

Influence of Kupffer cell phagocytosis blockade on the production of ovalbumin-specific IgE and IgG1 antibodies in an experimental model

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Summary

The aim of the present study was to evaluate the influence of Kupffer cell phagocytosis blockade (KCPB) on the production of reaginic (IgE) and non-reaginic (IgG1) ovalbumin antibodies in an experimental animal model. Forty-two female heterozygous Gunn rats were injected with two 100 µg doses of ovalbumin separated by 13 days, into jugular vein (Group I, $n=10$), portal vein (Group II, $n=10$), jugular vein with prior KCPB (Group III, $n=10$) and portal vein with prior KCPB (Group IV, $n=12$). KCPB was induced with gadolinium chloride (5 mg/kg body weight, 24 hr before each ovalbumin administration). Antibodies were determined by passive cutaneous anaphylaxis in sera obtained 12 days after the first dose of ovalbumin and 8 days after the second one. No antibodies were detected at any time in Group II. The maximum response was observed in Group IV in which, after two doses of ovalbumin, 100% of the animals presented IgG1 and 58% presented detectable IgE antibodies. Differences between group IV and the other groups were statistically significant. This phenomenon does not seem to be due to a systemic effect of gadolinium chloride since humoral response was not increased in Group III with respect to Group I. It is concluded that the liver represents a barrier to IgE and IgG1 sensitization. KCPB not only eliminates this barrier, but also clearly increases antibody production to a protein antigen (ovalbumin) arriving at the liver through the portal vein.

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Introduction

Kupffer cells, the fixed hepatic macrophages, represent the 90% of the total body phagocytic activity and occupy a strategic position in relation to the terminal branches of the portal vein. They form the first line of defence, clearing the circulation of a number of antigens and other potentially immunostimulatory materials which cross the liver from the gastrointestinal tract [1].

It has been suggested that hepatic macrophages might play a role in the phenomenon of oral tolerance. The existence of antigen-specific systemic unresponsiveness after feeding antigens has long been recognized [2] but the precise mechanisms responsible for this phenomenon are not well understood. Chase, in 1946, first demonstrated that specific immunological unresponsiveness to simple

chemicals, such as picryl chloride, may be induced in adult guinea-pigs by prior feeding of this hapten [3]. The mechanisms involved in this phenomenon were not entirely explained but, it was later suggested that the liver might play a critical role since the introduction of minute doses of picryl chloride into the mesenteric veins produced the same state of tolerance to this antigen [4]. Furthermore, portacaval transposition, diverting flow away from the liver, abolishes the phenomenon of tolerance [5,6]. Several more reports have suggested a tolerogenic effect of the liver to different antigens introduced into the portal venous system [7–11]. Besides, indirect evidence for this hepatic effect is provided by the finding of raised titres of antibodies to gut-associated bacteria and polyclonal hypergammaglobulinaemia in patients with chronic liver diseases and impaired Kupffer cell function [12]. The mechanisms by which hepatic macrophages may induce tolerance are not completely

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compared with endothelial cells, the tolerogenic effect of Kupffer cells could be inhibited when their phagocytosis is blocked. However, this explanation is no more than speculation and our data do not permit a conclusion to be drawn about the genesis of the observed effect. Further studies are needed to clarify this point, particularly the intrahepatic cellular distribution of ovalbumin after gadolinium-induced KCPB. Likewise, more studies are necessary to determine if the observed effect is restricted to particular antigens such as ovalbumin or to particular Kupffer-cell blocking agents such as gadolinium chloride. If confirmed, these data may be relevant to food allergy, which could be favoured in circumstances where hepatic phagocytosis is impaired. In this sense, altered liver reticuloendothelial function has been suggested as one of the bases of the increased serum antibody levels against cows' milk proteins in children with chronic liver diseases [28], thus supporting the theory that the liver is an integral part of the enteric mucosal immune system [29].

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References

- 1 Rogoff TM, Lipsky PE. Role of the Kupffer cells in local and systemic immune responses. *Gastroenterology* 1981; 80:854-60.
- 2 Dakin R. Remarks on a cutaneous affection produced by certain poisonous vegetables. *Am J Med Sci* 1829; 4:98-101.
- 3 Chase MW. Inhibition of experimental drug allergy by prior feeding of the sensitizing agent. *Proc Soc Exp Med Biol* 1946; 61:257.
- 4 Battisto JR, Miller J. Immunological unresponsiveness produced in adult guinea pigs by parenteral introduction of minute quantities of hapten or protein antigen (27717). *Proc Soc Exp Med Biol* 1962; 111:111-5.
- 5 Cantor HM, Dumont AE. Hepatic suppression of sensitization to antigen absorbed into the portal system. *Nature* 1967; 215:744-5.
- 6 Callery MP, Kamei T, Flye MW. The effect of portacaval shunt on delayed-hypersensitivity responses following antigen feeding. *J Surg Res* 1989; 46:391-4.
- 7 Triger DR, Cynamon MH, Wright R. Studies on hepatic uptake of antigen. I. Comparison of inferior vena cava and portal vein routes of immunization. *Immunology* 1973; 25:941-50.
- 8 Callery MP, Kamei T, Flye MW. Kupffer cell blockade inhibits induction of tolerance by the portal venous route. *Transplantation* 1989; 47:1092-3.
- 9 Qian J, Hashimoto T, Fujiwara H, Hamaoka T. Studies on the induction of tolerance to alloantigens. I. The abrogation of potentials for delayed-type-hypersensitivity responses to alloantigens by portal venous route inoculation with allogeneic cells. *J Immunol* 1985; 134:3656-61.
- 10 Fujiwara H, Qian J, Satoh S, Kokudo Sh, Ikegami R, Hamaoka T. Studies on the induction of tolerance to alloantigens. II. The generation of serum factor(s) able to transfer alloantigen-specific tolerance for delayed-type-hypersensitivity by portal venous inoculation with allogeneic cells. *J Immunol* 1986; 136:2763-8.
- 11 Boeckx W, Sobis H, Lacquet A, Gruwez J, Vandeputte M. Prolongation of allogeneic heart graft survival in the rat after implantation on portal vein. *Transplantation* 1975; 19:145-9.
- 12 Triger DR, Alf MH, Wright R. Bacterial and dietary antibodies in liver disease. *Lancet* 1972; 1:60-3.
- 13 Tomasi TB. Oral tolerance. *Transplantation* 1980; 29:353-5.
- 14 Feldmann M. T cell suppression in vitro. I. Role in regulation of antibody responses. *Eur J Immunol* 1978; 120:660-4.
- 15 Richman LK, Chiller JM, Brown WR, Hanson DG, Vaz NM. Enterically induced immunologic tolerance I. Induction of suppressor T lymphocytes by intragastric administration of soluble proteins. *J Immunol* 1978; 121:2329-433.
- 16 Miller SD, Hanson DG. Inhibition of specific immune responses by feeding protein antigens. IV. Evidence for tolerance and specific active suppression of cell-mediated immune responses to ovalbumin. *J Immunol* 1979; 123:2344-50.
- 17 Stechschulte DJ, Austen KF, Bloch KJ. Antibodies involved in antigen-induced release of slow reacting substance of anaphylaxis (SRS-A) in the guinea pig and rat. *J Exp Med* 1967; 125:127-47.
- 18 Biozzi G, Benacerraf B, Halpern BN. Quantitative study of the granulopoietic activity of the reticuloendothelial system. II. A study of the kinetics of the granulopoietic activity of the RES in relation to the dose of carbon injected. Relationship between the weight of the organs and their activity. *Br J Exp Pathol* 1953; 34:441-57.
- 19 Husztk E, Lázár G, Párducz A. Electron microscopic study of Kupffer cell phagocytosis blockade induced by gadolinium chloride. *Br J Exp Pathol* 1980; 61:624-30.
- 20 Koudstaal J, Dijkhuis FWJ, Hardonk MJ. Selective depletion of Kupffer cells in rats by gadolinium chloride. Selected Abstracts of the 5th International Symposium on Cells of the Hepatic Sinusoid. Tucson (Arizona), U.S.A., August 26-30, 1990.
- 21 Haley Th. Pharmacology and toxicology of the rare earth elements. *J Pharm Sci* 1965; 54:663-70.
- 22 Magnusson G. The behavior of certain lanthanons in rats. Studies on the excretion, subcellular liver distribution, and toxicology after intravenous administration. *Acta Pharmacol Toxicol* 1963; 20 (suppl 3):1-95.
- 23 Souhami RL, Addison IE, Bradfield WB. Increased antibody production following depression of hepatic phagocytosis. *Clin Exp Immunol* 1975; 20:155-9.
- 24 Carter L, Barrington PJ, Cooper GN, Jackson GD. Antibody synthesis in the rat liver: an association between

- antibody-forming cells in the liver and biliary antibodies following intravenous injection of horse erythrocytes. *Int Arch Allergy Appl Immunol* 1987; 82:153–8.
- 25 Carter L, Barrington PJ, Jackson GD. Antibody response in the liver and bile of rats injected with horse erythrocytes. *Immunol Cell Biol* 1989; 67:135–9.
- 26 Stang E, Kindberg GM, Berg T, Roos N. Endocytosis mediated by the mannose receptor in liver endothelial cells. An immunocytochemical study. *Eur J Cell Biol* 1990; 52:67–76.
- 27 Kindberg GM, Magnusson S, Berg T, Smedsrød B. Receptor-mediated endocytosis of ovalbumin by two carbohydrate-specific receptors in rat liver cells. The intracellular transport of ovalbumin to lysosomes is faster in liver endothelial cells than in parenchymal cells. *Biochem J* 1990; 270:197–203.
- 28 Lerner A, Park BH, Rossi TM, Lebenthal E. Increased serum antibody levels against cow's milk proteins in children with chronic liver disease. *Hepatology* 1985; 5:488–91.
- 29 Kleinman RE, Harmatz PR, Walker WA. The liver: an integral part of the enteric mucosal immune system. *Hepatology* 1982; 2:379–84.