Determination of Kupffer Cell Fc Receptor Function *In Vivo* following Injury (42994)

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Abstract. **This study was carried out to determine whether Kupffer cell Fc receptor function is depressed after injury. Three approaches to the determination of Fc receptor function were evaluated: IgG-coated erythrocytes (EIgG) were used as the receptor probe with a perfused liver system, EIgG were used as the receptor probe *in vivo,* and small aggregates of IgG (AIgG) were used as the receptor probe *in vivo.* Nearly half of the injected dose of EIgG was taken up by the perfused liver (nonrecirculating, serum-free system). In contrast, only 2.6% of erythrocytes not coated with IgG were taken up, and only 5.6% of erythrocytes coated with IgM were taken up by the perfused liver. Thus, there was little nonspecific or complement-dependent uptake of EIgG by the liver. The uptake of EIgG by the perfused liver was depressed following thermal injury, endotoxemia, and the phagocytosis of EIgG. These results were interpreted as indicating that Kupffer cell Fc receptor function was depressed under these conditions. The results obtained with the hepatic uptake of EIgG *in vivo* were very similar to those with EIgG in the perfused liver. However, since it was found that complement receptors as well as Fc receptors were probably involved in the *in vivo* clearance of EIgG, these results could be due to a depression of one or both of these receptors. The hepatic uptake of AIgG was not depressed by complement depletion, but was decreased by the injection of large aggregates of IgG. However, the hepatic uptake of AIgG was not depressed following thermal injury, endotoxemia, or the phagocytosis of EIgG. Thus, AIgG was not sensitive to the effects of injury on Kupffer cell function, whereas the uptake of EIgG by the perfused liver may provide an indication of Kupffer cell Fc receptor function. The depression of Kupffer cell Fc receptor function following injury may contribute to the impairment of host defense caused by injury.** [P.S.E.B.M. 1989, Vol 192]

Kupffer cells are considered to play an important role in host defense against systemic bacterial infection. One of the lines of evidence that has contributed to our understanding of the contribution of Kupffer cells to host defense is the demonstration that *in vivo* Kupffer cell complement receptor function is depressed in several states of increased susceptibility to infection (1, 2). While *in vivo* complement receptor function has been studied, Kupffer cell Fc receptor function has not been evaluated (1). There are clear differences in the function of these two types of receptors, e.g., complement receptors are important for the binding of particulate material to Kupffer cells *in vivo* (especially erythrocytes), and Fc receptors are important for phagocytosis and stimulation of the respiratory burst (1, 3, 4). Therefore, it is of interest to know the function of both of these receptors under conditions of depressed host defense such as occurs following injury (1, 2).

Evaluation of macrophage Fc receptor function *in vitro* can be readily accomplished. However, a method for the *in vivo* determination of Kupffer cell Fc receptor function has not been fully developed. The principal difficulty with the *in vivo* evaluation of Kupffer cell Fc receptor function is the important role played by complement and complement receptors in the clearance of test particles by Kupffer cells. Small immune complexes circumvent this role of complement because their clearance from the blood by Kupffer cells is not depressed when serum complement is depleted with cobra venom factor (5, 6). Indeed, Jimenez and Mannik (7) suggested that small aggregates of IgG are an Fc receptor-specific probe for Kupffer cells *in vivo.* Another approach to the determination of Fc receptor function was evaluated in the present study. This approach employed IgG-

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coated erythrocytes (EIgG) as the receptor probe in a liver perfused with serum-free media. This allows the removal of serum complement so that EIgG do not become coated with complement and their binding to Kupffer cells may be mediated by Fc receptors. Since the liver was perfused for a short time, it was assumed that the measurement of Fc receptor function reflected the *in vivo* function of these receptors. Binding of EIgG to Kupffer cells *in vivo* is mediated by IgG and C3b/C3bi on the surface of the erythrocytes (1, 3). After EIgG bind to Kupffer cells, the IgG mediates phagocytosis of the erythrocytes by interacting with Fc receptors (8). Reduction of the amount of IgG on the surface of the erythrocytes to the point where complement is not activated greatly reduces the hepatic uptake of EIgG (3).

The objective of this study was to determine whether Kupffer cell Fc receptor function is depressed following injury. Three approaches to the determination of Kupffer cell Fc receptor function *in vivo* were evaluated: first EIgG were used as the receptor probe with a perfused liver system; second, EIgG were used as the receptor probe *in vivo*; and third, small aggregates of IgG were used as the receptor probe *in vivo*. Receptor function was assessed following surgical injury and thermal injury, as well as following endotoxemia and the phagocytosis of EIgG. Each of these interventions has been shown to depress Kupffer cell complement receptor function and/or impair host defense against bacterial infection (1, 8–10).

Materials and Methods

Determination of Fc Receptor Function. *EIgG as the receptor probe with the in situ perfused rat liver.* National Institutes of Health guidelines for the use of laboratory animals were adhered to throughout this study. Male Sprague-Dawley rats weighing 200–250 g were used for all experiments. Animals were anesthetized with sodium pentobarbital (3 mg/100 g body wt iv) and heparinized (100 units /100 g). The hepatic artery was ligated and the portal vein cannulated. A nonrecirculating system was used to perfuse the liver *in situ* at a pressure of 15 cm of water. The perfusate was Krebs-Ringer bicarbonate gassed with 95% O_2-5% CO_2 (pH 7.4) and contained 1% bovine serum albumin. The flow rate was 10–13 ml/min for all experiments. The liver was first perfused for 2 min, then EIgG (1×10^9/100 g) were added to 2 ml of perfusate, and finally the liver was perfused for an additional 2 min. A small amount of colloidal carbon was added to the last milliliter of perfusate to verify homogenous perfusion. EIgG labeled with ^{51}Cr were prepared as for *in vivo* use and hepatic uptake was determined from the radioactivity present in the liver. Rat erythrocytes coated with anti-erythrocyte IgM (EIgM) were prepared as described previously (10). The amount of IgM was adjusted to obtain 70–80% hepatic uptake of EIgM *in vivo* at 10 min after injection (3×10^8/100 g). Serum complement levels were depleted by the ip injection of purified cobra venom factor (20 units/100 g) 18 hr before study. Immunoreactive C3 levels were determined by radial immunodiffusion.

EIgG as the receptor probe in vivo. EIgG were prepared as described previously (10). Briefly, washed rat erythrocytes, labeled with ^{51}Cr, were incubated with anti rat erythrocyte IgG (U.S. Biochemical Corp.) at 37°C for 30 min. The concentration of antibody was adjusted to obtain 70–80% hepatic localization of EIgG at 10 min after injection of 2.9×10^8 EIgG/100 g. Erythrocytes not coated with IgG were prepared in the same manner as the EIgG except that no antibody was used. For the determination of Fc receptor function, EIgG were injected at a dose of 2.9×10^8/100 g and hepatic localization was determined at 30 min after injection.

Aggregated IgG (AIgG) as the receptor probe in vivo. To obtain small aggregates of IgG, human IgG (Sigma Chemical Co.) was dissolved at 20 mg/ml in 0.1 *M* Tris-HCl buffer (pH 7.5) containing 0.15 *M* NaCl. The IgG was aggregated by heating at 63°C for 10 min, and then centrifuged at 5000*g* to remove insoluble aggregates.The solution was passed through a Bio-Gel 1.5 *M* column. The elution profile (A280) of this column was determined as follows: first, a small peak at the void volume of large aggregates; second, a broad fraction of small aggregates (containing about 3–10 IgG molecules); third, a large peak of monomeric IgG. The small aggregate fraction was concentrated to 0.3 mg of IgG/ml, labeled with ^{125}I using the iodine monochloride method (11), and dialyzed for 48 hr. This preparation of AIgG contained 5–10% free ^{125}I as determined from trichloroacetic acid-nonprecipitable radioactivity. Large soluble aggregates of IgG (containing more than 10 IgG molecules) were prepared as described for the small aggregates except that the IgG solution was prepared at 50 mg/ml and heated at 63°C for 30 min and the first peak eluted from the column was used. Large aggregates were injected at a dose of 750 μg/100 g 15 min before determining Fc receptor function with AIgG.

Initial studies characterized the clearance from the blood and organ localization of AIgG. AIgG was injected at doses of 50, 100, and 500 μg/100 g, and blood levels were determined at 2, 4, 6, 8, and 10 min after injection for the determination of the clearance rate. Organ localization (liver, spleen, lungs, heart, and kidneys), as well as blood levels of trichloroacetic acid-precipitable and -nonprecipitable radioactivity, was determined at 5, 10, 15, 30, and 60 min after injection of AIgG. For determination of Fc receptor function, AIgG was injected at a dose of 100 μg/100 g and the hepatic localization was determined at 10 min after injection. Organ localization of radioactivity was not corrected for the blood that was present in the organs.

Effect of Surgical Injury, Thermal Injury, Endotoxemia, and Phagocytosis of EIgG on Fc Receptor Function. *Surgical injury.* Animals were anesthetized with ether, and a 5-cm laparotomy and 1.5-cm enterotomy were performed with immediate closure (9). Receptor function was determined 2 hr after injury. Control animals received no treatment prior to evaluation.

Thermal injury. Animals were anesthetized with ether and the dorsum was immersed in 90°C water for 30 sec (9). The burn involved 26–28% of the body surface area. Sterile saline was injected ip (10% body wt) at the time of injury. This fluid therapy has been shown to reduce the mortality rate of this injury from 80% to less than 10% at 48 hr postinjury. Receptor function was determined 2 hr after injury. Control animals received no treatment prior to evaluation.

Endotoxin. Salmonella enteritidis (lipopolysaccharide b, Difco Labs) was injected at a dose of 0.2 mg/100 g iv. Receptor function was determined 30 min after injection of endotoxin. Control animals received an equal volume of phosphate-buffered saline (PBS) (0.9% NaCl, 5 m*M* phosphate buffer (pH 7.4)).

Phagaocytosis of EIgG. Phagocytosis of erythrocytes was induced by the injection of EIgG (1.74×10^9/100 g) (8). Receptor function was determined 30 min after the injection of EIgG. Controls received an equal volume of PBS.

Statistics. Data are expressed as the mean ± the standard error of the mean. Data were analyzed using a one-way analysis of variance and the Newman-Keuls multiple range test. The level of confidence was placed at 95% for all experiments.

Results

EIgG as the Receptor Probe with the Perfused Liver. The uptake of EIgG by the *in situ* perfused liver was 46.5 ± 2.7% of the injected dose (% ID) (Table I). The localization of erythrocytes not coated with IgG in the perfused liver was 2.6 ± 0.3% ID. The C3 level in the liver effluent was 0.5 ± 0.15% of control after 25 ml of perfusion and was 0.4 ± 0.12% of control after 50 ml of perfusion. Localization of EIgM (3×10^8/100 g) in the perfused liver was 5.6 ± 0.6% ID. Additionally, administration of cobra venom factor which depleted serum C3 levels to less than 10% of normal had no effect on the hepatic uptake of EIgG (44.7 ± 4.0% ID) in the perfused liver ($n = 5$).

Results obtained with EIgG as an Fc receptor probe in the perfused liver are shown in Figure 1. Surgical injury did not cause a change in the hepatic uptake of EIgG, but there was a decrease in the hepatic uptake of the receptor probe following thermal injury, injection of endotoxin, and phagocytosis of EIgG. None of these interventions was associated with a change in the rate of perfusion of the liver *in situ.*

EIgG as the Receptor Probe *In Vivo.* The *in vivo* organ localization of EIgG (2.9×10^8/100 g) at 10 min after injection was: liver, 72.2 ± 2.4% ID; spleen, 11.5 ± 0.6% ID; lungs, 1.8 ± 0.2% ID; and at 30 min after injection was: liver, 76.5 ± 1.2% ID; spleen, 10.4 ± 0.4% ID; and lungs, 2.5 ± 0.2% ID (Table I). Blood radioactivity plus the localization in these organs gave a label recovery of 95–105%. Less than 3% of the blood radioactivity was present in the plasma, indicating that there was very little intravascular lysis of the EIgG. Hepatic localization of erythrocytes not coated with IgG was 4.2 ± 0.2% ID. Depletion of serum complement to less than 10% of normal C3 levels with cobra

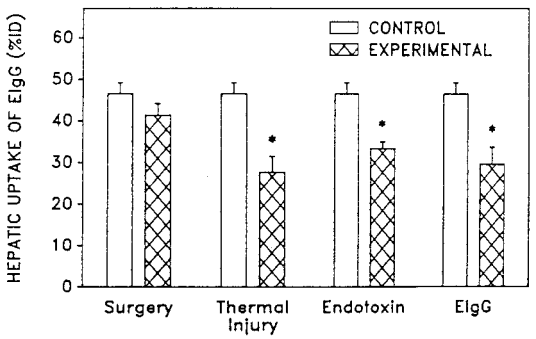

Figure 1. Uptake of EIgG (labeled) in the isolated perfused liver following surgical injury, thermal injury, injection of endotoxin, and phagocytosis of unlabeled EIgG. The liver was perfused *in situ* via the portal vein with a nonrecirculating system. Labeled EIgG (1×10^9/100 g) were added to the perfusate after 2 min of perfusion and uptake was determined after an additional 2 min of perfusion. Animals were evaluated at 2 hr after surgical and thermal injury and 30 min after the injection of endotoxin (0.2 mg/100 g) and unlabeled EIgG (1.74×10^9/100 g). Values are expressed as the percentage of the injected dose of EIgG localized in the liver and are the mean ± SE with five to six animals per group. *$P < 0.05$ compared with the control group.

Table I. Organ Localization of the Fc Receptor Probes in Normal Animals

Receptor probe	Dose	Organ localization (% injected dose)[a]		
		Liver	Spleen	Lungs
EIgG, perfused liver	1×10^9/100 g	46.5 ± 2.7		
EIgG, *in vivo*	2.9×10^8/100 g	76.5 ± 1.2	10.4 ± 0.4	2.5 ± 0.2
AIgG, *in vivo*	100 μg/100 g	24.8 ± 0.6	1.2 ± 0.1	2.1 ± 0.2

[a] In the perfused liver, the perfusion was continued for 2 min after the addition of EIgG to the perfusate, before determining the liver uptake of EIgG. Organ localization *in vivo* was determined 30 min after injection of EIgG and 10 min after injection of AIgG. Values are the mean ± SE with five to six animals per group.

venom factor decreased the hepatic uptake of EIgG to 54% of the uptake in untreated control animals at 30 min after injection. Therefore, the clearance of EIgG from the blood is probably mediated by complement receptors as well as Fc receptors on Kupffer cells.

The results obtained when EIgG were used *in vivo* are shown in Figure 2. Surgical injury did not cause a change in the hepatic uptake of EIgG, but each of the other interventions (thermal injury, injection of endotoxin, phagocytosis of EIgG) caused a decrease in the hepatic uptake of this receptor probe.

AIgG as the Receptor Probe *In Vivo*. Initial studies characterized the clearance from the blood and organ localization of AIgG. Half-time of AIgG in the blood was estimated to be 11–18 min. However, a more accurate half-time for AIgG could not be determined because blood radioactivity did not follow a monoexponential decrease during the first 10 min after injection. Hepatic localization of AIgG injected at doses of 50, 100, and 500 μg/100 g was 24.5 ± 0.6% ID, 24.8 ± 0.6% ID, and 20.4 ± 0.4% ID at 10 min after injection, respectively. The time course of the hepatic localization of the 100 μg/100 g dose of AIgG was: 5 min, 21.9 ± 0.7% ID, 10 min, 24.8 + 0.6% ID; 15 min, 20.9 ± 0.5% ID; 30 min, 16.2 ± 0.3% ID; and 60 min, 11.4 ± 0.4% ID. The decrease in hepatic localization between 10 min and 60 min was associated with an increase in free ^{125}I in the blood from 4.8 ± 0.2% to 9.5 ± 0.2%. Localization of AIgG in other organs at 10 min after injection was: spleen, 1.2 ± 0.1% ID; lungs, 2.1 ± 0.2% ID; kidneys, 2.1 ± 0.1% ID; and heart, 0.22 ± 0.1% ID. Depletion of serum complement with cobra venom factor had no effect on the hepatic localization of AIgG (control, 24.8 ± 0.6% ID; cobra venom factor 25.5 ± 0.3% ID).

The results obtained when AIgG was used as an Fc receptor probe (100 μg/100 g, hepatic uptake at 10 min) are shown in Figure 3. There was no change in the hepatic uptake of AIgG following thermal injury, injection of endotoxin, or the phagocytosis of EIgG. The injection of large aggregates of IgG (more than 10 IgG molecules) did cause a decrease in the hepatic uptake of the receptor probe (Fig. 3).

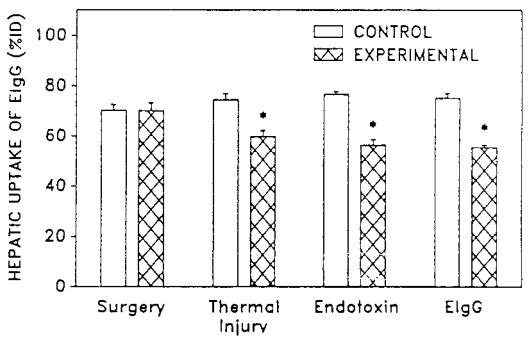

Figure 2. Hepatic uptake of EIgG (labeled) *in vivo* following surgical injury, thermal injury, injection of endotoxin, and phagocytosis of unlabeled EIgG. For the assessment of receptor function, labeled EIgG were injected at a dose of 2.9×10^8/100 g and hepatic uptake was determined at 10 min after injection. Animals were evaluated at 2 hr after injury, and 30 min after the injection of endotoxin (0.2 mg/100 g) and unlabeled EIgG (1.74×10^9/100 g). Values are expressed as the percentage of the injected dose of EIgG present in the liver, and are the mean ± SE with six animals per group. $^*P < 0.05$ compared with the control group.

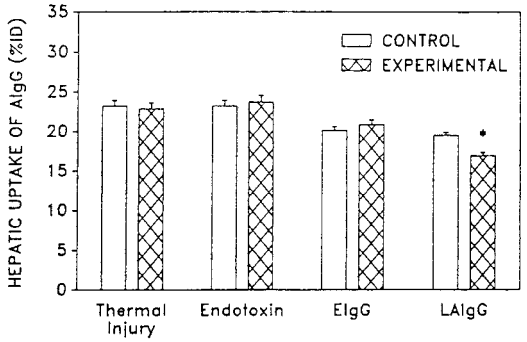

Figure 3. Hepatic uptake of AIgG after thermal injury, injection of endotoxin, EIgG, and large aggregates of IgG (LAIgG). For the assessment of receptor function, labeled AIgG was injected (100 μg/100 g) and hepatic uptake was determined 10 min after injection. Animals were evaluated 2 hr after thermal injury, 30 min after the injection of endotoxin (0.2 mg/100 g) and EIgG (1.74×10^9/100 g), and 15 min after the injection of unlabeled large aggregates of IgG (LAIgG) (750 μg/100 g). Values are expressed as the percentage of the injected dose of labeled AIgG present in the liver, and are the mean ± SE with five to six animals per group. $^*P < 0.05$ compared with the control group.

Discussion

The uptake of EIgG by the *in situ* perfused liver was probably due to binding to Fc receptors. This assertion is supported by three observations. First, the low localization of erythrocytes not coated with IgG indicates very low nonspecific trapping or binding of the erythrocytes in the liver. Second, the lack of an effect of complement depletion with cobra venom factor on hepatic uptake of EIgG and the low localization of EIgM in the liver indicates that complement played a small role in the hepatic uptake of EIgG under these conditions. Measurement of C3 in the effluent indicated that the brief perfusion was adequate to wash essentially all of the serum C3 from the liver. Third, previous work with electron microscopy has shown that EIgG do not bind to endothelial cells in the liver (8). Therefore, a decrease in hepatic uptake of EIgG was interpreted as indicated a depression of Fc receptor function. On this basis, Fc receptor function was depressed following thermal injury, endotoxemia, and the phagocytosis of EIgG, but not following surgical injury. None of these interventions caused a change in the perfusion rate of the liver, so that the rate of delivery of the receptor probe to the Kupffer cells was not altered.

The use of EIgG as an Fc receptor probe *in vivo* gave results similar to those obtained with EIgG in the perfused liver. EIgG are rapidly removed from the blood by the liver when injected at the dose employed

(3×10^8/100 g) (3, 10). Electron microscopy has shown that the hepatic uptake of EIgG is due to phagocytosis of the erythrocytes by Kupffer cells (8). It was found that serum complement was responsible for about half of the hepatic uptake of EIgG at 30 min after injection, which is consistent with the observations of Kurlander and Hall (12). This indicates that the hepatic uptake of EIgG may be mediated by complement as well as by Fc receptors. The hepatic uptake of EIgG was depressed following thermal injury, endotoxemia, and the phagocytosis of EIgG, but not after surgical injury. Our previous studies have shown that the changes in serum complement levels or hepatic blood flow caused by these interventions are not great enough to decrease the hepatic uptake of EIgG (9, 10). Therefore, the depression in hepatic uptake of EIgG *in vivo* caused by these interventions was not caused by changes in serum complement levels or hepatic blood flow, but may have been due to a depression of Kupffer cell Fc receptor and/or complement receptor function.

Kupffer cell complement receptor function as determined from the *in vivo* hepatic uptake of EIgM is depressed following each of the forms of challenge evaluated in this study (8–10, 13). It is interesting to note that surgical injury did not cause a depression of Fc receptor function, but did depress complement receptor function. Additionally, lack of a depression of EIgG hepatic uptake *in vivo* following surgical injury suggests that this approach may provide more of an indication of Fc receptor function than of complement receptor function. Further studies are required to fully verify this possibility.

Jimenez and Mannik (7) have suggested that Kupffer cell Fc receptor function can be evaluated *in vivo* using small aggregates of IgG. The aggregates were removed from the blood primarily by the liver. They observed that prior injection of immune complexes depressed the clearance rate and hepatic uptake of AIgG in a dose-dependent fashion. The present study sought to extend these observations by assessing the use of AIgG as an Fc receptor probe following injury.

The AIgG employed in the present study was similar to the preparation used by Jimenez and Mannik (7). The size of the AIgG (less than 10 IgG per aggregate) was less than that required for complement-dependent binding and degradation by macrophages *in vitro* (14). The hepatic uptake of this preparation of AIgG was not influenced by depletion of serum complement which is consistent with previous studies with small immune complexes (5, 6). We also found that prior injection of large aggregates of IgG caused a depression in the hepatic uptake of the small AIgG. However, there was no change in the hepatic uptake of AIgG following thermal injury, endotoxemia, or the phagocytosis of EIgG. This latter observation may be explained by the observations by Laan-Klamer *et al.* (15) that immune complexes bind to endothelial cells and hepatocytes as well as to Kupffer cells in the liver. Thus, the inability of AIgG to detect possible changes in Kupffer cells caused by injury may be due to high non-specific binding of AIgG in the liver. An alternative interpretation of this observation is that the clearance of EIgG and AIgG is mediated by different types of Fc receptors and that only those receptors responsible for EIgG clearance are depressed by injury. It is well established that human cells of the monocyte-macrophage lineage have three types of Fc receptor and that mice probably have similar types (16). Although Fc receptors on rat phagocytes have not been well characterized, it is likely that they have receptors corresponding to the high affinity FcRI and low affinity FcRII and FcRIII. The high affinity receptors have the highest affinity for AIgG, and the low affinity receptors have been shown to mediate the clearance of EIgG in mice and primates (17–19).

The mechanism for the depression of Fc receptor function following injury remains to be elucidated. A recent study from this laboratory has shown that Kupffer cell complement receptor function is depressed by β-receptor agonists and that the depression of complement receptor function caused by thermal injury can be reduced by β-receptor blockade (20). Additionally, it has been shown that the depression of complement receptor function caused by endotoxin can be fully blocked by the prior administration of ibuprofen or dexamethasone (21). These drugs had no effect on the depression of complement receptor function caused by the phagocytosis of EIgG. Thus, it appears that several factors may contribute to the depression of Kupffer cell receptor function under different conditions. Whatever the mechanism of the depression of receptor function, the present study suggests that a depression of Kupffer cell Fc and complement receptor function probably contributes to the impairment of host defense that is caused by injury.

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