Specificity of Fc Receptors Induced by Herpes Simplex Virus Type 1: Comparison of Immunoglobulin G from Different Animal Species

P. J. HUGO JOHANSSON,[1,2]* ERLING B. MYHRE,[3] AND JONAS BLOMBERG[1]

*Sections of Virology[1] and Bacteriology,[3] Institute of Medical Microbiology, and Department of Infectious Diseases,[2]
University of Lund, S-223 62 Lund, Sweden*

Cells infected with herpes simplex virus type 1 (HSV-1) express a cell surface receptor able to bind the Fc portion of immunoglobulin G (IgG). Of the four human IgG subclasses, the HSV-1 Fc receptor, like staphylococcal protein A, binds to all except IgG3. In this paper, we describe the binding of a number of animal IgG and IgG subclass molecules to HSV-1-infected cells and compare this binding to that of protein A. Although only few representatives from each animal order were tested, we found that IgG from *Carnivora* and *Rodentia* did not bind or bound only slightly to the HSV-1 receptor, whereas IgG from *Primates, Lagomorpha,* and *Artiodactyla* bound well. This pattern was clearly different from the species spectrum of IgG binding of protein A. Differences between the two receptors were also found when animal IgG subclasses were tested. The pronounced differences in affinity for the HSV-1 Fc receptor between immunoglobulins from, for example, mouse and rabbit may influence the interpretation of animal studies with this virus.

Cells infected with herpes simplex virus (HSV) express on their surface a receptor which is able to bind the Fc portion of immunoglobulin G (IgG) (2, 24, 25). This receptor has been identified as a glycoprotein (gE) with a molecular weight of 65,000 to 80,000 (2) which is coded for in the unique portion of the S component of the HSV genome (20). The receptor is also present on the surface of HSV virions (19, 23).

Of the human immunoglobulin classes IgG, IgA, IgM, and IgD, only IgG binds to HSV type 1-(HSV-1) infected cells in a nonimmune manner (4, 7). We have recently described that of the four human IgG subclasses IgG3 does not bind to HSV-1-infected cells, whereas the binding of the remaining subclasses differs according to the sequence IgG4 > IgG1 ≥ IgG2 (7).

Most strains of *Staphylococcus aureus* carry a surface component, protein A, which also has the capacity to combine with the Fc portion of human IgG (5, 8, 10, 11). Like the Fc receptor of HSV-1, protein A reacts with the three human IgG subclasses IgG1, IgG2, and IgG4, while IgG3 is nonreactive (10). This similarity in binding spectrum between the HSV Fc receptor and protein A towards the human IgG molecule raises the question whether they exhibit a similar specificity towards other IgG molecules.

Immunoglobulins from many mammalian species are known to bind to protein A in a nonimmune way (9, 12, 15, 16). Similar information regarding the species specificity of the HSV-1 Fc receptor exists only to a limited extent (25, 26). We therefore undertook binding studies with IgG preparations from different animal species and compared the binding spectrum of the HSV-1 Fc receptor with that of *S. aureus* Cowan I, known to carry protein A.

MATERIALS AND METHODS

Cells. African green monkey kidney cells of strain AH1 (GMK AH1) (6) were cultured in Eagle minimal essential medium (Flow Laboratories, Irvine, United Kingdom) supplemented with 10% fetal calf serum (Flow), 0.3 mg of glutamine per ml, and 50 μg of gentamicin per ml. For use in

immunoglobulin-binding studies, the cells were grown in 1 ml of the same medium in glass roller tubes (1.5 by 10 cm) to a density of ca. 10^5 cells per tube. After 4 days, when the cells were confluent, they were washed once with tissue culture medium (RPMI 1640; Flow) lacking serum but supplemented with gentamicin and glutamine. The tubes were then used as described below in the section on protein binding and inhibition assay.

Virus. HSV-1 F (3) was inoculated at a low multiplicity onto GMK AH1 cells and harvested at the first day of full cytopathic effect (generally after 3 days) to obtain a seed stock. After homogenization of the cells, the suspension was clarified by centrifugation at 200 × g for 10 min. A 100-μl portion of the supernatant containing 5 × 10^6 PFU was used for inoculation of GMK AH1 cells in roller tubes.

Immunoglobulins. The following chromatographically purified animal immunoglobulins or immunoglobulin fragments were used: human IgG Fc fragment (lot 16199), rabbit IgG (lot 154502), rabbit IgG Fc fragment (lot 16513), guinea pig IgG (lot 16210), hamster IgG (lot 12130), goat IgG Fc fragment (lot 12360), sheep IgG (lot 19582), cow IgG (lot 12632), and chicken IgG (lot 15991), all from Cappel Laboratories, Cochranville, Pa. The purity of each preparation had been certified by immunoelectrophoresis by the same supplier. Mouse IgG (lot 108), rat IgG (lot 752), dog IgG (lot 1140), cat IgG (lot 149), and horse IgG (lot 181) were obtained with purity certificate (immunoelectrophoresis; ChromPure) from Jackson Immuno Research Laboratories Inc., Avondale, Pa. Mouse myeloma proteins belonging to IgG1 (lot 231-70-6), IgG2a (lot AB011), IgG2b (lot 231-58-2), and IgG3 (lot 231-54-4) were obtained from Litton Bionetics Inc., Kensington, Md. Their purity had been assessed by the supplier by polyacrylamide electrophoresis and agar gel diffusion against class-specific immune sera. Chromatographically purified preparations of the rat IgG subclasses IgG1, IgG2a, IgG2b, and IgG2c were kindly provided by R. Nilsson, The Wallenberg Laboratory, University of Lund, Sweden (18). IgG from swine was isolated by preparative block electrophoresis followed by gel filtration on a Sephadex G-150 (Pharmacia, Uppsala, Sweden) column. IgG1 and IgG2 subclasses from goat and sheep were prepared by ion

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* Corresponding author.

exchange chromatography of serum samples from unimmu-nized animals (16). Horse IgG(ab), IgG(c), and IgG(T) sub-classes were isolated from horse serum with ion exchange chromatography, preparative block electrophoresis, and gel filtration (16). The bovine IgG1 and IgG2 subclasses were purchased from Miles Laboratories, Inc., Elkhart, Ind. The purification and characterization of the human myeloma protein IgG4 5764 has been described previously (7).

Protein iodination. The lactoperoxidase (13, 21) and the chloramine T (22) methods were employed for ^{125}I labeling. The exact procedures have been published elsewhere (7). All immunoglobulins and Fc fragments except sheep IgG1, mouse IgG1, mouse IgG2a, mouse IgG2b, and mouse IgG3 were iodinated by the lactoperoxidase method. Specific activities of 10 to 20 μCi/μg of protein were obtained.

Protein binding and inhibition assay. Binding to GMK AH1 cells in roller tubes containing 1 ml of serum-free RPMI 1640 was performed as previously described (7). Briefly, triplicate tubes with uninfected cells and cells infected with HSV-1 at a multiplicity of 50 PFU per cell were incubated with rotation in a roller drum at 37°C for 20 h. The medium was removed, and 100 μl of phosphate-buffered saline (PBS)–0.2% ovalbumin–10 mM sodium azide with or without 13 μg of competing unlabeled human IgG Fc fragment or 40 μg of competing unlabeled animal immunoglobulin was added. After 1 h at 37°C with rotation, 100 μl of PBS–0.2% ovalbumin–10 mM sodium azide containing 5 ng of radiola-beled immunoglobulin or IgG Fc fragment (around 200,000 cpm) was added to each tube. After another hour of rotation at 37°C, the cells were washed three times with 4 ml of PBS, followed by centrifugation at 200 × g for 10 min. The cell-bound radioactivity (up to around 10,000 cpm) was measured in a gamma counter. The HSV-specific binding was calculated by subtraction of radioactivity bound to uninfected cells from that bound to HSV-infected cells. The Fc specificity of the binding was always demonstrated by inhibition with unlabeled human IgG Fc fragment in separate triplicate tubes. Fc-specific binding was calculated by sub-traction of the radioactivity bound to infected cells inhibited in this way from the radioactivity bound without presence of unlabeled Fc fragment. As a control of the cell number, two additional tubes were in some experiments processed iden-tically and after trypsination enumerated with a hema-cytometer. For unlabeled human IgG Fc fragment versus iodinated immunoglobulin and versus iodinated human IgG Fc fragment, the molar excesses were 7,800- and 2,600-fold, respectively. A 2,700-fold molar excess of unlabeled immu-noglobulin versus iodinated human IgG Fc fragment was employed.

To compensate for the variations between different exper-iments, the HSV-specific binding of individual animal immu-noglobulins was calculated relative to that of radiolabeled human IgG Fc fragment. In the same way the decrease of binding of animal immunoglobulins to infected cells caused by addition of unlabeled human IgG Fc fragment was calcu-lated relative to the same inhibition of binding of radiola-beled human Fc fragment.

Bacterial Fc receptor binding. *S. aureus* Cowan I, known to carry protein A, the human group G streptococcus strain G 148 which carries a type III IgG Fc receptor (15), and the human streptococcus group B strain B1, which has no Fc receptor activity (negative control strain) were utilized in the bacterial binding studies. Bacteria were grown, suspended, and tested for immunoglobulin binding as previously de-scribed (7, 15). Briefly, 5 ng of radiolabeled immunoglobulin in 200 μl of PBS containing 0.02% sodium azide and 0.05%

Tween 20 was added to duplicate tubes containing 2 × 10^8 bacteria per tube. After 1 h at room temperature, 2 ml of PBS–0.02% sodium azide–0.05% Tween 20 was added to each tube. The bacteria were spun down, the supernatant was removed, and binding was expressed as the radioactiv-ity of the bacterial pellet as a percentage of that of the added labeled immunoglobulin.

RESULTS

Binding of iodinated human and animal immunoglobulins. The binding assays with iodinated human and animal immu-noglobulins were performed as shown in Fig. 1. The nonim-mune nature of the binding was assured by inhibition with an excess of unlabeled human IgG Fc fragment. The amount of binding to HSV-1-infected cells varied between the different immunoglobulins. Iodinated mouse and chicken IgG did not bind more to infected than to uninfected cells and were not affected by addition of unlabeled human IgG Fc fragment. In contrast, iodinated human IgG Fc (included as a control), swine IgG, and sheep IgG exhibited a clear increase in binding after infection and were also inhibited by an excess of unlabeled human IgG Fc fragment. The inhibition of binding of labeled human IgG Fc fragment caused by unla-beled human IgG Fc was 70 to 90% of the increase after HSV infection (Fig. 1).

Figure 2 shows the HSV-specific binding of labeled immu-noglobulins relative to that of labeled human IgG Fc (set as 100%). In addition, the inhibition of binding of labeled immunoglobulins to infected cells caused by an excess of unlabeled human IgG Fc was expressed relative to the same inhibition of HSV-specific binding of labeled human IgG Fc (set as 100%). The bars represent the means of two to nine separate determinations, with an intertest variability of below 30%. It can be seen that the agreement between the two methods of measuring HSV-specific binding was good. IgG and IgG Fc fragments from reacting species (human, rabbit, swine, goat, sheep, and cow) all bound in a nonim-mune way, i.e., were inhibited by an excess of unlabeled human IgG Fc fragment.

The extents of binding varied in the following decreasing order: human IgG4, rabbit IgG, swine IgG, human IgG Fc, cow IgG, rabbit IgG Fc, sheep IgG, and goat IgG Fc. However, differences in the state of aggregation may to some extent have influenced this order (7). Mouse, guinea pig, hamster, rat, dog, cat, horse, and chicken IgGs did not bind or bound only slightly. Human IgG Fc fragment bound less than a human IgG4 myeloma protein, and rabbit IgG Fc fragment bound less than rabbit IgG. In addition to these interspecies differences, there were differences in binding ability between different IgG subclasses from the same species. In certain cases, the ability to bind was confined to one IgG subclass (sheep IgG1 and cow IgG2). These prefer-ences could either be similar (cow) or contrary (sheep and goat) to that of staphylococcal protein A. With mouse, rat, and horse immunoglobulins, we could not detect significant binding to any of the subclasses.

Binding of iodinated human IgG Fc fragment and its inhibition by unlabeled animal immunoglobulins. To ascertain that the iodination procedure did not change the interaction of the immunoglobulins with the HSV Fc receptor and to confirm the direct binding results at another ligand concen-tration, the ability of animal immunoglobulins to inhibit the binding of labeled human IgG Fc fragment was investigated (Fig. 3). An excess of unlabeled human IgG Fc fragment, rabbit IgG, and sheep IgG were able to inhibit the binding of labeled human IgG Fc fragment to different extents, whereas
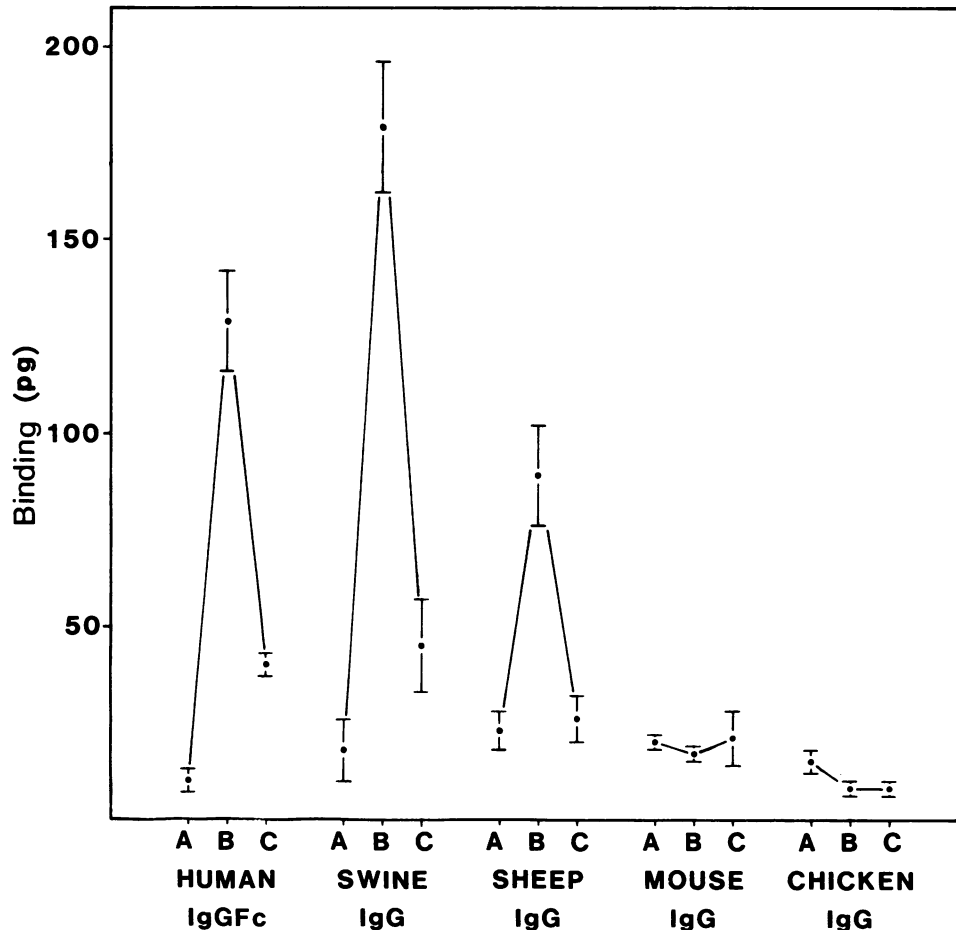
FIG. 1. Binding of iodinated human and animal immunoglobulins to HSV-infected cells and its inhibition by unlabeled human IgG Fc fragment. Means of triplicates with one standard deviation are shown. Binding is expressed in picograms (pg). Symbols: A, uninfected cells; B, HSV-1-infected cells; C, inhibition of binding to HSV-1-infected cells by unlabeled Fc fragment of human IgG.

no inhibition was seen with rat or chicken IgG. The degree of inhibition caused by 12 different animal immunoglobulins is shown in Table 1. Rabbit, goat, sheep, and cow IgG yielded a significant inhibition. The results were in agreement with those seen in Fig. 2.

Binding of iodinated human and animal immunoglobulins to bacteria. The results of the binding of iodinated human and animal immunoglobulins to the three different bacterial strains (Fig. 2) agreed with previously published results (15, 16, 18). This proved the functionality of our iodinated immunoglobulins with respect to Fc binding ability.

Comparison of immunoglobulin binding spectrum of the HSV-1 Fc receptor and that of protein A from *S. aureus*. Similarities were found in the binding pattern of the HSV-induced Fc receptor and protein A (*S. aureus* Cowan I) (Fig. 2). Human, rabbit, swine, sheep, and cow IgG bound to both receptors. No or weak binding was recorded for rat and chicken IgG and IgG subclasses from rat and horse. IgG subclasses from cow also bound similarly to the two receptors. However, there were also disagreements in the binding ability both for IgG (mouse, guinea pig, hamster, dog, cat, and horse) and IgG subclasses (mouse, goat, and sheep).
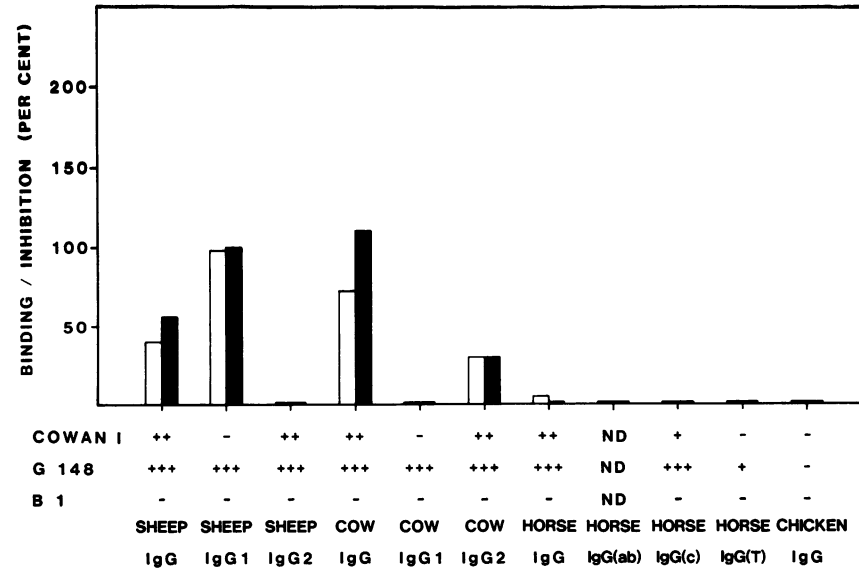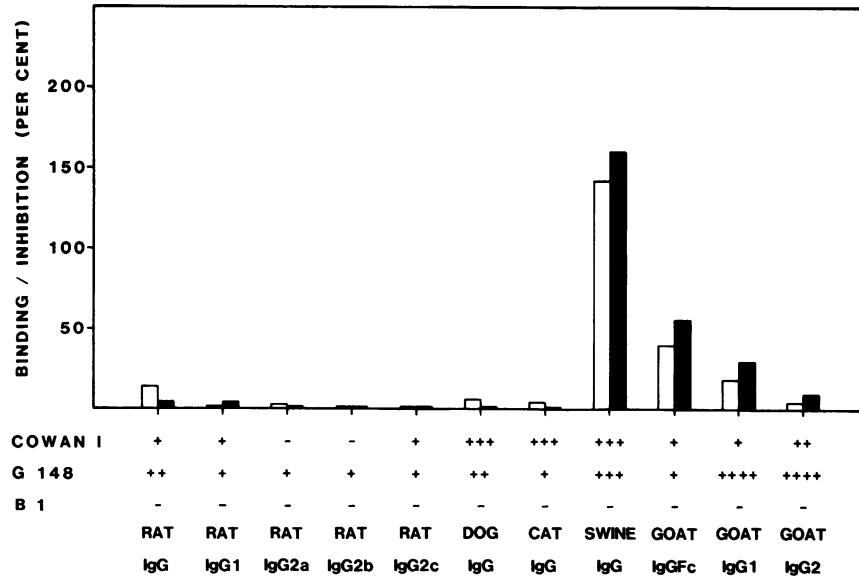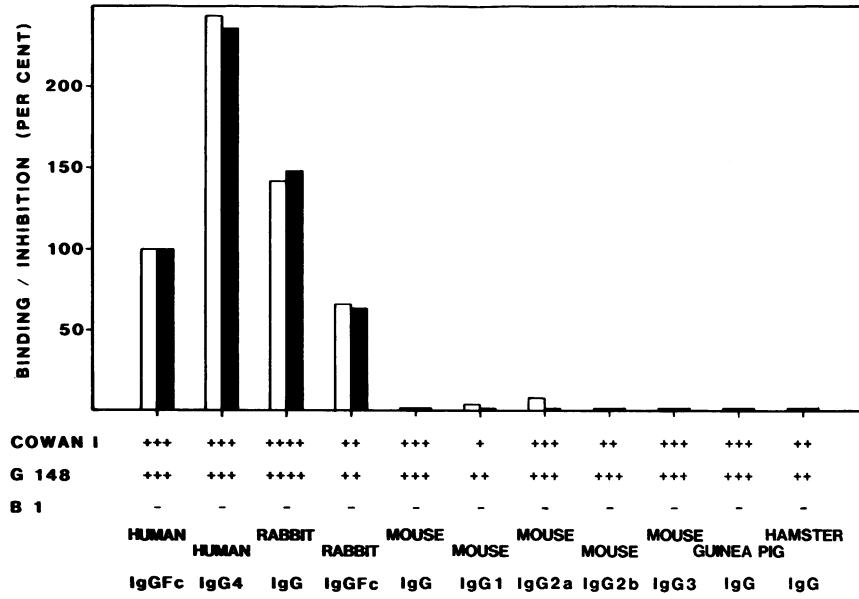
DISCUSSION

Ability of IgG from various species to bind to the HSV-1 Fc receptor. In this paper we report the ability of the HSV-1-induced IgG Fc receptor to bind in a nonimmune way to different animal IgG molecules. Large extents of binding were found with IgGs from only a few species. These belonged to the mammalian orders *Primates* (human), *Lagomorpha* (rabbit), and *Artiodactyla* (swine, sheep, goat, and cow), whereas IgG originating from *Rodentia* (guinea pig, hamster, mouse, and rat), *Carnivora* (cat and dog), or *Perissodactyla* (horse) bound slightly or not at all. IgG from one representative of the *Aves* class (chicken) did not bind. We found no clear-cut correlation between the evolutionary distance between the animal orders and the ability to bind to the HSV-1 receptor.

Many animal IgGs, like human IgG, exist in subclasses. For some species we had access to purified IgG subclass molecules. Within the same species, all, some, or none of the subclasses exhibited binding to the viral receptor. However, it cannot be excluded that for the nonreactive animal IgGs there exist minor subclasses not tested here which exhibit nonimmune binding to the HSV-1 Fc receptor.

Comparison with staphylococcal protein A. Despite the similarity of binding specificity of the two proteins with respect to human IgG, clear-cut differences were found in the pattern of binding to animal IgGs. The Fc receptor of HSV-1 interacted with IgG from a narrower range of species. In addition, marked differences within the same animal species were found for some IgG subclasses. This proves

Figure (top panel): BINDING / INHIBITION (PER CENT) vs various immunoglobulins.

COWAN I	+++	+++	++++	++	+++	+	+++	++	+++	+++	++
G 148	+++	+++	++++	++	+++	++	+++	+++	+++	+++	++
B 1	-	-	-	-	-	-	-	-	-	-	-

HUMAN | HUMAN | RABBIT | RABBIT | MOUSE | MOUSE | MOUSE | MOUSE | MOUSE | GUINEA PIG | HAMSTER

IgGFc | IgG4 | IgG | IgGFc | IgG | IgG1 | IgG2a | IgG2b | IgG3 | IgG | IgG

Figure (middle panel): BINDING / INHIBITION (PER CENT)

COWAN I	+	+	-	-	+	+++	+++	+++	+	+	++
G 148	++	+	+	+	+	++	+	+++	+	++++	++++
B 1	-	-	-	-	-	-	-	-	-	-	-

RAT | RAT | RAT | RAT | RAT | DOG | CAT | SWINE | GOAT | GOAT | GOAT

IgG | IgG1 | IgG2a | IgG2b | IgG2c | IgG | IgG | IgG | IgGFc | IgG1 | IgG2

Figure (bottom panel): BINDING / INHIBITION (PER CENT)

COWAN I	++	-	++	++	-	++	++	ND	+	-	-
G 148	+++	+++	+++	+++	+++	+++	+++	ND	+++	+	-
B 1	-	-	-	-	-	-	-	ND	-	-	-

SHEEP | SHEEP | SHEEP | COW | COW | COW | HORSE | HORSE | HORSE | HORSE | CHICKEN

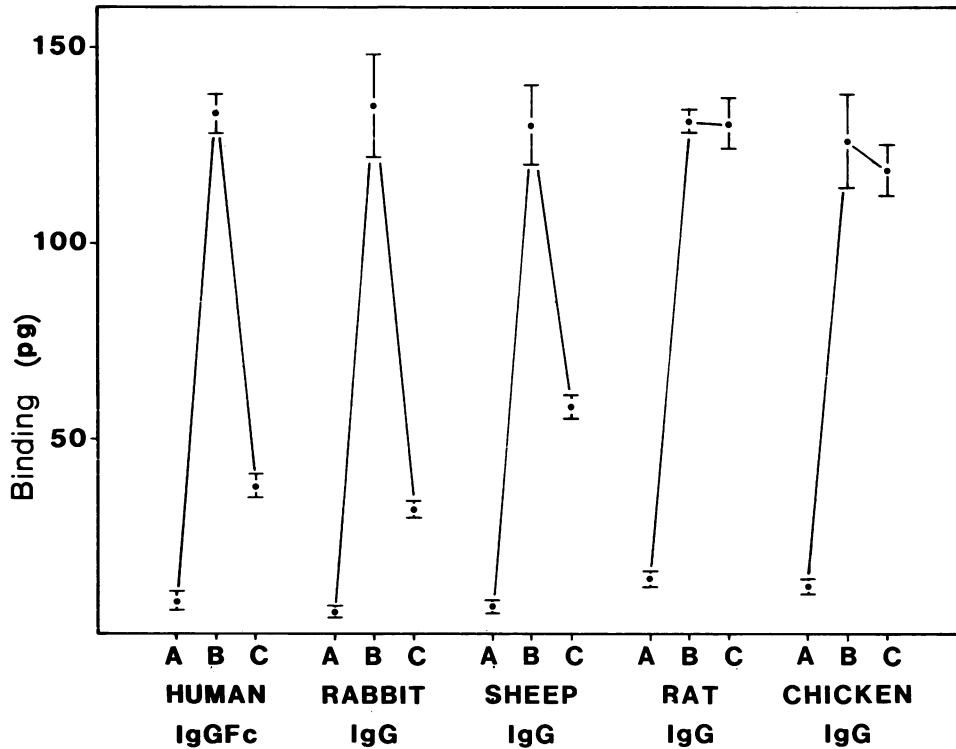IgG | IgG1 | IgG2 | IgG | IgG1 | IgG2 | IgG | IgG(ab) | IgG(c) | IgG(T) | IgG

FIG. 3. Inhibition of binding of iodinated human IgG Fc fragments to HSV-infected cells by unlabeled human and animal immunoglobulins. The means of triplicates with one standard deviation are shown. Binding is expressed in picograms (pg). Symbols: A, uninfected cells; B, HSV-infected cells; C, inhibition of binding to HSV-infected cells by unlabeled human and animal immunoglobulins.

that protein A and the HSV-1 Fc receptor have different structural requirements for interaction with the IgG molecule.

Methodological considerations. This binding study involved only one concentration of ligand. Therefore, the conclusions drawn must be limited to relatively rough comparisons of extent of binding. Further, the conditions employed in the bacterial system (fewer washes and presumably higher receptor concentration) may have favored low affinity binding to a greater extent than those employed in the HSV-infected cell system. The narrower species range of the HSV-1 receptor could partly have resulted from this methodological difference. However, in several animal orders we did not observe the simple pattern of low HSV-1 binding and high protein A binding which would have been a consequence. In addition, the immunoglobulin concentration employed in the inhibition tests was around a thousandfold higher than in the direct binding test. Still, the species specificity of the inhibition test agreed well with that of the direct binding test.

The functional integrity of the radioiodinated proteins was ascertained with (i) a bacterial strain (group G streptococcus G 148) known to bind to most IgGs and (ii) competition experiments with a large excess of uniodinated ligand.

HSV-induced immunoglobulin binding could be measured by subtracting from the binding of HSV-infected cells either that of uninfected cells or that of infected cells in the presence of an excess of human Fc fragment (Fig. 1). The similarity of the results of the two methods proves that anti-HSV antibodies did not contribute significantly to the binding.

Although it may seem unlikely, we cannot exclude that cell-dependent modifications like glycosylation (cf. reference 14) could have influenced the species specificity of the Fc receptor. Our studies were only performed with monkey cells.

Implications for the coevolution of virus and host. The existence of species-specific members of the family *Herpesviridae* in most mammalian species is well documented (e.g., reference 17). It remains to be seen whether these viruses, like HSV, can induce Fc receptors and in that case also exhibit binding to IgG from a relatively narrow range of species, including that of the normal host. Such a pattern of coevolution would be expected if the presence of the viral Fc receptor had a survival value for either virus or host.

The ability of immunoglobulins from some animal orders to bind to the viral receptor is indicative of a common

FIG. 2. Binding and inhibition of binding of human and animal immunoglobulins to HSV-infected cells. The HSV-specific binding of iodinated immunoglobulins is expressed relative to that of iodinated human IgG Fc fragment (set as 100%) (☐). The inhibition of binding of iodinated immunoglobulins caused by an excess of unlabeled human IgG Fc fragment is also shown (■). This was expressed relative to the inhibition of HSV-specific binding of labeled human Fc caused by unlabeled human Fc (set as 100%). As a comparison, the nonimmune binding of the same labeled immunoglobulins to three bacterial strains (*S. aureus* Cowan I, streptococcus group G strain G 148, streptococcus group B strain B1) is presented. The binding relative to that of iodinated human IgG Fc fragment towards Cowan I staphylococci (set as 100%) was classified in five groups: −, <10%; +, 10 to 39%; ++, 40 to 79%; +++, 80 to 119%; and ++++, >120%. ND, Not done.

TABLE 1. Inhibition of binding of iodinated human IgG Fc fragment to HSV-infected cells by unlabeled human IgG Fc fragment and 12 animal immunoglobulins[a]

IgG	Human Fc bound to HSV-infected cells (pg)		Difference (pg)[b]
	Without animal immunoglobulin	With animal immunoglobulin	
Human Fc	132 ± 5	38 ± 2	94 (100)
Rabbit	135 ± 14	32 ± 2	103 (110)
Mouse	127 ± 14	137 ± 7	<0 (0)
Guinea pig	134 ± 4	138 ± 3	<0 (0)
Hamster	129 ± 2	149 ± 8	<0 (0)
Rat	122 ± 1	122 ± 7	0 (0)
Dog	140 ± 7	133 ± 2	7 (7)
Cat	130 ± 8	134 ± 4	<0 (0)
Goat Fc	126 ± 22	55 ± 1	71 (76)
Sheep	130 ± 11	58 ± 2	72 (77)
Cow	153 ± 14	92 ± 6	61 (65)
Horse	129 ± 8	132 ± 9	<0 (0)
Chicken	138 ± 13	129 ± 7	9 (10)

[a] The means of triplicates with one standard deviation with and without competing animal immunoglobulin are presented.

[b] Values in parentheses show percent inhibition relative to human IgG Fc.

structure due to either evolutionary relatedness between IgG molecules or randomly generated cross-reactivity between evolutionarily unrelated immunoglobulins. Further virological and molecular biological experimentation is needed.

Implications for the use of animal models in HSV research. Rabbits and mice have been extensively utilized in studies regarding the immune response and the mechanisms of latency and carcinogenesis after HSV infection (1). We have found that mouse IgG binds weakly or not at all to the receptor of HSV-1, whereas rabbit IgG bound very well. If the Fc receptor is important in virus-host interactions in any way, this difference could give rise to major misinterpretations of such animal experiments.

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