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Inhibition of Blood Clearance and Hepatic Tissue Binding of *Escherichia coli* by Liver Lectin-Specific Sugars and Glycoproteins

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The effects of sugars and glycoproteins that are known to bind to lectins of liver tissue on the clearance of cells of *Escherichia coli* from mouse blood was investigated. The administration of 100 mg per mouse of methyl-α-D-mannoside, methyl-α-D-glucoside, or methyl-α-D-fucoside, but not of methyl-α-D-galactoside or L-rhamnose, markedly inhibited the blood clearance of cells of *E. coli* 346. Clearance was similarly inhibited by 0.1 and 1.0 mg per mouse of asialofetuin or ovalbumin, respectively, whereas fetuin had no effect. The inhibitory effects of the sugars on blood clearance was abolished by pretreating the *E. coli* cells with antibodies against whole organisms. All of these effects were equal for fimbriated and nonfimbriated phenotypes of *E. coli* 346. Homogenates of mouse liver tissue coaggregated with nonfimbriated cells of *E. coli*. The aggregation was blocked by 100 mM solutions of methyl-α-D-mannoside, or methyl-α-D-glucoside, 1 mg of bacterial lipopolysaccharide per ml, or 10 mM EDTA but not by L-rhamnose. These results suggest that the mannose-*N*-acetylglucosamine hepatic lectin recognizes specific sugars on the surface of *E. coli* and may be centrally involved in the nonimmune clearance of nonfimbriated *E. coli* from the blood of the infected host.

It has long been known that in nonimmune animals the liver clears the blood of invading bacteria (5, 18). In a recent study (36) employing 21 different isolates of *Escherichia coli*, it was found with each isolate that the majority of the bacteria became lodged in the liver within less than 1 h after intravenous injection. The mechanism by which the bacteria was recognized and trapped by liver cells, however, remains unknown.

During the past decade, evidence has accumulated to suggest that liver membranes possess specific sugar-binding proteins (lectins) (2–4, 19, 21, 30) that apparently serve as receptors for various asialoglycoproteins and, hence, are responsible for the blood clearance of these compounds by receptor-mediated endocytosis. At least three liver lectins specific for galactose-*N*-acetylgalactosamine (Gal-GalNac), mannose-*N*-acetylglucosamine (Man-GlcNac), and fucose (Fuc) residues have been isolated from mammalian livers. These have now been characterized and shown to be responsible for the blood clearance of glycoproteins. Thus, the blood clearance of asialoglycoproteins and the interaction of such glycoproteins with liver membrane fragments is inhibited by various simple sugars or neoglycoproteins, which presumably block the corresponding hepatic receptors (lectins).

The present work was undertaken to examine the possibility that liver lectins may be involved in the nonimmune blood clearance of *E. coli* 346 in mice by a mechanism similar to that of the blood clearance of glycoproteins. For this purpose, the inhibitory activities of various sugars and glycoproteins on both blood clearance and bacteria liver membrane aggregation were evaluated.

MATERIALS AND METHODS

Bacterial growth and fractionation of MS^+ and MS^- phenotypes. A urinary isolate of *E. coli* (strain 346) was grown in brain heart infusion broth at 37°C under static conditions for 48 h. The bacteria were fractionated into fimbriated (MS^+) and nonfimbriated (MS^-) phenotypes by the yeast cell aggregation technique as described previously (23). Lack of fimbriae on the MS^- phenotype was confirmed by electron microscopy.

Preparation of antibodies to *E. coli*. Antibodies against whole organisms were raised in rabbits as described previously (23) by intravenous injection of whole organisms. The sera were collected at 5 weeks and stored at −20°C.

Assays of the survival of bacteria in fresh mouse blood in vitro. The assay mixtures consisted of 0.5 ml of fresh mouse blood supplemented with 20 U of heparin per ml and 0.05 ml of *E. coli* suspension containing 10^6 to 10^7 bacteria per ml. The test mixtures were tumbled end-over-end at 37°C for 60 min, diluted first in distilled water (1:10) and then in 0.02 M phosphate–0.15 M NaCl (phosphate-buffered saline) (pH 7.4), and plated on nutrient agar to assess CFU. The results were expressed as percent change in the number of CFU as compared with the inoculum.

Blood clearance of bacteria in mice. ICR mice weighing 14 to 18 g were injected in the tail vein with 0.5 ml of phosphate-buffered saline containing ca. 10^8 bacteria and 50 U of heparin, and whenever desired, the following compounds were added to the bacterial suspension: 100 mg of sugar, 1 mg of ovalbumin, or 0.1 mg of fetuin or asialofetuin. In some experiments, bacteria were pretreated with a 1:10 dilution of anti-*E. coli* serum before being injected into the tail vein. At specified time intervals after injection, 20-μl samples of blood were withdrawn in disposable Micro Pipettes (Brand) by severing the end of the tail. The blood samples were diluted in distilled water and then in phosphate-buffered saline and plated on nutrient agar as described above.

Preparation of mouse liver tissue homogenate (liver membranes). Livers from three ICR mice were removed, washed, blotted dry, minced, and homogenized at 4°C in a laboratory mixer emulsifier (Silverson Machines) in 50 ml of 1.0 mM sodium bicarbonate buffer (pH 7.5) containing 0.5 mM $CaCl_2$ (26). The homogenate was sonicated in a sonicator (MSE Scientific Instruments) for 2 min at an amplitude of 8 μm. The sonicated mixture was centrifuged for 20 min at 1,000 × *g* to remove the remaining cells and tissue particles. The

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supernatant was then centrifuged for 5 min at 12,000 rpm in a 5414 Eppendorf centrifuge. The pellet which contained membrane fragments was suspended in 0.05 M Tris-hydrochloride (pH 7.5) containing 0.1 M NaCl, 0.01 M $CaCl_2$, and 1.0 mg of bovine serum albumin per ml for further assay.

Aggregation of liver membranes with bacteria. One drop of liver membrane suspension containing 6 mg of protein per ml was mixed on a glass slide with 1 drop of bacterial suspension containing 10^9 bacteria per ml. After 2 to 3 min of gentle mixing, agglutination was observed. To test the ability of various compounds to inhibit liver membrane-*E. coli* agglutination, the desired compounds were added in a 10-μl volume to the drop of membrane suspension before mixing with bacteria.

Sedimentation assay of MS⁻ bacteria with concanavalin A. The assay mixture contained 0.5 ml of 1 mg of concanavalin A per ml, 0.05 ml of phosphate-buffered saline containing 250 mg of the desired sugar per ml, and 0.05 ml of bacterial suspension containing 10^9 bacteria per ml. The test mixtures were left to sediment at room temperature for 15 h, after which decrease in turbidity was measured and expressed as percent sedimentation as compared with that of the control with no sugar added.

Yeast aggregometry. The bacterial MS fimbrial lectin activity was monitored by yeast aggregometry as described previously (23). Percent inhibition of the activity by various sera was calculated as previously described (7).

Chemicals. All chemicals used in this study were of the highest quality and purity available. Asialofetuin was prepared by removing *N*-acetylneuramininic acid residues from fetuin by acid treatment by the method of Kim et al. (13).

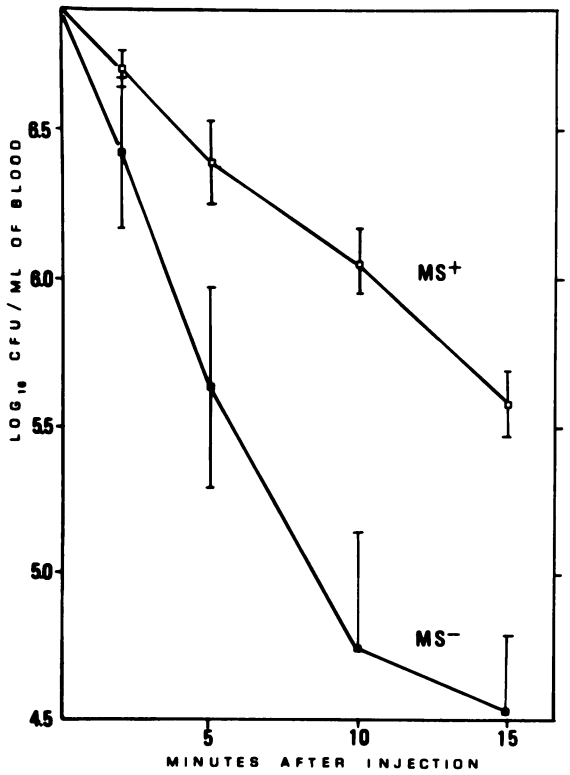

FIG. 1. Blood clearance of MS⁺ and MS⁻ phenotypes of *E. coli* 346 in mice.

TABLE 1. Inhibition of MS fimbrial lectin activity (yeast aggregation) of *E. coli* 346 by various mammalian sera

Serum	Dilution	% Inhibition (± SD)
Human	1:1	89.2 (±8.0)
	1:2	78
	1:8	0
Absorbed with concanavalin A	1:1	18.5
Mouse	1:1	91.0 (±8.2)
	1:3	73
Rabbit	1:1	94.0 (±3.6)
	1:4	0

RESULTS

Survival of *E. coli* bacteria in mouse blood in vitro and in vivo. A comparison was made between the survival of the bacteria in mouse blood in vitro and their clearance from the blood in vivo. We found that 108.7 ± 48.6% (n = 10) of bacteria remained viable during 60 min of incubation with whole fresh blood, whereas only 4.8 ± 2.6% (n = 11) of viable organisms remained in the blood of mice 15 min after intravenous injection.

The in vitro experiments suggested that blood clearance of viable organisms was not due to killing by blood phagocytes or serum bactericidal substances. Because the liver has long been recognized as the main organ involved in blood clearance of various soluble substances and particles including bacteria (5, 18), we investigated two possible mechanisms by which the liver could clear organisms from the blood stream. One involves the interaction of the bacterial fimbrial lectin (28) with mannose residues on hepatic cells, and the other involves the interaction of sugars on the bacterial surface with hepatic lectins (2, 4, 30). The results depicted in Fig. 1 indicate that organisms devoid of fimbrial lectin (MS⁻ phenotype) were cleared equally or even better than organisms expressing mannose-specific fimbrial lectin. Moreover, whole serum from various mammalian species inhibited the lectin activity of the MS⁺ phenotype (Table 1). These results suggested that the mannose-specific fimbrial lectin was not responsible for the rapid clearance of viable bacteria from the blood. To avoid any possible involvement of the bacterial fimbrial lectin in blood clearance, further experiments were performed with nonfimbriated bacteria (MS⁻ phenotype).

Inhibition of blood clearance of *E. coli* by sugars and by glycoproteins. Clearance of asialoglycoproteins from blood via hepatic lectins is specifically inhibited by sugars (1, 3, 24). Figure 2 shows that clearance of *E. coli* was inhibited by methyl-α-D-mannoside (MeαMan), methyl-α-D-glucoside (MeαGlc), and methyl-α-D-fucoside (MeαFuc) but not by methyl-α-D-galactoside (MeαGal) or L-rhamnose. The inhibitory effect of the sugar MeαMan was abolished by pretreating the bacteria with antibodies. Similar results were obtained when MS⁺ bacteria were employed (data not shown). Since the hepatic lectins bind specifically asialoglycoproteins (21, 22, 37), we attempted to block clearance of the organisms by various glycoproteins. As little as 0.1 mg of asialofetuin and 1.0 mg of ovalbumin, a mannose-rich glycoprotein devoid of sialic acid residues (29), markedly inhibited the blood clearance, whereas fetuin, which contains a terminal sialic acid residue, was without effect (Fig. 3).

Interaction of liver cell membranes with *E. coli*. Cells of *E.*

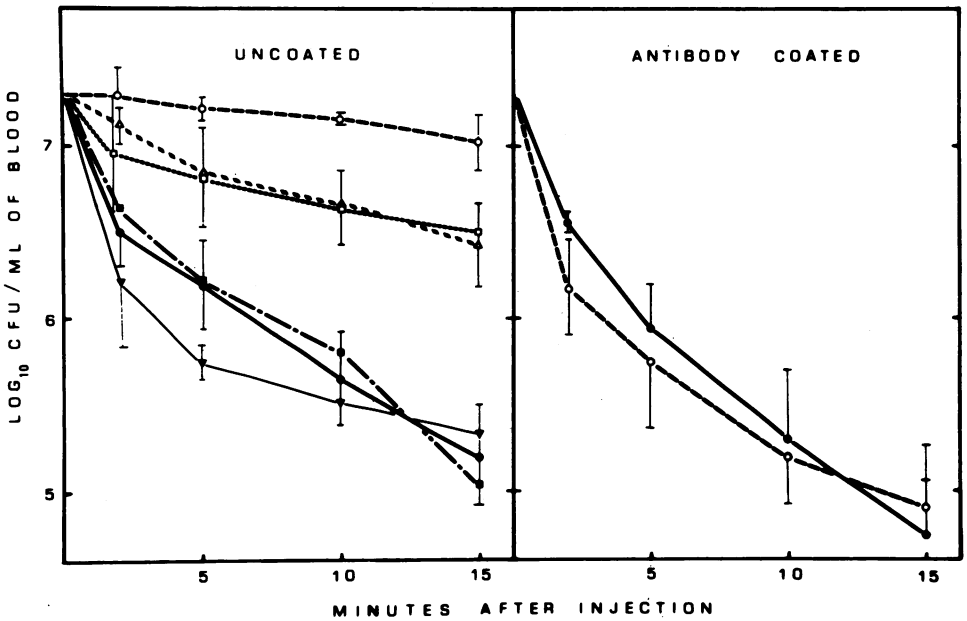

FIG. 2. Blood clearance of MS⁻ *E. coli* coated and uncoated with antibodies in the presence of 100 mg per mouse of the following sugars: MeαMan (○), MeαGlc (□), MeαFuc (△), MeαGal (▼), L-rhamnose (■), and none (●).

coli 346 agglutinated liver cell homogenates. The aggregates were found to consist of pieces of membrane to which many bacteria were attached (Fig. 4A). The formation of *E. coli* liver membrane aggregates was inhibited by 100 mM solutions of MeαMan or MeαGlc (Fig. 4B) as well as by 1 mg of lipopolysaccharide per ml extracted from the bacteria but not by L-rhamnose. The aggregation was sensitive to 10 mM EDTA, and the membranes lost their ability to aggregate bacteria after incubation at 4°C for 1 week.

Interaction of *E. coli* with plant lectins. The availability of sugar residues on the surface of *E. coli* organisms was monitored by aggregation of the bacteria with plant lectins specific for various sugar residues (Table 2); concanavalin A, a lectin specific for mannose and glucose residues, agglutinated the organisms. Wheat germ agglutinin, peanut agglutinin, *Ricinus communis* agglutinin, and mucosal lectin, which are specific for GlcNac, Gal(1→3)GalNac, Gal, and Fuc residues, respectively, did not agglutinate the bacteria. Furthermore, no agglutination of bacteria was observed with either fetuin or asialofetuin, suggesting that the organisms lack detectable receptors for these glycoproteins on their surface.

DISCUSSION

Our results can be best explained in conjunction with the numerous studies showing that lectins on the surface of hepatic cells (Kupffer cells, reticuloendothelial cells, and hepatocytes) are responsible for rapid blood clearance and endocytosis of glycoconjugates possessing terminal sugars specific for the corresponding hepatic lectins (2, 4, 19). At least three different hepatic lectins having specificities for Gal-GalNAc, Man-GlcNac, or Fuc have been isolated (2, 11, 12, 34, 35). The evidence that such hepatic lectins are involved in the blood clearance of glycoproteins is based on the inhibition of their blood clearance by specific sugars and by defined neoglycoproteins and on their in vitro interaction with hepatic cells or their membranes or isolated lectins (1, 8, 12, 14, 21, 24, 33, 35, 37). By the same analogy, we have shown that the blood clearance of the *E. coli* strain employed in this study is inhibited by the sugars MeαMan, MeαGlc, and MeαFuc as well as by the glycoproteins asialofetuin and ovalbumin but not by MeαGal, L-rhamnose, or fetuin. The

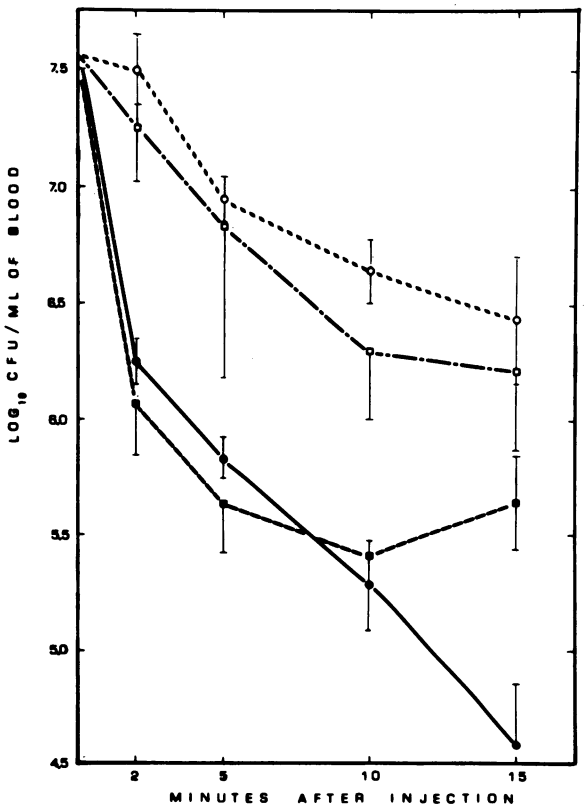

FIG. 3. Blood clearance of MS⁻ *E. coli* in the absence (●) and presence of 0.1 mg of fetuin (■) and asialofetuin (□) per mouse and 1 mg of ovalbumin (○) per mouse.

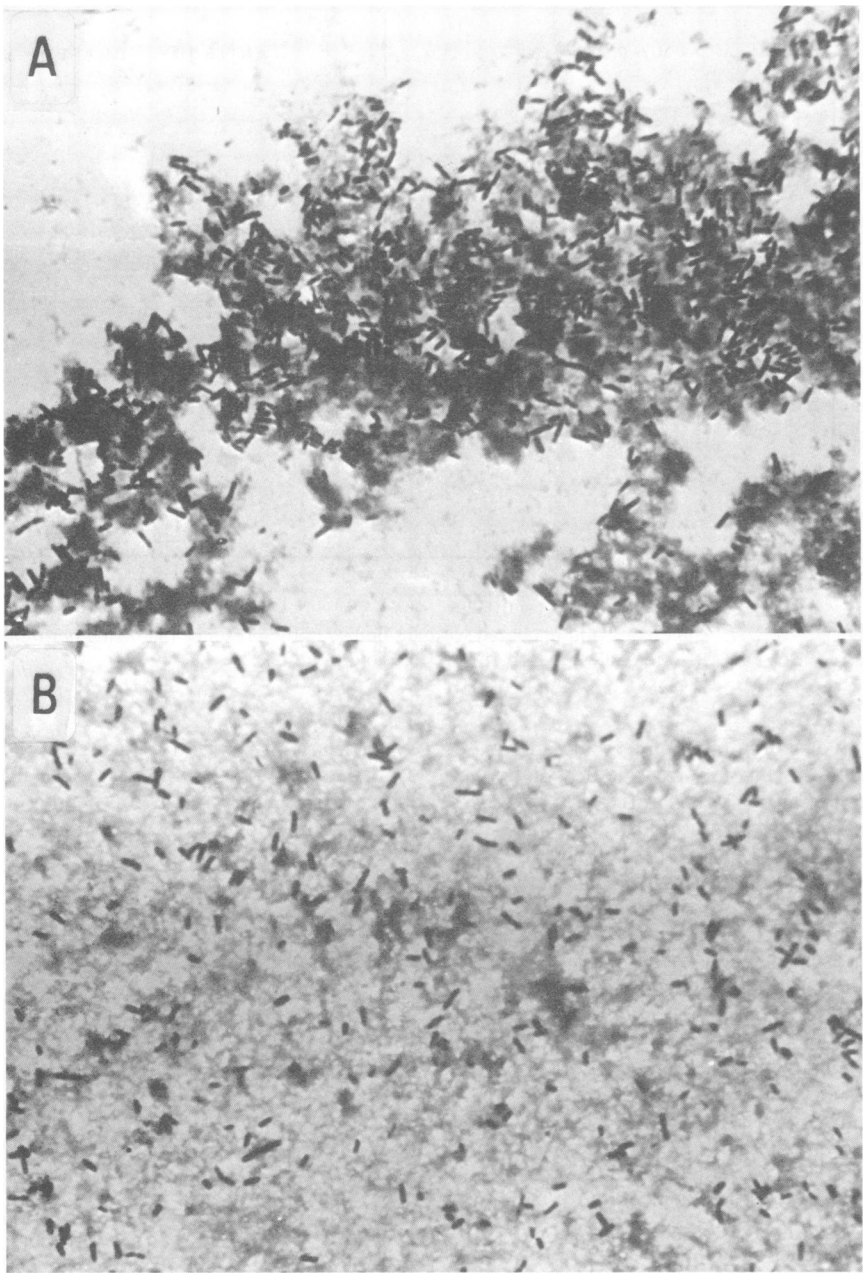

FIG. 4. Coaggregation of mouse liver membrane-fraction with MS$^-$ *E. coli* bacteria (stained with Hemacolor Rapid Stain; E. Merck AG, Darmstadt, Federal Republic of Germany). (A) Uninhibited aggregation; (B) aggregation inhibited by 100 mM Meα/Glc.

specificity of this inhibition is further shown by the inability of the sugar MeαMan to inhibit the blood clearance of bacteria coated with antibodies, which modifies the bacterial surface and hence the mechanism of blood clearance. The organisms were shown to interact with hepatic membranes, and this interaction was inhibited by the same sugars which inhibited the blood clearance of the organisms; the lipopolysaccharide extracted from the test bacteria was also found to inhibit the interaction. Furthermore, the finding that asialofetuin but not fetuin inhibited blood clearance of the bacteria is in agreement with previous studies showing that hepatic lectins fail to recognize glycoproteins with terminal sialic acid residues (14, 20, 21, 37).

Our results suggest that hepatic lectins clear the blood of *E. coli* 346 presumably by binding to complementary sugars on the bacterial surface. The question as to which of the known hepatic lectins mediates the uptake of organisms depends on what type of oligosaccharides are available to the lectins on the bacterial surfaces. It is not likely that the galactose-specific lectin is involved because: (i) organisms were not agglutinated by peanut agglutinin or *R. communis* agglutinin which are galactose-specific lectins; (ii) galactose did not inhibit blood clearance of the organisms; and (iii) glucose, which was previously found to lack the ability to inhibit the blood clearance of the neoglycoprotein galactose-bovine serum albumin (24), did inhibit blood clearance of the

TABLE 2. Interaction of MS⁻ phenotype of *E. coli* 346 with lectins and with glycoproteins

Lectin or glycoprotein	Sugar specificity of lectin	Slide agglutination	Bacterial sedimentation rate: % of control (± SD)
None		−	100.0 (± 6.3)
Concanavalin A	α-Mannose, α-glucose	+	552.7 (±12.3)
Concanavalin A + MeαMan		−	169.7 (±46.5)
Concanavalin A + MeαGlc		−	172.3 (±2.6)
Concanavalin A + MeαGal		+	552.7 (±6.3)
Concanavalin A + L-rhamnose		+	574.4 (±10.7)
Wheat germ agglutinin	*N*-acetylglucosamine	−	ND[a]
Peanut agglutinin	Galactose (1→3)-*N*-acetylgalactosamine	−	ND
R. communis agglutinin	β-Galactose	−	ND
Mucus lectin (9)	Fucose	−[b]	ND
Fetuin		−	ND
Asialofetuin		−	ND
Ovalbumin		−	ND

[a] ND, Not done.
[b] Tested by M. Izhar and D. Mirelman, unpublished data.

organisms. The finding that asialofetuin with terminal galactose inhibited blood clearance of the organisms may be interpreted that the asialofetuin blocked the hepatic lectin which recognizes sugar residues other than galactose in its oligosaccharide chain. Indeed, Maynard and Baenziger (17) recently found that a Man-GlcNac-specific hepatic lectin was able to interact with asialofetuin, although the sugar specificity of the lectin was directed toward residues other than galactose in the oligosaccharide chain. Of the other two hepatic lectins described, it is likely that the Man-GlcNac rather than the Fuc-specific lectin is responsible for the blood clearance of *E. coli* 346 since (i) the organisms were agglutinated by concanavalin A, a mannose- and glucose-specific lectin, but not by a Fuc-specific lectin, suggesting that either glucose or mannose or both but not Fuc residues are available on the bacterial surface; (ii) studies on blood clearance of fucosylated glycoproteins (2, 8) revealed that neither glucose nor mannose inhibited clearance of the glycoprotein, whereas both of these sugars inhibited blood clearance of *E. coli*; (iii) although MeαFuc inhibited blood clearance of the organisms, a bovine serum albumin derivative of this sugar strongly inhibited the binding of radiolabeled mannan to purified Man-GlcNac receptor (35), suggesting that the latter lectin is able to recognize fucosyl residues; and (iv) the blood clearance of GlcNac-bovine serum albumin in mice via the Man-GlcNac receptor was inhibited by glucose (24), which also inhibited the blood clearance of our test strain of *E. coli*.

In summary, the pattern of inhibition of bacterial blood clearance by various compounds are compared with that of blood clearance of glycoproteins, suggests that the Man-GlcNac hepatic lectin is involved in the clearance of *E. coli* 346 from mouse blood. This notion is in agreement with the results obtained from the aggregation of bacteria with various plant lectins. Further experiments with purified hepatic lectins are required, however, to confirm which of the hepatic lectins is responsible for the blood clearance of *E. coli* 346.

It should be pointed out that a mannosyl receptor (lectin) also may be expressed by various tissue macrophages but not by blood neutrophils or monocytes (31). Recently, Weir and Blackwell (38) suggested that such sugar receptors on macrophages may be involved in phagocytosis of bacteria by recognizing sugar residues on bacterial surfaces. As yet, the phagocyte lectin(s) has not been isolated or defined.

Our results do not exclude the possibility that a fimbrial lectin may mediate blood clearance of other bacteria. Recently, Leunk and Moon (16) demonstrated that blood clearance as well as liver trapping of a type 1 fimbriated *Salmonella* strain was inhibited by mannose but not by glucose. It is difficult to compare our results with those of Leunk and Moon because these investigators did not assay inhibition of blood clearance of nonfimbriated bacteria by sugars nor did they assay mouse serum for inhibition of the mannose-specific fimbrial *salmonella* lectin, as we did with *E. coli* 346. It is possible that the concentrations of putative serum inhibitors which block the lectin of *E. coli* are not sufficient to block the *Salmonella* lectin, in which case the latter organisms may more readily be cleared from the blood via their fimbrial lectin. Such a possibility cannot be excluded in light of the recent finding by Firon et al. (7) who showed that the concentrations of various sugar inhibitors needed to inhibit *E. coli* lectin are different from those needed to inhibit *Salmonella* lectin.

Our results may have relevance to bacteremic infections. Bacteria possess an array of surface sugars available for binding to corresponding lectins (10, 27). At least three hepatic lectins for a wide range of sugars were described in laboratory animals (2) and humans (6). We have shown that the mammalian lectins may be responsible for blood clearance by recognizing bacterial surface sugars. It is possible that in certain septicemias or bacteremias the pathogens mask their surface sugars to prevent recognition by hepatic lectins and hence their blood clearance. Work in progress in our laboratory is aimed at examining this hypothesis.

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