CLEARANCE OF CIRCULATING IgA IMMUNE COMPLEXES IS MEDIATED BY A SPECIFIC RECEPTOR ON KUPFFER CELLS IN MICE

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The ability of the hepatic mononuclear phagocytes to bind, ingest, and degrade circulating IgG immune complexes is recognized as a fundamental feature of the immune defense mechanisms (1). This process involves specific interaction of IgG molecules in immune complexes with Fc receptors on the Kupffer cells (2–5). The general aspects of the Fc receptor structure and the secondary events associated with receptor–immune complex interactions are detailed in comprehensive reviews (6, 7).

Clinical and experimental studies have demonstrated that IgA immune complexes (IgA-IC)[1] play an important role in certain nephritides (8–10). The mechanisms, however, that govern circulation and tissue deposition of IgA immune complexes remain largely unknown.

A recent study demonstrated that soluble immune complexes of dimeric (dIgA) and monomeric IgA (mIgA) behave similarly in circulation. The rate of removal of these complexes from circulation was directly related to the number of IgA molecules in the immune complexes and the liver was the primary organ involved in removal of circulating IgA immune complexes if four dIgA or eight mIgA molecules were present in the complex (11, 12).

We have considered the possibility that the hepatic removal of IgA-IC from the circulation might be mediated by specific receptors. In the studies reported here, we used kinetic, morphologic, and binding specificity criteria, suggested by Silverstein et al. (7), to demonstrate in vivo the presence of specific receptors on Kupffer cells that bind and remove IgA-IC from circulation.

Materials and Methods

Preparation of Antibodies and Immune Complexes. Mouse IgA anti-dinitrophenyl (DNP) was purified from the ascites of plasmacytoma MOPC-315 (obtained through the courtesy of Dr. M. Potter, National Institutes of Health) as previously described (9). Covalently cross-linked multimeric IgA immune complexes were prepared with bivalent affinity-

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[1] *Abbreviations used in this paper:* Anti-DNP, antibodies to DNP; BDPE, bis-2,4-dinitrophenyl pimelic ester; BBS, borate-buffered saline; dIgA, dimeric IgA; DNP, 2,4-dinitrophenyl; IgA-IC, IgA immune complexes; K_{el}, elimination rate constant; mIgA, monomeric IgA; PBS, phosphate-buffered saline, pH 7.4; TCA, trichloroacetic acid.

labeling antigen, bis-2,4-DNP pimelic ester (BDPE) (courtesy of Dr. P. Plotz, NIH) by previously described procedures (11, 13). Complexes of varying lattice size were obtained by gel filtration on sequential 1.6 × 90-cm columns of Ultrogel AcA-22 and AcA-34 (LKB Instruments, Gaithersburg, MD). Fractions containing large or a mixture of large- and intermediate-latticed complexes eluted between 41 and 51% of the total column volume and were pooled and concentrated by negative pressure in a collodion sac (Schleicher & Schuell, Keene, NH). These covalently linked polymers were stable in borate-buffered saline (BBS), pH 8.0, and had no tendency to change size upon concentration and storage. Purified fractions of dIgA were also pooled, concentrated, and used as control preparations.

Immune complexes containing mouse IgG were prepared with purified IgG anti-DNP and BDPE as describe above. The IgG anti-DNP was produced and purified as previously described (3). Purified immune complexes or dIgA were radiolabeled, 200 μCi/mg, with carrier-free Na-^{125}I (New England Nuclear, Boston, MA) using an iodine monochloride method (14).

Preparation of Aggregated Proteins. Heat-aggregated mouse IgG was prepared by slight modification of the method described by Dickler and Kunkel (15). Purified mouse IgG (Cappel Laboratories, Cochranville, PA) was dissolved in phosphate-buffered saline (PBS), pH 7.4, to a concentration of 10 mg/ml, heated for 30 min at 63°C, and centrifuged at 106,000 *g* for 60 min. The gelatinous pellet was redissolved and diluted in PBS to the original concentration. The aggregated mouse IgG preparation was used only within 24 h of preparation.

Aggregated human serum albumin was prepared as described (5). Human serum albumin (Sigma Chemical Co., St Louis, MO) dissolved in BBS at a concentration of 30 mg/ml was heated for 30 min at 79°C with continuous shaking. Aggregates of human serum albumin were purified by gel chromatography on a Sepharose 4B column (Pharmacia Fine Chemicals, Piscataway, NJ).

Animal Experiments. Female 2–3-mo-old C57BL/6J mice (18–25 g) were obtained from The Jackson Laboratory, Bar Harbor, ME. Varying doses of radioiodinated immune complexes in 0.25 ml of BBS were injected into the tail vein. Blood samples, 20 μl, were obtained with heparinized micropipettes from the retroorbital venous plexus at different time intervals. Blood samples were expelled from the micropipettes into 0.5 ml of BBS in small glass tubes and an equal volume of 20% trichloroacetic acid (TCA) was added. After centrifugation at 2,000 *g* for 15 min, the TCA pellet and supernatant were counted separately in an automatic gamma counter. The values of TCA-precipitable radioactivity remaining in the blood were used to derive clearance curves; the first three data points were used to extrapolate the zero time value by linear regression analysis. The means and standard deviations were calculated for each time point, plotted, and analyzed by graphic peeling (16). The elimination rate constant (K_{el}) was derived from the slope of the curve (slope = $K_{el}/2.303$), which was calculated by a regression analysis program on a Hewlett-Packard 9845B computer-plotter. The half-life ($t_{½}$) of circulating immune complexes was determined from the expression, $t_{½} = 0.693/K_{el}$. The clearance velocity of the injected IgA-IC was calculated with the formula, $V = 2.3026\ SY_0$, where V is the clearance velocity, Y_0 the Y intercept, and S the slope of the clearance curves at varying doses, as previously used for the study of immune complexes containing IgG (2).

Immunofluorescence Microscopy. Mouse hepatic tissue was snap-frozen in *n*-hexane and cut with a cryostat into 4-μm sections. The sections were air-dried, fixed in acetone for 10 min at room temperature, washed twice with PBS, and then fluorescein-labeled goat antibodies to mouse IgA (Meloy Laboratories, Springfield, VA) were applied. Slides were incubated for 30 min at 37°C in a humid chamber, washed three times in PBS, and mounted with Aqua-Mount (Lerner Laboratories, New Haven, CT). These preparations were examined with a Zeiss microscope equipped with a Ploem-type vertical illuminator and a 100 W mercury light source.

Light and Electron Microscope Autoradiography. The ^{125}I-radiolabeled IgA-IC, 7 μCi (28.7 μg) in BBS, were administered intravenously. Mice were sacrificed 5 min after the injection and liver slices (1–3 mm) were fixed overnight with 1.5% glutaraldehyde in 0.1

M sodium cacodylate buffer, pH 7.2. After 1.5 h postfixation in 1% OsO_4, the liver specimens were dehydrated in graded ethanol and propylene oxide and embedded in Epon epoxy resin. 1.0-μm sections were coated with NTB-2 nuclear tract emulsion (Eastman Kodak, Rochester, NY). The coated slides were exposed for 2–6 wk at 4°C. The emulsion was then developed with D19 (Kodak) and fixed with 20% sodium thiosulfate. The slides were stained with Toluidine Blue.

The flat substrate technique described by Williams (17) was selected for electron microscope autoradiography. Ultrathin sections, 60–90 nm, were stained with uranyl acetate and Reynold's citrate and coated with carbon. Ilford nuclear research emulsion L4 (Polysciences, Inc., Warrington, PA) was applied to the slides. Emulsion-coated sections were exposed at 4°C for 6–12 wk, developed with D19 (Kodak), and transferred to grids. The preparations were examined with a Siemens 102 electron microscope (Siemens Corp., Iselin, NJ) operated at 60 kV.

Light microscope autoradiographs were analyzed by counting grains over hepatocytes and nonparenchymal cells, then calculating the percentage of grains associated with each cell type. Electron micrographic prints, taken at random at a final magnification of 10,950, were analyzed for the area occupied by autoradiographic grains over each identified cell type, using an overlay transparency of a calibrated grid. The results were expressed as the area of silver grains in μm^2 per 100 μm^2 of cell area. Ultrastructural characteristics were used to categorize the nonparenchymal cells. Kupffer cells were identified by the following features: variable, stellate shapes; irregular plasma membrane with microvilli; numerous cytoplasmic dense bodies that are heterogeneous in density, shape, and diameter; numerous, large cytoplasmic vacuoles. Endothelial cells were identified by the streamlined shape of cell body and the thin, extended cytoplasm with numerous fenestrations. The infrequent fat-storing cells, localized usually within the space of Disse or in the recesses between the parenchymal cells, were easily recognized by the characteristic fat droplets in the cytoplasm.

Liver Perfusion Experiments. A previously described system was used (18). Briefly, under pentobarbital anesthesia, a long mid-line abdominal incision was made. The portal vein was isolated and a 22-gauge Angiocath (Deseret Co., Sandy, UT) was passed to the porta hepatis. The inferior vena cava was also cannulated with an Angiocath. The liver was flushed via the portal vein with Krebs-Henseleit buffer, pH 7.4, and then connected to the perfusion apparatus and perfused with oxygenated Krebs-Henseleit buffer warmed to 32°C, at a final flow rate of 3.5 ml/min. The outflow from the inferior vena cava was collected by a fraction collector at 1.8 ml/fraction.

After the initial liver washout with plain perfusion fluid, a known amount of radioiodinated test material in a 1-ml volume was introduced into the inflow perfusate, followed by 15 min of continued perfusion with oxygenated Krebs-Henseleit buffer. After the perfusion, the liver was removed and the amount of radioactivity in the liver and the total outflow were measured. The total recovery of radioactivity in liver, inferior vena cava outflow, and the residual in the injection tube was >95%. Percent hepatic uptake was expressed as: [Radioactivity in liver/(radioactivity in liver + radioactivity in outflow)] × 100.

In the blocking studies, a large amount of the potential inhibitor was premixed with 1 μg of the IgA-IC. The mixture was introduced into the perfusate and the outflow was collected and measured as described above. The effect of the test substance was expressed as the percent decrease of the hepatic uptake of radiolabeled IgA-IC.

Results

Clearance of IgA-IC by the Liver. To characterize the clearance of multimeric IgA-IC, a pooled mixture of large- and intermediate-latticed polymers of IgA were isolated by gel filtration. The injection of a small dose (1 μg) of IgA-IC was used to characterize the disappearance of radioactivity from circulation during a 60-min period. At the end of this time, <10% of the injected radioactivity was TCA precipitable. The disappearance curve consisted of two exponential com-

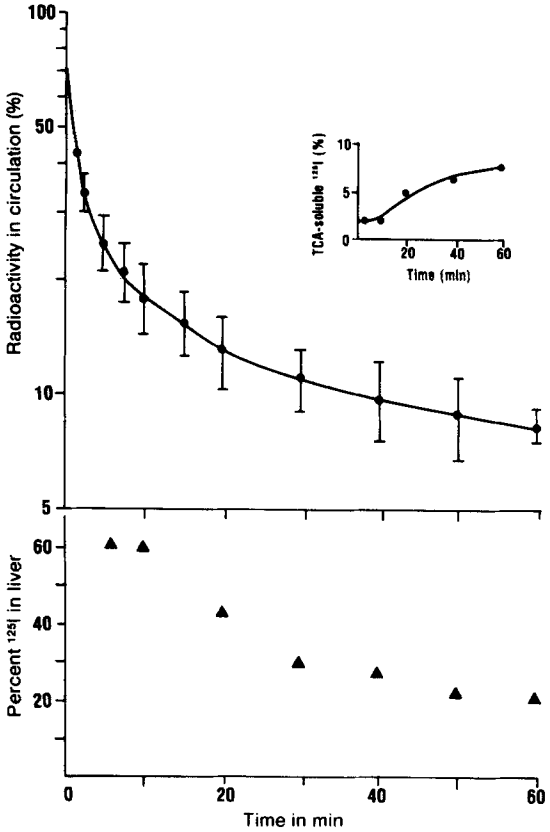

FIGURE 1. Clearance curve and hepatic content of IgA immune complexes. Mice were injected with 1 μg of ^{125}I-IgA-IC; the percent of radioactivity remaining in circulation (mean ± 1 SD for three mice) is plotted against time after injection (●). The clearance curve consisted of two exponential components, $t_{½}$ = 1.1 min and $t_{½}$ = 60 min. TCA-soluble radioactivity appeared in circulation with a 10-min lag period, as shown in the insert. The hepatic content of radioactivity is shown as percent of injected dose (▲), determined in the blood-free liver. The radioactivity removed from circulation appeared principally in the liver.

ponents, determined by graphic peeling in conjunction with linear regression analysis. The initial fast component had a mean $t_{½}$ of 1.1 min with 86.2 ± 1.3% of the TCA-precipitable radioactivity eliminated from circulation at this half-life. The second component had a mean $t_{½}$ of 60 min with 15.7 ± 1.1% of the TCA-precipitable radioactivity removed from circulation at this half-life (Fig. 1).

At 10 min, 18% of the administered dose was in the circulation while 77% of the amount removed from circulation was localized in the liver. The gradual decrease in hepatic content of radioactivity after 10 min was accompanied by an increase in TCA-soluble radioactivity in circulation (insert, Fig. 1). The radioactivity of intact gallbladder, monitored between 10 and 60 min, constituted only 0.34 ± 0.14% of the injected dose. These observations suggest that the hepatic uptake and degradation of the used IgA-IC occurred without a significant transport of radioactivity into the bile.

Hepatic Localization of IgA-IC. In previous studies (11), a liver cell separation technique was used to determine the cell type responsible for IgA-IC removal

from circulation. Due to the elapse of 30–45 min between the administration of complexes and the final separation step in those studies, nonspecific cell to cell transfer of radioactivity could not be ruled out. Therefore, immunofluorescence microscopy was used to detect the site of IgA-IC in the liver 5 min after the intravenous injection. The IgA deposits were localized along the sinusoidal walls in a granular pattern consistent with the distribution of nonparenchymal cells (Fig. 2*A*). The IgA-IC immunofluorescence pattern was very similar to that detected with mouse IgG immune complexes (data not shown). Mice that received a larger dose of dIgA did not show any fluorescence in the liver (Fig. 2*B*).

By light microscope autoradiography, performed on specimens obtained 5 min after the administration of ^{125}I-IgA-IC, 94.4% of the counted 2015 autoradiographic grains were associated with nonparenchymal cells. By electron microscope autoradiography Kupffer cells were identified as the predominant nonparenchymal cells associated with the autoradiographic grains. The results were expressed as the area of autoradiographic grains in μm^2 per 100 μm^2 of cell area. This value was 9.6 for Kupffer cells, 1.1 for endothelial cells, and 0.18 for hepatocytes. All identified Kupffer cells were heavily labeled (Fig. 3), whereas 75% of the identified endothelial cells contained no autoradiographic grains. Furthermore, the endothelial cells with autoradiographic grains were in close proximity to Kupffer cells and therefore the possibility remains that these grains were caused by ^{125}I in adjacent Kupffer cells.

Effect of Increasing Dose on Disappearance Kinetics of IgA-IC. If the removal of IgA-IC from circulation is mediated by a receptor system, it should be saturable with higher doses of the complexes. When the concentration of large-latticed IgA-IC was progressively increased, from 28 to 560 μg by the addition of unlabeled IgA-IC to 2 μg ^{125}I-IgA-IC, the elimination rate was decreased from 0.99 to 0.12, respectively (Fig. 4). The data from these experiments were used to calculate the clearance velocity of each dose of injected IgA-IC and plotted against the injected dose. The clearance velocity initially increased with the injected dose and then plateaued at the level of 21 μg/ml per minute (Fig. 5). These results are consistent with a saturable receptor-like process.

Specificity of IgA-IC Clearance. To determine whether saturation was specific for the IgA-IC under study, various potential receptor blocking agents were injected simultaneously with 2 μg of IgA-IC (Fig. 6). A large dose (2 mg) of aggregated mouse IgG that effectively inhibits the clearance and hepatic uptake of IgG immune complexes (5, 19) had no effect on the clearance or hepatic uptake of IgA-IC. Similarly, 2 mg of microaggregated human serum albumin failed to influence the disappearance pattern and hepatic uptake of IgA-IC. In contrast, the simultaneous injection of 0.5 mg unlabeled IgA-IC with 2 μg ^{125}I-IgA-IC increased the $t_{1/2}$ from 1.1 to 12.1 min (Fig. 6). To exclude the possibility that a secretory component on the surface of hepatocytes might act as a receptor for IgA-IC, 2 mg of dIgA, which combines avidly with secretory component (20), was administered simultaneously with 1 μg of IgA-IC. No inhibitory effect was observed with free dIgA. These results suggest that saturation was specific for IgA and occurred when these antibody molecules are polymerized in immune complexes.

Studies in the Perfused Mouse Liver. The potential contribution of complement

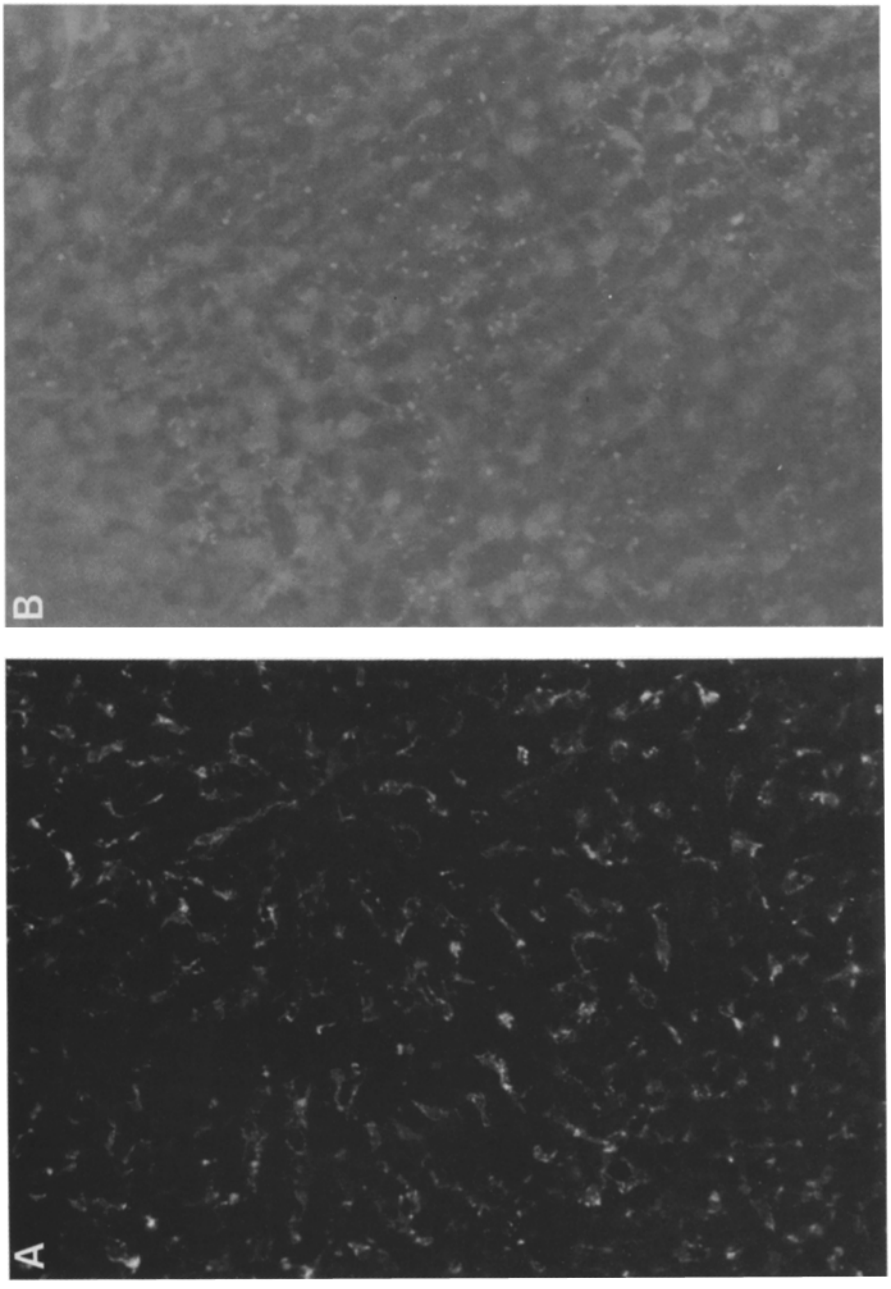

FIGURE 2. Hepatic immunofluorescence patterns after staining with fluoresceinated goat antibodies to mouse IgA. (*A*) At 5 min the staining was predominantly sinusoidal in mice that received 50 μg of IgA-IC. (*B*) No green fluorescence was seen in mice that received 200 μg of purified dIgA; only the yellow fluorescence of lipofuchsin was noted. A longer exposure time was used for this photograph to visualize the liver architecture.

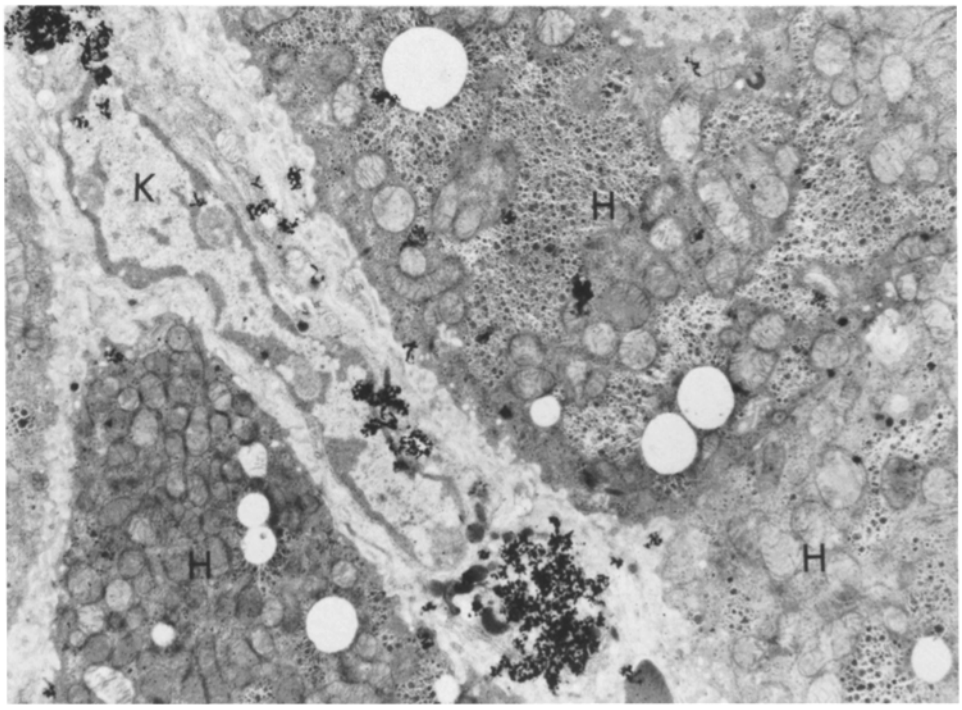

FIGURE 3. Electron microscope autoradiograph of mouse liver 5 min after injection of ^{125}I-IgA-IC. Dense collections of autoradiographic grains are associated with a Kupffer cell (K) and not with hepatocytes (H). The tissue was examined 6 wk after the coating with nuclear emulsion. × 7,070.

components or other serum proteins to IgA-IC clearance could not be ruled out by in vivo studies. For this reason studies were done with mouse liver perfused with a buffer, thus avoiding the presence of serum proteins.

When a normal liver was perfused with 2 μg of dIgA, <3% hepatic uptake was observed in a single passage (Fig. 7). In contrast, a significant amount, 43.5 ± 4.9%, of large-latticed IgA-IC in Krebs-Henseleit buffer was removed. Virtually identical results were obtained with IgA-IC preincubated for 30 min at 37°C with heat-inactivated or fresh mouse serum before addition to the perfusate. Thus, neither complement nor any other serum proteins contributed to hepatic removal of the tested IgA-IC.

This perfusion system was also used to test the effect of large amounts of different agents on the hepatic binding of a trace dose of IgA-IC. Fucose is the terminal sugar reisude added to MOPC-315 IgA prior to secretion (21). To rule out the involvement of the fucose receptor on hepatocytes (22) in uptake of IgA-IC, 6 mg of fucoidin was perfused simultaneously with 1 μg ^{125}I-IgA-IC. Fucoidin did not alter the hepatic uptake of IgA-IC. Similarly, 2 mg aggregated mouse IgG, 2 mg aggregated human serum albumin, and 5 mg purified dIgA did not influence the uptake of IgA-IC. In contrast, 1 mg of unlabeled IgA-IC caused an 88% decrease in hepatic uptake of the radiolabeled IgA-IC. These results

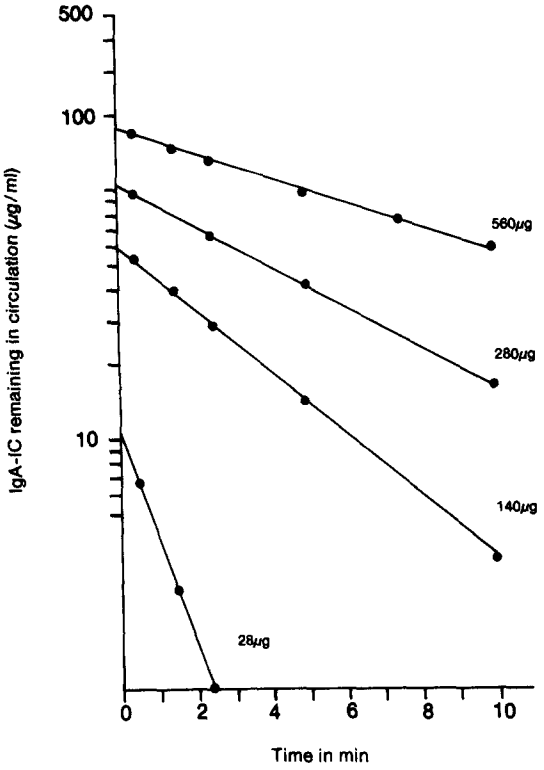

FIGURE 4. Clearance curves of increasing doses of IgA-IC. The concentration (μg/ml) of IgA-IC remaining in circulation was plotted against time during the initial rapid removal of injected complexes. Mice were given IgA-IC containing 2 μg of ^{125}I-IgA-IC with increasing amounts of unlabeled IgA-IC with the same lattice. The μg/ml remaining were calculated from the radioactivity in 20 μl of blood and the specific activities of each preparation. The K_{el} was 0.99, 0.30, 0.19, and 0.12 for 28, 140, 280, and 560 μg of IgA-IC, respectively. Each point represents the observed mean value of three mice in each experiment.

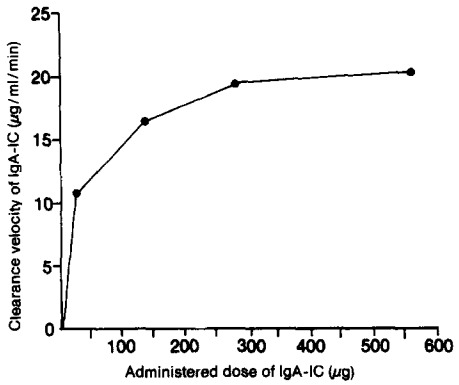

FIGURE 5. Effect of increased doses of injected IgA-IC on the initial clearance of these complexes. The clearance velocity ($\mu g/ml \cdot min^{-1}$) was calculated using the data presented in Fig. 3. With the higher doses the clearance velocity reached a maximum, indicating a saturable process.

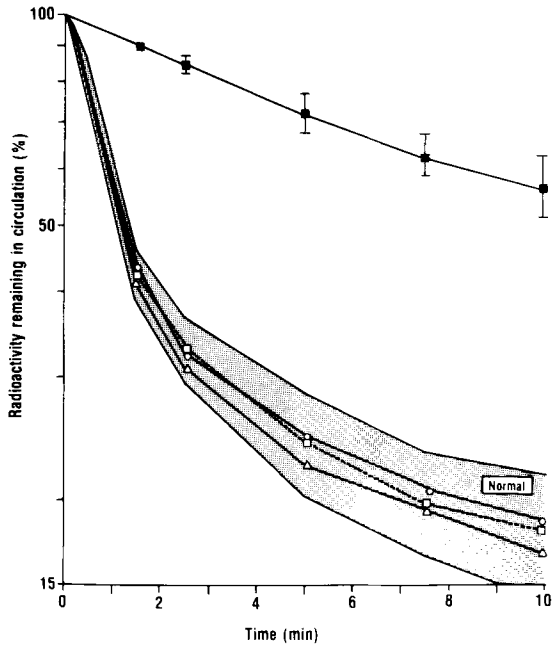

FIGURE 6. Clearance of 2 μg of ^{125}I-IgA immune complexes administered simultaneously with a 2 mg dose of heat-aggregated mouse IgG (□), aggregated human serum albumin (○), and purified dIgA (△). The clearance of ^{125}I-IgA-IC was inhibited only by 0.5 mg unlabeled IgA-IC (■). The dotted area represents the clearance of the test dose of ^{125}I-IgA-IC (mean ± SD). Each point represents the mean value of three mice.

agreed well with the in vivo data and confirmed the specificity of the receptor for IgA-IC.

Discussion

The presented data permit a conclusion that distinct receptors exist on mouse Kupffer cells for the removal of circulating IgA in immune complexes. First, the clearance of a small dose of radiolabeled mouse IgA immune complexes was rapid and it progressively decreased by the addition of increasing amounts of identical, unlabeled IgA immune complexes (Fig. 4). The clearance velocity of the IgA immune complexes increased with the dose of injected complexes and approached a maximum value with the highest doses (Fig. 5). Second, 5 min after the injection of the IgA immune complexes, they were associated by immunofluorescence and light microscope autoradiography with nonparenchymal cells in the liver. Electron microscope autoradiography disclosed that the radioactivity was predominantly within Kupffer cells. Third, the rapid clearance from circulation of the test dose of IgA immune complexes was slowed by the unlabeled IgA immune complexes and not by IgG immune complexes or aggregated human serum albumin (Fig. 6). Thus, the criteria proposed by Silverstein et al. (7) for the existence of specific receptors for the uptake of circulating materials were fully met. As previously documented, the rapid hepatic uptake of mouse IgA immune complexes occurred when eight or more IgA molecules

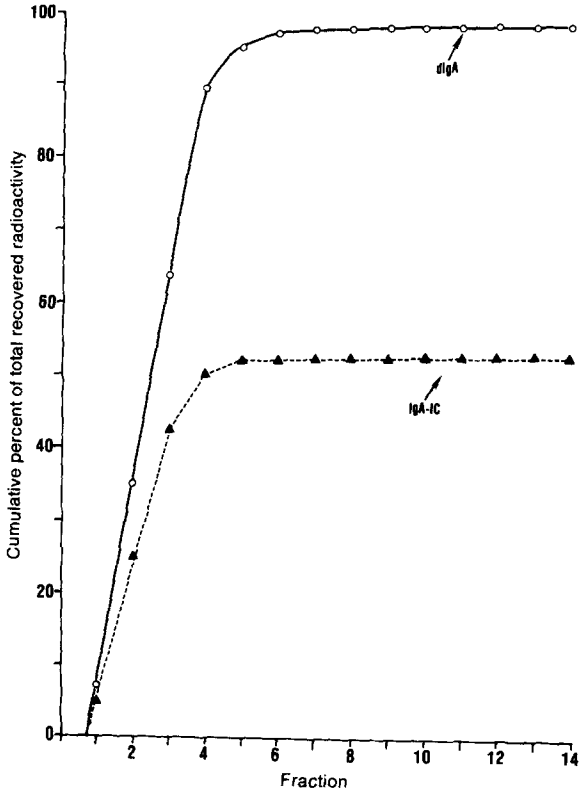

FIGURE 7. Recovery of radioactivity from the inferior vena cava after perfusion of the liver with 1 μg of ^{125}I-IgA-IC or ^{125}I dIgA in Krebs-Henseleit buffer. The cumulative percent of infused radioactivity was calculated after the addition of each successive 1.8-ml fraction of hepatic outflow. Less than 3% of the injected dIgA (○) was removed by the liver, but 43% of the IgA-IC (▲) was removed in a single passage through the liver.

were present in the complexes (11). This minimum could be achieved either by eight monomeric IgA molecules or by four dimeric IgA molecules. Thus, the IgA-specific receptor on mouse Kupffer cells does not distinguish monomeric and dimeric IgA molecules.

Several other points need to be considered in view of the presented data. The role of the secretory component on rat hepatocytes in hepato-biliary transport of polymeric IgA is well established in rats (23–25). Three lines of evidence ruled out the participation of secretory component as a receptor for large-latticed IgA-IC in our studies. First, the amount of radioactivity detected in the bile at different intervals was extremely low, <0.5% of the injected dose. Second, large amounts of native dIgA failed to influence the IgA-IC clearance pattern (Fig. 6) or hepatic uptake in liver perfusion studies. Third, morphological evidence showed uptake of IgA-IC by Kupffer cells. The variance of these results with studies in rats is of interest but not unique, since morphological and functional studies in humans (26, 27) and other species (28) showed little or no hepatobiliary transport of polymeric IgA.

In vitro experiments with isolated rat hepatocytes have suggested that recog-

nition of a galactose or *N*-acetyl-galactosamine on polymeric IgA by a receptor on hepatocytes may mediate uptake of IgA (29, 30). Such a mechanism for removal of IgA-IC in mice appears unlikely since in the presented data native dIgA did not affect the clearance or hepatic uptake of IgA-IC. In addition, fucoidin, a blocker of fucose receptor on hepatocytes, failed to influence hepatic uptake of complexes containing IgA derived from MOPC-315. As indicated above, this IgA possesses fucose as terminal sugar residue on the oligosaccharide chain. Furthermore, Brown et al. (31) showed that galactose or mannose receptor blockers did not affect hepatic uptake of IgA-IC (31). These observations collectively suggest that a glycosidic moiety of IgA-IC is not involved in the interaction of these immune complexes with the specific receptor on Kupffer cells.

The possibility was considered that the uptake of IgA-IC by Kupffer cells was mediated by complement receptors after the injected IgA-IC reacted with mouse complement (32). This possibility, however, was also excluded by the liver perfusion studies that showed hepatic uptake of IgA-IC in the absence of any serum proteins. Furthermore, mouse IgA immune complexes were shown not to bind C3 or its components (33).

Thus, these studies demonstrated the existence of specific receptors on Kupffer cells that mediate the binding and clearance of IgA-IC in mice. Saturation or dysfunction of similar receptors in humans might contribute to the increased serum levels and glomerular deposition of circulating, soluble IgA-IC reported in patients with IgA nephropathy, Schönlein-Henoch purpura, and glomerulonephritis associated with alcoholic liver cirrhosis.

Summary

To characterize the physiology of circulating IgA immune complexes (IgA-IC), the dynamics of IgA-IC removal by the liver were examined. After intravenous injection, covalently cross-linked IgA antibodies to the dinitrophenyl determinant were rapidly removed from the circulation by the liver. Immunofluorescence microscopy and light and electron microscope autoradiography showed that the IgA-IC were associated with Kupffer cells. With increasing doses of injected IgA-IC the clearance velocity approached a maximum, thus prolonging the circulation of IgA-IC. All these observations indicated a receptor-mediated process. Saturating doses of various potential receptor-blocking agents, heat-aggregated mouse IgG, microaggregated human serum albumin, and purified dimeric IgA did not influence the clearance pattern and hepatic uptake of radiolabeled IgA-IC. Mouse livers were also perfused via the portal vein with 1 μg of IgA-IC. In the presence or absence of serum proteins, 43% of the perfused IgA-IC were removed in a single passage. This liver uptake was not reduced with simultaneous perfusion of large doses of aggregated mouse IgG, aggregated human serum albumin, or purified free dimeric mouse IgA. In contrast, the liver uptake of radiolabeled IgA-IC was decreased by 88% with the addition of 1 mg unlabeled IgA-IC. These observations support the conclusion that removal of IgA-IC from circulation is mediated by a specific IgA receptor on Kupffer cells.

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