sorensen NS, Heegaard PM and Jensen HE. Early pathogenesis and inflammatory response in experimental bovine mastitis due to Streptococcus uberis. J Comp Pathol 2003, 128:156-164.

32. Lampreave F, Gonzalez-Ramon N, Martinez-Ayensa S, Hernandez MA, Lorenzo HK, Garcia-Gil A and Pineiro A. Characterization of the acute phase serum protein response in pigs. Electrophoresis 1994, 15:672-676.

33. Gonzalez-Ramon N, Hoebe K, Alava MA, Van Leengoed L, Pineiro M, Carmona S, Iturralde M, Lampreave F and Pineiro A. Pig MAP/ITIH4 and haptoglobin are interleukin-6-dependent acute-phase plasma proteins in porcine primary cultured hepatocytes. Eur J Biochem 2000, 267:1878-1885.

34. Peters M, Odenthal M, Schirmacher P, Blessing M, Fattori E, Ciliberto G, Meyer zum Buschenfelde KH and Rose-John S. Soluble IL-6 receptor leads to a paracrine modulation of the IL-6-induced hepatic acute phase response in double transgenic mice. J Immunol 1997, 159:1474-1481.

35. Yoshioka M, Watanabe A, Shimada N, Murata H, Yokomizo Y and Nakajima Y. Regulation of haptoglobin secretion by recombinant bovine cytokines in primary cultured bovine hepatocytes. Domest Anim Endocrinol 2002, 23:425-433.

36. Kim H and Baumann H. The carboxyl-terminal region of STAT3 controls gene induction by the mouse haptoglobin promoter. J Biol Chem 1997, 272:14571-14579.

37. Wang Y, Kinzie E, Berger FG, Lim SK and Baumann H. Haptoglobin, an inflammation-inducible plasma protein. Redox Rep 2001, 6:379-385.

38. Marinkovic S and Baumann H. Structure, hormonal regulation, and identification of the interleukin-6- and dexamethasone-responsive element of the rat haptoglobin gene. Mol Cell Biol 1990, 10:1573-1583.

39. Pajovic S, Jones VE, Prowse KR, Berger FG and Baumann H. Species-specific changes in regulatory elements of mouse haptoglobin genes. J Biol Chem 1994, 269:2215-2224.

40. Cullor JS, and JW Tyler. Mammary gland health and disorders. Pages 1178 1193 in Large Animal Internal Medicine. BP Smith, ed. Mosby, St. Louis, MO. 1996.

41. Eckersall PD, FJ Young, C McComb, CJ Hogarth, S Safi, A Weber, T McDonald, AM Nolan, and JL Fitzpatrick. Acute phase proteins in serum and milk from dairy cows with clinical mastitis. Vet. Rec. 2001, 148:35–41.

42. Gronlund U, C Hulten, PD Eckersall, C Hogarth and KP Waller. Haptoglobin and serum amyloid A in milk and serum during acute and chronic experimentally induced Staphylococcus aureus mastitis. J. Dairy Res. 2003, 70:379–386.

43. McDonald TL, MA Larson, DR Mack, and A Weber. Elevated extrahepatic expression and secretion of mammaryassociated serum amyloid A 3 (M-SAA3) into colostrum. Vet. Immunol. Immunopathol. 2001, 83:203–211.

44. Friedrichs WE, AL Navarijoashbaugh, BH Bowman, and F Yang. Expression and inflammatory regulation of haptoglobin gene in adipocytes. Biochem. Biophys. Res. Commun. 1995, 209:250–256.

45. Yang FM, WE Friedrichs, AL Navarijoashbaugh, LA DeGraffenried, BH Bowman, and JJ Coalson. Cell-type-specific and inflammatory-induced expression of haptoglobin gene in lung. Lab. Invest. 1995, 73:433–440.

46. Urieli-Shoval S, P Cohen, S Eisenberg, and Y Matzner. Widespread expression of serum amyloid A in histologically normal human tissues: Predominant localization to the epithelium. J. Histochem. Cytochem. 1998, 46:1377–1384.

47. Urieli-Shoval S, RP Linke, and Y Matzner. Expression and function of serum amyloid A, a major acute-phase protein, in normal and disease states. Curr. Opin. Hematol. 2000, 7:64–69.

48. Vreugdenhil ACE, MA Dentener, AMP Snoek, J-WM Greve, and WA Buurman. Lipopolysaccharide binding protein and

serum amyloid A secretion by human intestinal epithelial cells during the acute phase response. J. Immunol. 1999, 163:2792–2798.

49. Molenaar A, G Rajan, M Pearson, M Miles, R Petrova, S Davis, and K Stelwagen. A serum amyloid protein homologue is expressed by the mammary gland in a similar pattern to lactoferrin. Proc. 3rd Eur. Colloq. Anim. Acute Phase Proteins. E Gruys, ed. Doorn, The Netherlands. 2002.

50. Hiss S, M Mielenz, RM Bruckmaier, and H Sauerwein. Haptoglobin concentrations in blood and milk after endotoxin challenge and quantification of mammary HpmRNA expression. J. Dairy Sci. 2004, 87:3778–3784.

51. Lim YK, A Jenner, A bin Ali, YP Wang, SIH Hsu, SM Chong, H Baumman, B Halliwell, and SK Lim. Haptoglobin reduces renal oxidative DNA and tissue damage during phenylhydrazine-induced hemolysis. Kidney Int. 2000, 58:1033–1044.

52. Hari-Dass R, C Shah, DJ Meyer, and JG Raynes. Serum amyloid A protein binds to outer membrane protein A of Gramnegative bacteria. J. Biol. Chem. 2005, 280:18562–18567.

53. Larson MA, SH Wei, A Weber, DR Mack, and TL McDonald. Human serum amyloid A3 peptide enhances intestinal MUC3 expression and inhibits EPEC adherence. Biochem. Biophys. Res. Commun. 2003, 300:531–540.

54. Liang CC. The formation of complexes between haemoglobins and plasma proteins in a variety of animals. Biochem. J, 1957, 66, 552-558.

55. Neuhaus 0WI! & Sogoian VP. The presence of haptoglobin in synovial fluid. Nature, 1961, 192, 558559.

56. Bremner KC. Studies on haptoglobin and haemopexin in the plasma of cattle. Aust. J. Exp. Biol. Med. Sci., 1964, 42, 643-656.

57. Richter H. Haptoglobin bei haussaugetieren III. Arch. Exper. Vet. Med., 1974, 28,505-519.

58. Richter H. Haptogiobin bei haussaugetieren IV. Arch. Exper. Vet. Med., 1975, 29,217-230.

59. Spooner RL & Millar JK. The measurement of haemoglobin reactive protein as an aid to the diagnosis of acute inflammation. Vef. Rec., 1971, 88, 2-4.

60. Travis JC & Sanders RG. Haptoglobin evolution: polymeric forms of HP in the bovidae and cervidae. J. Exp. Zool., 1972, 180, 141-148 .

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TABLES

Table1: Synthesis and Functions of some APP

Sl. No	Positive Acute Phase Protein	Site of Synthesis	Function
1	Alpha 1-antichymotrypsin	Liver	Serpin, down regulates inflammation
2	Alpha 1-antitrypsin	Liver	Serpin, down regulates inflammation
3	Alpha 2-macroglobulin	Liver	a. Inhibitor of coagulation by inhibiting thrombin. b.Inhibitor of fibrinolysis by inhibiting plasmin.
4	Ceruloplasmin	Liver	Oxidizes iron, facilitating for ferritin, inhibiting microbe iron uptake.
5	Complement factors	Liver	Opsonization, lysis and clumping of Target cells, Chemotaxis
6	C-reactive protein	Liver	Opsonin on microbes
7	Ferritin	Liver	Binding iron, inhibiting microbe iron uptake
8	Fibrinogen, Prothrombin, Factor VIII, Von Willebrand factor	Liver	Trapping and invading microbes in blood clots. Some cause chemotaxis.
9	Haptoglobin	Liver, Skin, Lung, Kidney	Binds hemoglobin (Hb), inhibiting microbe iron uptake.
10	Hepcidin	Liver	Stimulates the internalization of ferroportion, preventing release of iron bound by ferritin within intestinal enterocytes and macrophages.
11	Mannan-binding lectin	Liver derived collagen like serum protein	Mannan-binding pathway of complement activation
12	Orosomucoid (Alpha-1-acid glycoprotein, AGP)	Liver	Steroid carrier
13	Plasminogen	Liver	Degradation of blood clots
14	Serum amyloid P component		Opsonin
15	Serum amyloid A	Liver	1. Recruitment of immune cells to inflammatory sites. 2. Induction of enzymes that degrade extracellular matrix.

Sl. No	Negative Acute Phase Protein	Site of Synthesis	Function
1	Albumin	Liver	Carrier protein for steroids, fatty acids, Thyroid hormones and stabilize extracellular fluid volume Major contributors to oncotic pressure of Plasma
2	Antithrombin III	Liver	Similar to Plasma protease inhibitors such as Alpha 1-antichymotrypsin, Alpha 2-antiplasmin, Heparin cofactor II.
3	Retinol-binding protein	Liver	Carrier proteins that bind retinol
4	Transcortin	Liver	Major transport protein for glucocorticoids and progestins in blood
5	Transferrin	Liver	Associated with innate immunity. Bind iron very tightly but reversibly
6	Transthyretin	Liver, Choroid plexus, retinal pigment epithelium	Carrier of thyroxine (T4) and retinal binding protein bound to retinol

FIGURES

Fig. 1: The acute-phase protein response is regulated both directly and indirectly by a complex network of intercellular signaling molecules involving cytokines, cytokine modulators and other hormones. (Kushner et al., 2001)