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A comparison of IgA in portal and peripheral venous blood

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SUMMARY

A comparison of IgA in portal and peripheral venous blood was made to elucidate further any possible role of the liver in IgA functions in man. Over fifty paired samples of portal and peripheral blood were obtained from patients undergoing abdominal surgery. The samples were examined for total IgA and secretory IgA content, IgA immune complexes, and the proportion of polymeric IgA and IgA antibodies to *Streptococcus mutans* and *Escherichia coli*. No significant differences in the overall IgA concentration in portal and peripheral venous blood were found, but the concentration of secretory IgA was raised in portal blood ($P<0{\cdot}02$). The IgA content of immune complexes (PEG precipitates) was significantly raised in portal sera compared with peripheral sera. Antibody levels to *S. mutans* or *E. coli* were not significantly different in the paired samples. A mean of 18·1% of the IgA in portal blood was greater than 7S in size compared with a mean of 15·3% in peripheral blood ($P<0{\cdot}01$). Detectable differences between IgA in portal and peripheral venous blood could indicate some role of the liver in the transport of polymeric IgA and IgA complexes from serum to bile in man, but could represent increased production of these types of IgA in tissues drained by the portal vein.

INTRODUCTION

In man the majority of serum IgA is in a monomeric (7S) form, with between 10% and 20% in a dimeric or polymeric form (Brandtzaeg, 1971; Mestecky *et al.*, 1980). The proportion of the polymeric form of IgA is significantly increased in patients with cirrhosis (Kutteh *et al.*, 1982; Newkirk *et al.*, 1983; Kalsi, Delacroix & Hodgson, 1983), and the latter authors also found an increase in the concentration of monomer IgA. These observations suggest that the liver plays a role in the maintenance of normal levels of serum IgA. The liver may also be involved in the maintenance of secretory IgA (sIgA) since raised levels of sIgA are also found in patients with liver cirrhosis (Thompson *et al.*, 1973; Delacroix & Vaerman, 1981).

Recent investigations using mice and rats have clearly shown that in these species the lver can actively transport large amounts of polymeric IgA (pIgA) from plasma to bile (Lemaitre-Coelho, Jackson & Vaerman, 1978; Hall & Andrew, 1980), suggesting a role for the liver in the secretory immune system of the gut. A biological function of this process is suggested by the observation that antigens complexed with pIgA antibodies transported from plasma to bile (Russell, Brown & Mestecky, 1981; Socken *et al.*, 1981; Peppard *et al.*, 1982) and may be a way of preventing damaging antigens from reaching the general circulation. The transport is mediated in these species by secretory component (SC) on hepatocytes which acts as a receptor for pIgA (Birbeck *et al.*, 1979; Renston *et al.*, 1980; Limet *et al.*, 1980). Although SC on human hepatocytes has been reported (Hsu & Hsu, 1980), it seems more likely that in man SC is present on bile duct cells rather than on hepatocytes (Nagura *et al.*, 1981; Hopf *et al.*, 1978).

Human bile contains high levels of pIgA (Dive & Heremans, 1974; Delacroix & Vaerman, 1983) but the origin of this IgA is not clear. It is possible that it is derived from local synthesis in the region of the bile ducts, or that a route exists for the transfer of pIgA from plasma to bile that differs from that found in many animals species, or that both mechanisms are operative. It is of interest that the half-life of mIgA in human plasma is about 7 days, whereas the half-life of pIgA is about 2·5 days (Delacroix & Vaerman, 1983), which suggests a preferential clearance mechanism for pIgA in man (Orlans *et al.*, 1983).

In this investigation, a comparison of IgA characteristics in portal and peripheral venous blood from the same subjects revealed differences in the amount of sIgA, pIgA, and IgA immune complexes, and thus supported the concept of a possible role of the liver in IgA homeostasis in man.

MATERIALS AND METHODS

Patients used in this study

Matched samples of peripheral and portal blood were taken from 55 patients undergoing some form of abdominal surgery. The ages of the patients ranged from 18 to 88 years, with a mean ($\pm$SD) age of 57 ± 17 years. These patients were subdivided into three groups as outlined in Table 1: Group A comprised 20

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Table 1. Diagnosis of 55 patients in an IgA study

Group	Diagnosis	No. patients
(A)	Cholelithiasis (cholecystitis/ cholecystectomy/gall stones)	20
(B)	Crohn's disease	3
	Pancreatitis	3
	Pyloric stenosis	2
	Hernia (external)	2
	Duodenal ulcer	2
	Laparotomy	1
	Appendicectomy	1
		14
(C)	Carcinoma of stomach	8
	Carcinoma of rectum	4
	Carcinoma of large bowel	5
	Carcinoma of breast	1
	Carcinoma of cervix	1
	Carcinoma of bronchus	1
	Carcinoma of pancreas	1
		21

patients diagnosed as having cholelethiasis (cholecystitis or gall stones), Group B a miscellaneous group including those with Crohn's disease, pancreatitis etc., and Group C 21 patients with various types of carcinoma. Peripheral blood samples were also taken from 24 healthy controls whose mean age and age range (52 ± 18 years) was similar to that of the patient groups.

Preparation of polymeric IgA
Polymeric IgA was separated from colostrum by the method of Johnstone & Thorpe (1982). Briefly, 20 ml of human colostrum were mixed with 10 ml of isotonic saline and centrifuged at 100,000 ***g*** for 1 hr at 4°. The aqueous layer was removed and the pH brought to 4 using concentrated HCl. This was centrifuged at 30,000 ***g*** for 30 min at 4°. The supernatant was neutralized with 2 M Tris, and after centrifugation was separated by a gel filtration on a Sephadex G-200 column ($90 \times 2{\cdot}5$ cm). The fractions were eluted by 0·1 M $NaPO_4$ pH 6·8 and the IgA content of each fraction was assayed by double diffusion using an anti-IgA antiserum (Oxoid Ltd, Basingstoke, Hants) and an anti-secretory component antiserum (Oxoid). The fractions containing IgA and secretory component, and IgA without secretory component were pooled and the protein concentration assayed (Lowry *et al.*, 1951).

Radioimmunoassay for sIgA
A solid-phase radioimmunoassay was used to determine the concentration of secretory IgA. Removawells (Dynatech Ltd, Billinghurst, Sussex) were incubated overnight at room temperature with the IgG fraction of an anti-secretory component antiserum (Oxoid) at a concentration of 1 μg/ml. After blocking, samples were assayed (at a dilution of 1:100) for 90 min at 37°. Serial dilutions of purified secretory IgA were assayed at dilutions from 1:100 to 1:100,000 at four-fold dilution steps. After incubation, radiolabelled anti-IgA (Oxoid) was used at a concentration of 100 μg/ml and the plates incubated for 90 min at 37° before washing and counting. A standard curve was constructed from the serial dilutions of secretory IgA and the concentration of samples read from the standard curve and expressed as ng/ml. A sample dilution of 1:100 was selected since values fell on the linear portions of the standard curve. Purified monomeric or dimeric IgA controls were negative.

Sandwich method for assay of immunoglobulin concentrations
A solid-phase sandwich radioassay was used to determine concentrations of monomeric and dimeric IgA in polyethylene glycol (PEG) precipitates and some of the column eluates. Removawells (Dynatech) were coated overnight at room temperature with the IgG fractions of rabbit anti-human IgG, IgA or IgM (Dako, High Wycombe, Bucks) at 2 μg/ml. After blocking with the PBS/BSA for 1 hr the samples were added at a dilution of 1:100 for PEG precipitates, 1:10 for column eluates and 1:400 for serum samples, since at these dilutions values fell on the linear portion of the standard curve. The samples were incubated for 90 min at 37° and, after washing, were treated with the same antisera as attached to the solid phase but this time radiolabelled with ^{125}I. The latter was added at 10 μg/ml and the plates incubated at 37° for 90 min before being washed and counted. Standard curves were constructed from a pooled human serum containing a known amount of IgA, IgG and IgM at dilutions from 1:100 to 1:100,000. For dimeric IgA, curves were constructed using the purified colostral IgA prepared as indicated above.

Polyethylene glycol (PEG) precipitation of serum
PEG precipitated at a final concentration of 2% as described by Williams & Lehner (1977). One-millilitre samples of serum were incubated with PEG overnight at 4° and, after centrifugation at 16,000 ***g***, the supernatant was removed and the pellet resuspended in 2% PEG. After washing, the pellet was resuspended in 0·1 ml of normal saline to give a 10-fold concentration. The IgG, IgA and IgM contents of the PEG precipitates were assayed using the sandwich solid-phase radioimmunoassay as detailed above and expressed as ng/ml.

Single radial immunodiffusion
The concentrations of IgG, IgA and IgM in serum were measured by the single radial immunodiffusion as detailed previously (Challacombe, 1976). The antisera were used at a dilution of 1:40.

Separation of serum into monomeric and polymeric IgA
Samples of serum were separated into monomeric and polymeric IgA by gel filtration on columns of Biogel A 0·5 m ($50 \times 1{\cdot}6$ cm). Two-hundred and fifty microlitres of serum were passed down the column and eluted with 0·1 M Tris/HCl buffer pH 7·4 containing 0·5 M NaCl. Fifteen drop fractions were collected and assayed for IgA, IgG and secretory component content as detailed above. Graphs were constructed for every sample (see Fig. 1) and the proportion of pIgA expressed as a percentage of the total IgA. In some experiments serum samples were separated as described using an Ultragel AcA 22 column ($62{\cdot}5 \times 1{\cdot}5$ cm).

Antibodies to Streptococcus mutans *and* Escherichia coli
Serum samples were assayed for antibodies to *S. mutans* and *E.*

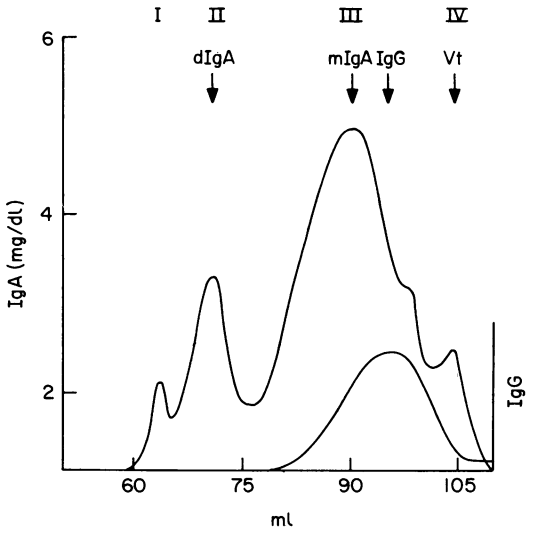

Figure 1. Typical profile of the IgA concentration after separation of 250 μl of human serum on Biogel A 0·5 m (50 × 1·6 cm). The profile of IgG is shown for comparison. IgA was found in two main peaks corresponding to dimeric IgA (II) and monomeric IgA (III). Many sera show an additional peak of higher molecular weight polymeric IgA.

coli by solid-phase radioimmunoassay essentially as described previously (Czerkinsky *et al.*, 1983). Microorganisms were bound to the solid phase using 0·3% methyl glyoxal. The antibody content was compared with a standard curve constructed using a pooled human serum. For *S. mutans*, antibodies could be expressed as μg/ml since the normal serum contained a known amount of antibody. Antibodies to *E. coli* were expressed in units assuming the standard serum to have 10^4 units/ml.

RESULTS

Immunoglobulin concentration

The immunoglobulin concentrations were examined in 52 matched pairs of portal and peripheral blood. The results were compared with the concentrations in peripheral blood of 24 age-matched controls. The results are shown in Table 2. No significant differences were found in the total IgG, IgA or IgM content when portal blood was compared with peripheral, and the immunoglobulin concentrations were not significantly different from those in controls (Table 2).

Table 2. Immunoglobulin concentration in paired samples of portal and peripheral sera (mean ± SD)

	Controls (24)*	Portal (52)	Peripheral (52)	td†	*P*
IgG	1318 ± 335	1357 ± 441	1305 ± 459	0·747	NS‡
IgA	307 ± 77	269 ± 120	281 ± 116	0·869	NS
IgM	101 ± 37	142 ± 92	129 ± 82	1·580	NS

Concentrations assayed by single radial immunodiffusion. Units = mg%.

* Number of subjects are given in parentheses.

† td, t-dependent value in Student's *t*-test.

‡ NS, not significant.

Secretory IgA concentration

The concentrations of secretory IgA was assayed in 44 matched samples of peripheral and portal blood and the results compared with the sIgA concentration in peripheral blood of 24 controls. The mean concentration of secretory IgA in portal blood was 18 μg/ml, compared with 15 μg/ml in peripheral blood. The difference was significant ($P < 0·05$, Fig. 2). Analysis of the patient groups revealed that the sIgA was significantly raised only in the carcinoma group, and that this accounted for most of the raised levels found in the patients as a whole (Fig. 2).

Polymeric IgA in portal and peripheral blood

The proportion of polymeric (i.e. non-monomer) IgA was determined in matched serum samples from 52 patients. The mean percentage of polymeric IgA in portal blood was 18·1% compared with a mean of 15·3% in peripheral blood ($P < 0·01$, Fig. 3). The proportion of polymeric IgA in these samples from patients undergoing surgery was greater than the proportion in controls (Fig. 3). In the three patient subgroups the differences in the mean values in the portal and peripheral samples did not reach statistical significance.

Polyethylene glycol precipitates

The immunoglobulin contents of immune complexes derived from PEG precipitates were examined in 54 matched samples of

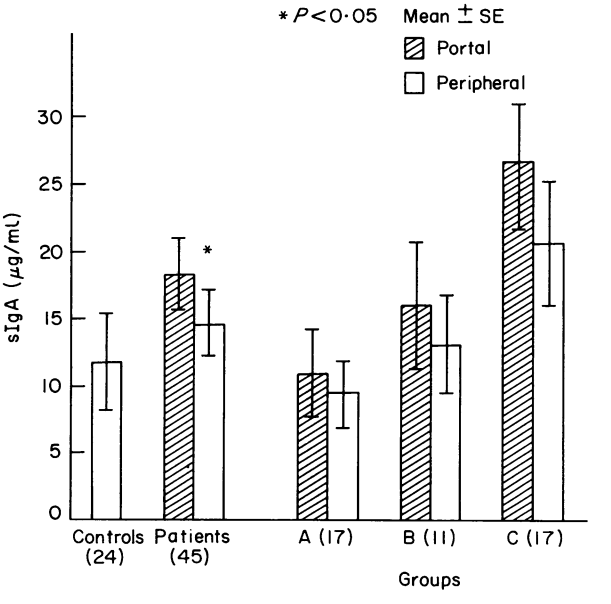

Figure 2. Concentration of secretory IgA (sIgA) in portal and peripheral sera in patients and in patient subgroups. sIgA was assayed by radioimmunoassay as detailed in the Materials and Methods. The mean value in portal sera was significantly greater than that in peripheral sera ($P < 0·05$). Patients in Group C (carcinoma) showed raised levels of sIgA ($P < 0·02$). The number of samples assayed are given in parentheses.

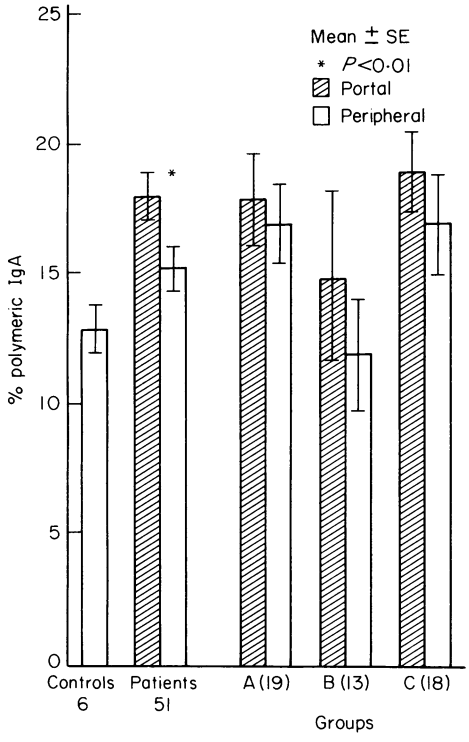

Figure 3. Percentage of polymeric IgA in portal and peripheral sera in patients and in patient subgroups. The percentage of polymer was determined by separation of samples on Biogel A 0·5 m or Ultragel AcA 22 (see Materials and Methods). IgA concentration was determined by radioimmunoassay. The number of samples assayed are given in parentheses.

portal and peripheral blood, and values compared with 24 age-matched controls. The IgG and IgM concentrations were not significantly different in complexes derived from portal or peripheral blood, but a small though statistically significant difference was found in the IgA content of these precipitates. The mean IgA value in complexes from the portal blood was 45 μg/ml, compared with 37 μg/ml in the peripheral blood samples ($P<0{\cdot}05$, Table 3). The mean immunoglobulin values in patients were raised with respect to each isotype in comparison with the age-matched controls ($P<0{\cdot}02$, Table 3). In the control group 11/24 subjects showed IgG values over 100 μg/ml and 11/24 IgM values over 100 μg/ml in the PEG precipitates. This was similar to the proportion of patients showing values over 100 μg/ml, although some patients showed values in excess of 1000 μg/ml. There was no significant difference in the proportion of patients showing IgG complexes in portal (23/54) or peripheral (21/54) samples, nor IgM (23/54 in portal, 21/54 in peripheral). With IgA 28/54 patients showed values above 30 μg/ml in portal compared with 18/54 in peripheral ($P<0{\cdot}05$). Nine of the 24 age-matched controls showed IgA in complexes above 30 μg/ml.

The immunoglobulin content of immune complexes in the three disease groups was also examined. It appeared that the significant difference between the IgA levels in complexes from portal and peripheral blood found in the patient group as a whole (Table 3) was mainly due to the differences found in Group A, consisting of patients with gall bladder disorders. In this group IgA concentration in portal complexes of 40 μg/ml compared with 27 μg/ml in peripheral samples. Values in Group B (other gut disorders) and Group C (carcinomas) did not reach statistical significance. There were no significant differences in the IgM concentrations in the complexes from portal and peripheral samples, and no differences in the IgG concentrations, except for Group A where higher IgG values were present in complexes from the portal samples (Table 3).

Antibodies to *Streptococcus mutans* and *Escherichia coli*

Antibodies of the IgG, IgM and IgA isotypes were examined in matched samples from 49 patients. No significant differences in the mean antibody titres were apparent either to *S. mutans* or to *E. coli* (Table 4). The mean serum antibody titres were not significantly different from those detected in the 24 age-matched controls.

DISCUSSION

In this study differences in the concentrations of sIgA, pIgA and IgA content of immune complexes were detectable between portal and peripheral blood, although the total IgA content and

Table 3. Immunoglobulin content of immune complexes in portal and peripheral sera in Groups A, B and C

	IgG		IgA		IgM	
Groups (*n*)	Portal	Peripheral	Portal	Peripheral	Portal	Peripheral
A(17)	76±18	52±22*	40±17	27±16†	199±78	161±75
B(11)	243±109	204±101	61±33	58±26	259±112	241±108
C(17)	215±195	191±163	37±9	29±9	122±54	108±55
Total (45)	201±86	178±76	45±10	37±9*	233±46	214±45
Control (24)	127±53		30±18		134±49	

Units = μg/ml (mean ± SEM). Complexes were separated by 2% polyethylene glycol, and immunoglobulin concentrations were determined by radioimmunoassay (see Materials and Methods).

* $P<0{\cdot}05$.

† $P<0{\cdot}02$.

Table 4. Concentration of antibodies to bacteria in paired samples of portal and peripheral sera

		Controls (24)	Portal (49)	Peripheral (49)	*P*
(A)	*Streptococcus mutans*				
	IgG	121±10	95±22	89±22	NS
	IgA	35±4	31±5	26±4	NS
	IgM	15±2	23±3	18±3	NS
(B)	*Escherichia coli*				
	IgG	33±5	38±4	32±3	NS
	IgA	28±5	39±5	34±4	NS
	IgM	29±4	34±3	32±3	NS

* Mean ± SEM. Antibodies to *S. mutans* expressed as μg/ml (see Materials and Methods) and antibodies to *E. coli* expressed as units/ml (number of subjects given in parentheses).

specific antibody content were similar. The results support the concept that in man the liver could play an active role in IgA homeostasis. However, not all the differences that have been detected between samples of portal and peripheral blood need be attributed to the liver. The portal vein receives the venous drainage from the gut and the spleen. Immunoglobulin output from the gut is largely drained via the intestinal lymph, whereas that from the spleen flows into the portal system first and is diluted in the peripheral system. Thus, differences might reflect this redistribution rather than any function of the liver.

In this regard it is of note that the mean values for many of the parameters examined were consistently greater in portal blood than in peripheral blood (Fig. 3), although the differences were not significant with regard to IgG and IgM concentrations (with the exception of a raised content of the PEG precipitates in portal samples in patients with gall bladder disease, Table 3).

No differences in the total IgG, IgA or IgM concentrations were found, and none have been reported elsewhere. However, a significant difference in the mean percentage of polymeric IgA was detected (Table 4), and the means of samples of portal blood were significantly greater than those of peripheral blood. The methods used were not sensitive enough to be confident of any differences in individual patients. Differences were not significant in any of the three subgroups but were revealed when all patients were analysed together. The mean pIgA concentration in the controls was similar to the 11·3% reported by Newkirk *et al.* (1983). The mean concentrations in the cholelethiasis group and in the carcinoma group were significantly greater than in the controls. Selective elevation of pIgA has been found with primary biliary cirrhosis and alcoholic liver disease (Newkirk *et al.*, 1983; Delacroix & Vaerman, 1983) but not in cholelethiasis.

The finding of a raised proportion of pIgA in portal blood is supported by the results of the 2% PEG precipitation. This revealed that the mean IgA concentration found in complexes from portal blood was significantly elevated compared with that of peripheral blood (Table 3). This elevation in the group as a whole was largely due to the cholelethiasis group, and significant differences were not found with the other two groups. The highest levels of immune complexes were found in the gut disease group (Table 3); this group contained patients with Crohn's disease etc., who were known to have raised immune complex concentrations (Shorter *et al.*, 1976). In all groups the IgA comprised a small proportion of the total immunoglobulin. Secretory IgA (sIgA) concentrations have recently been re-evaluated in a variety of gut diseases (Delacroix & Vaerman, 1981). Greatly elevated concentrations were reported in patients with hepatic cirrhosis, and the authors concluded that the liver was important for the maintenance of normal serum levels of sIgA (Delacroix & Vaerman, 1981). This conclusion is supported by the findings of this study since the mean concentration of sIgA in portal blood was significantly raised compared with peripheral blood (Fig. 2), although this was mainly due to the increased levels of sIgA found in the carcinoma group, most of whom suffered from carcinoma of the bowel (Table 1).

The liver could be involved with homeostasis of IgA in three respects: (i) the removal of pIgA from serum via a secretory component receptor on bile duct cells, (ii) the transport of pIgA by a non SC-dependent mechanism, and (iii) the transfer of sIgA by a mechanism that is not yet characterized. In man the main transfer of pIgA seems to occur via SC receptors on bile duct cells and not on hepatocytes (Delacroix & Vaerman, 1983) and seems to be some 50 times less efficient than that of the rat or the mouse. As well as sIgA, dimeric IgA devoid of SC is present in bile (Delacroix & Vaerman, 1983). This suggests that a non-SC-dependent transport system may exist for pIgA in man.

The study examined five aspects of IgA in a comparison of portal with peripheral blood samples from 54 patients. The selection of patients was dictated by availability and access, and it should be borne in mind that certain of the characteristics examined may have been altered by the disease state. A comparison of IgA in portal and peripheral blood does not provide direct evidence for the role of the liver in regulation of IgA in man since other factors apart from liver function, notably a simple dilution effect, could explain differences. Nevertheless, the observations of differences with respect to pIgA, sIgA and the IgA content of immune complexes are consistent with the view that the liver in man plays an important role in the delivery of pIgA and sIgA from plasma into the gut, where they could contribute to the local defence mechanisms (Walker, Isselbacher & Bloch, 1972).

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