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Effects of Androgen Treatment on Expression of Macrophage Fcγ Receptors

F. GOMEZ,* P. RUIZ, R. LOPEZ, C. RIVERA, S. ROMERO, AND J. A. BERNAL

Hospital Universitario de Puerto Real/S.A.S., Department of Medicine, School of Medicine, University of Cadiz, Cadiz, Spain

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Macrophage Fcγ receptors (FcγRs) play an important role in the host defense against infection and in the pathophysiology of immune cytopenias. Modulation of macrophage FcγR expression is a potential therapeutic approach to immune disorders. Glucocorticoids and progesterones decrease macrophage FcγR expression. We assessed the effect of treatment with androgens and antiandrogens on the expression of macrophage FcγRs using an experimental guinea pig model. Four androgens (testosterone, dihydrotestosterone, mesterolone, and danazol) and five antiandrogens (flutamide, nilutamide, cyproterone acetate, spironolactone, and finasteride) were studied. Following in vivo treatment of guinea pigs, we determined the clearance of immunoglobulin G (IgG)-sensitized erythrocytes in vivo, the binding of IgG-sensitized erythrocytes by isolated splenic macrophages, and splenic macrophage FcγR cell surface expression. All of the androgens impaired the clearance of IgG-sensitized erythrocytes by decreasing splenic macrophage FcγR expression. Dihydrotestosterone and mesterolone were more effective than testosterone or dihydrotestosterone. Flow cytometry and fluorescence microscopy with monoclonal antibodies demonstrated that the androgens decreased the cell surface expression of FcγR1,2 more than that of FcγR2. Antiandrogens did not significantly alter macrophage FcγR expression. Nevertheless, antiandrogens counteracted the effects of androgens on macrophage FcγR expression. These data indicate that androgens impair the clearance of IgG-coated cells by decreasing splenic macrophage FcγR expression. Thus, androgens other than danazol are candidate drugs for the treatment of immune disorders.

Macrophage Fcγ receptors (FcγRs) are relevant in the host defense against infection (9, 18) and in the pathologic process of immune cytopenias (2–4, 13, 19, 20). Therefore, regulation of macrophage FcγR expression is a potential therapeutic approach to immune disorders.

Sex hormones may affect the clinical activity of autoimmune disorders (10, 15) and immune cytopenias (11, 14, 25, 27, 29). In vitro data indicate that sex hormones have regulatory effects on lymphocyte and macrophage function (5, 12, 21, 30, 31). Although the precise mechanisms by which these steroid hormones affect the immune system are not fully understood, our studies indicate that one effect is on macrophage FcγR function (1, 5, 7, 21, 22).

We studied the effect of the administration of androgens and antiandrogens on splenic macrophage FcγR expression using an experimental guinea pig model (7, 8).

Our data indicate that the inhibition of macrophage FcγR expression observed with glucocorticoids and progesterones is also achieved with androgens other than danazol. Therefore, they should be considered as candidate drugs for the treatment of immune complex disease and immune cytopenias.

MATERIALS AND METHODS

All of the studies described here were performed with 500- to 600-g male Duncan-Hartley guinea pigs obtained from Criffa, Barcelone, Spain. Guinea pigs were injected with equal volumes of a homogeneous suspension of steroids in a vehicle (SSV) (5, 8, 17, 21). Sham-treated controls received 1 ml of SSV not containing a steroid. All animals were injected subcutaneously in the dorsal neck fat pad every afternoon for 7 consecutive days and studied on the day after the last injection. The androgens testosterone (T) and dihydrotestosterone (DHT) were obtained from Steraloids, Inc., Wilton, N.H. The androgens mesterolone (MT) and danazol (D) and the antiandrogens flutamide (FL), nilutamide (NL), cyproterone acetate (CA), spironolactone (S), and finasteride (FN) were obtained from the hospital pharmacy. Doses of androgens and antiandrogens were selected on the basis of those previously used in the treatment of human conditions. Rabbit immunoglobulin G (IgG) anti-guinea pig red blood cell (RBC) antibodies were prepared as previously described, were purified by Sephacryl S-300 gel filtration and QAE ion-exchange chromatography (Pharmacia, Piscataway, N.J.), and were free of IgM as determined by Ouchterlony analysis and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (5, 7, 8, 21).

Clearance of IgG-coated erythrocytes. Blood was drawn from anesthetized guinea pigs by cardiac puncture. Washed erythrocytes were radiolabeled with ^{51}Cr-sodium chromate (Amersham, Madrid, Spain) and sensitized with an equal volume of IgG antibody, so as to be coated with approximately 3,000 IgG molecules per erythrocyte as previously described (8, 17, 19). Treated animals were injected intravenously with 1.7×10^8 ^{51}Cr-labeled cells. Samples of blood were obtained 1 to 120 min after injection, and cell-associated radioactivity was measured in a gamma counter (Gamma 8000; Beckman Instruments, Inc., Fullerton, Calif.). Studies were also performed with heat-altered erythrocytes to investigate splenic trapping mediated by nonimmune clearance, not only in sham-treated controls but in animals treated with a high androgen or antiandrogen dose (5, 8, 19–21). Clearance curves were plotted by expressing the blood counts per minute at each time point as a percentage of the counts per minute at 5 min. Clearance at 60, 90, and 120 min was analyzed to calculate a *P* value for the difference between control and experimental clearance curves using the Student *t* test. In addition, for each day's clearance study, the percent inhibition of clearance (mean ± the standard error of the mean [SEM]) above control was calculated at 90 and 120 min as $100 \times [1 - (\text{cpm}_c - \text{cpm}_x)/(\text{cpm}_c - \text{cpm}_{ea})]$, where cpm_c refers to counts per minute of the untreated control animal injected with unsensitized cells, cpm_x is for the experimental animal treated with a steroid and injected with IgG-coated erythrocytes, and cpm_{ea} is for control animals treated with SSV only (no steroid) and injected with the control IgG-sensitized erythrocytes. A negative value for percent inhibition indicates enhancement of clearance. This formula compares treated animals with the control animals studied on the same experimental day and expresses the data as percent alteration of clearance, where 100% inhibition of clearance by steroids corresponds to the situation in which the clearance of IgG-sensitized erythrocytes (cpm_x) is identical to that of unsensitized erythrocytes (cpm_c) (5, 7, 8).

Binding of IgG-coated erythrocytes by splenic macrophages in vitro. Guinea pigs were sacrificed, splenectomy was performed immediately, and the spleens

* Corresponding author. Mailing address: Avda. de la Paz, 16, Valdelagrana, 11500, El Puerto de Santa Maria, Cadiz, Spain. Phone: 34-956-562714. Fax: 34-956-562714. E-mail: fgomez@telprof.es.

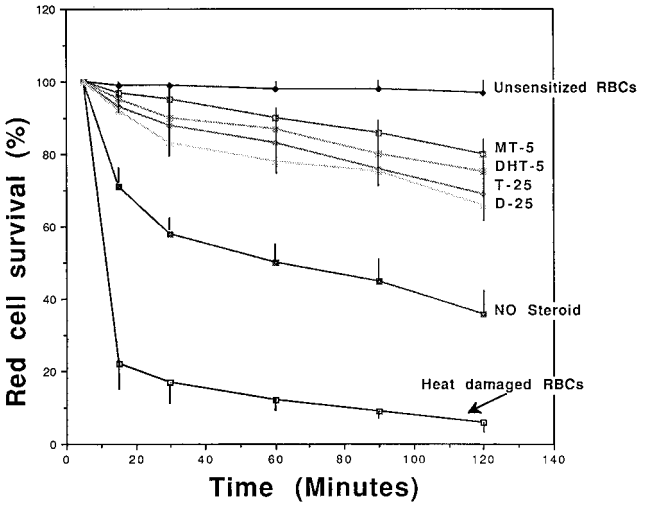

FIG. 1. In vivo clearance of IgG-sensitized RBCs in guinea pigs treated with a high dose of androgens. Numbers following abbreviations represent the androgen doses used (milligrams per kilogram per day). Red cell survival represents the percentage of ^{51}Cr-labeled, IgG-sensitized RBCs (mean ± SEM) remaining in the circulation at each time point. The dose-dependent effects of T, DHT, MT, and D are shown. The survival of heat-damaged RBCs (mean ± SEM) was not significantly different in androgen-treated animals compared to that in sham-treated controls.

were placed in RPMI 1640 medium–10% heat-inactivated fetal calf serum–glutamine (complete RPMI). Splenic macrophages were isolated by tissue grinding and sieving, discontinuous Percoll gradient centrifugation, and plastic adherence as previously described (7, 8, 17). More than 95% of the resultant cells were viable mononuclear cells as determined by their ability to exclude trypan blue, and >90% of the cells ingested latex beads and were stained with nonspecific esterase. Monolayers of adherent cells were prepared as previously described by incubating 10^6 cells on a glass coverslip in a 35-mm-diameter plastic petri dish at 37°C for 45 min under 5% CO_2 (4, 5, 12, 15, 30, 31). More than 95% of the cells were adherent to glass. For experiments studying FcγR activity in vitro, guinea pig erythrocytes were coated with 800 molecules of IgG per erythrocyte as described above and 1 ml of erythrocytes (5×10^7 cells/ml) was incubated with the macrophage monolayers at 37°C under 5% CO_2 for 20 min. The monolayers were washed, air dried, and Wright-Giemsa stained, and 200 consecutive macrophages were inspected under oil immersion for the number of erythrocytes bound per cell. The number of macrophages which bound three or more IgG-sensitized erythrocytes was then determined (7, 8, 17, 22).

Flow cytometry. Monoclonal antibodies (MAbs) with specificity for guinea pig macrophage FcγR1,2 (VIA2 IgG1) and FcγR2 (VIIA1 IgG1) (26) were utilized in indirect immunofluorescence binding studies to assess surface FcγR protein expression. These MAbs were the generous gift of Dr. Yamashita and Dr. Nakamura, Sapporo, Japan. Cells (5×10^5) were incubated with saturating concentrations of each MAb for 60 min. at 4°C and washed twice with phosphate-buffered saline containing 0.5% bovine serum albumin and 0.02% sodium azide. To measure bound antibody, a fluorescein isothiocyanate-labeled goat anti-mouse antibody (Tago, Inc., Burlingame, Calif.) was added and the mixture was incubated for 30 min at 4°C. The cells were again washed twice and fixed with 4% paraformaldehyde. Cell-associated fluorescence was measured using a FACSTAR cytometer with Consort-32 software (Becton Dickinson & Co., Mountain View, Calif.). For all samples, 10,000 events were recorded on a logarithmic fluorescence scale and the mean fluorescence intensity (MFI) of each sample was determined using Consort-32 software. In order to correct for autofluorescence, the MFI of a nonreactive murine IgG1 antibody (M3) was subtracted from the MFI of the anti-FcγR1,2- and anti-FcγR2-stained cells. Percent change in MFI was calculated as % change = [(MFI of anti-FcγR-treated cells − MFI of M3-treated cells)/(MFI of anti-FcγR-untreated cells − MFI of M3-untreated cells)]$^{-1} \times 100$. To demonstrate the specificity of the androgenic effect on FcγR expression, we included an additional control with an irrelevant guinea pig pan-macrophage surface antigen, GPB (Seralab Ltd., Sussex, England). Treatment with androgens or antiandrogens did not significantly alter the cell surface expression of this pan-macrophage antigen while inhibiting FcγR1,2 and FcγR2 expression.

In vivo effects of steroids on membrane mobility of FcγR1,2 and FcγR2. Immunofluorescence capping experiments were performed in order to examine any possible effects of in vivo-administered androgens or antiandrogens on the membrane mobility of FcγR1,2 and FcγR2. Splenic macrophages (5×10^5) from guinea pigs treated with different doses of the most effective androgens and antiandrogens for 7 days or from sham-treated animals were incubated with saturating concentrations of MAbs for 30 min at 0°C on ice. After two washes at 0°C in phosphate-buffered saline–0.5% bovine serum albumin without sodium azide, fluorescein isothiocyanate-labeled goat anti-mouse antibody was added as in the flow cytometry experiments. Cells were incubated at either 0 or 37°C for 20 min, washed, fixed in paraformaldehyde, and spun onto microscope slides in a centrifuge. Several hundred cells per slide were examined under epifluorescence with a fluorescence microscope (Carl Zeiss, Oberkochen, Germany) (data not shown).

RESULTS

Four androgens (T, DHT, MT, and D) and five antiandrogens (FL, NL, CA, S, and FN) were studied. We examined the clearance of IgG-sensitized RBCs in animals treated with androgens or antiandrogens for 7 days to assess their in vivo effects on the function of splenic macrophage FcγRs.

Treatment with any of the androgens (T, DHT, MT, or D), significantly impaired the clearance of IgG-sensitized erythrocytes in more than 86% of the animals at 120 min, compared with simultaneously sham-treated controls (Fig. 1 and Table 1). The inhibition of clearance was dose related (Fig. 1 and 2 and Table 1). No significant inhibition of clearance was observed at androgen doses below those indicated in Table 1.

The effects of androgens on splenic macrophage FcγR function were assessed in vitro after splenic macrophage isolation. Treatment with androgens or antiandrogens had no consistent effect on the yield or viability of mononuclear cells isolated from the spleen. FcγR activity was determined by the in vitro binding of IgG-sensitized erythrocytes (Table 2). Following treatment with androgens, the percentage of isolated splenic macrophages binding three or more IgG-sensitizied erythrocytes was significantly lower than that of macrophages isolated

TABLE 1. Inhibition of clearance of IgG-sensitized RBCs by treatment with androgens[a]

Treatment	Androgen dose (mg/kg)	Mean % red cell survival at 120 min ± SEM[b]
Sham		42 ± 3
T	1	52 ± 3[c]
	5	70 ± 3
	25	75 ± 3
	50	76 ± 3
DHT	1	63 ± 3
	5	70 ± 3
	25	72 ± 2
	50	76 ± 2
MT	1	62 ± 2
	5	80 ± 3
	25	84 ± 3
	50	86 ± 4
D	1	44 ± 2[d]
	5	60 ± 3
	25	62 ± 3
	50	63 ± 4
Heat damage		3 ± 4

[a] Animals (12 or more for each dose) were treated for 7 days with androgens at the daily doses indicated. The percentage of IgG-sensitized RBCs remaining in the circulation at 120 min over sham-treated controls, as an index of in vivo splenic macrophage FcγR function, is indicated.

[b] $P < 0.001$ versus the sham-treated control unless indicated otherwise.

[c] $P < 0.01$.

[d] No statistically significant difference.

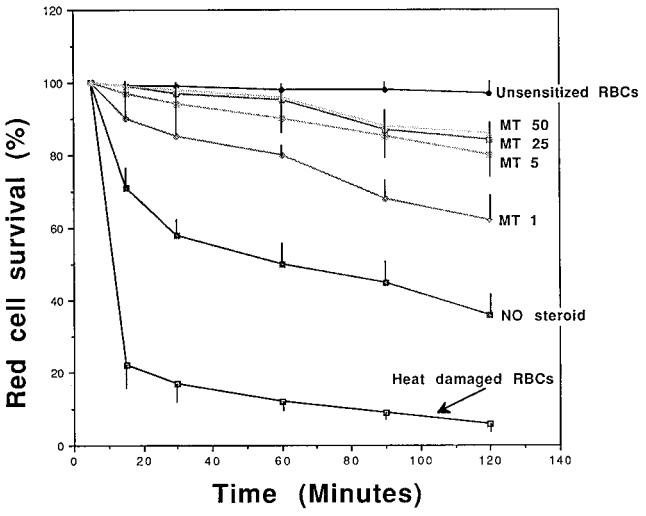

FIG. 2. In vivo clearance of IgG-sensitized RBCs in guinea pigs treated with various doses of MT. Numbers beside abbreviations represent the androgen doses used (milligrams per kilogram per day). Red cell survival represents the percentage of ^{51}Cr-labeled, IgG-sensitized RBCs (mean ± SEM) remaining in the circulation at each time point. The dose-dependent effect of MT is shown. Survival of heat-damaged RBCs (mean ± SEM) was not significantly different in androgen-treated animals compared to that in sham-treated controls.

from sham-treated animals (Table 2). The lowest androgen dose that inhibited the binding of IgG-sensitized erythrocytes by splenic macrophages is indicated in Table 2.

We further studied the effect of treatment with androgenic drugs on cell surface splenic macrophage FcγR expression.

TABLE 2. In vitro binding of IgG-sensitized RBCs by isolated splenic macrophages: inhibition by treatment with androgens[a]

Treatment	Androgen dose (mg/kg)	% of splenic macrophages binding ≥3 IgG-sensitized RBCs ± SEM[b]
Sham		59 ± 4
T	1	55 ± 2[c]
	5	53 ± 3[d]
	25	38 ± 2
	50	35 ± 1
DHT	1	47 ± 3
	5	42 ± 2
	25	30 ± 2
	50	27 ± 2
MT	1	45 ± 3
	5	37 ± 2
	25	20 ± 2
	50	20 ± 1
D	1	54 ± 2[c]
	5	53 ± 1[c]
	25	40 ± 2
	50	38 ± 2

[a] Splenic macrophages were isolated from animals treated for 7 days with androgens at the indicated daily doses. The percentage of splenic macrophages binding three or more IgG-sensitized RBCs over sham-treated controls, as an index of in vitro splenic macrophage FcγR function, is indicated.
[b] $P < 0.001$ compared with sham-treated control unless indicated otherwise.
[c] No statistically significant difference.
[d] $P < 0.01$.

TABLE 3. Inhibition of splenic macrophage FcγR MFI by treatment with androgens[a]

Androgen and dose (mg/kg)	Mean % of MFI inhibition ± SEM[b]	
	FcγR1,2	FcγR2
T		
1	10 ± 1[c]	6 ± 1[c]
5[c]	20 ± 1	12 ± 1[d]
25	36 ± 2	32 ± 1
50	46 ± 1	43 ± 2
DHT		
1[c]	20 ± 1	17 ± 2
5	40 ± 2	25 ± 2
25	52 ± 2	40 ± 3
50	62 ± 3	50 ± 3
MT		
1	25 ± 2	17 ± 2
5	38 ± 1	21 ± 2
25	61 ± 2	45 ± 2
50	60 ± 2	45 ± 3
D		
1	10 ± 2[c]	5 ± 1[c]
5	22 ± 2	15 ± 1[d]
25	39 ± 3	25 ± 2
50	37 ± 2	25 ± 1

[a] Animals were treated for 7 days with androgens at the daily doses indicated. Percent inhibition of MFI for both guinea pig macrophage FcγR1,2 and FcγR2 over sham-treated controls is indicated.
[b] $P < 0.001$ versus sham-treated control unless indicated otherwise.
[c] No statistically significant difference.
[d] $P < 0.01$.

Guinea pig macrophages express two classes of FcγRs: FcγR1,2 and FcγR2 (23). We examined the effects of androgens on the expression of both FcγR1,2 and FcγR2 by isolated splenic macrophages using flow cytometry with specific MAbs for these receptors (Table 3). Treatment with androgens significantly decreased the expression of both guinea pig macrophage FcγR1,2 and FcγR2. As shown in Table 3, the androgen-mediated inhibition of macrophage FcγR expression was dose dependent. Minimal effective doses are indicated in Table 3. DHT and MT were more effective than T or D and appeared to have a greater effect on FcγR1,2 than on FcγR2.

Treatment with antiandrogens for 7 days did not significantly alter the clearance of IgG-sensitized RBCs and had no significant effects upon macrophage FcγR expression, as shown by the assessment of the in vitro binding of IgG-sensitized erythrocytes and the cell surface expression of macrophage FcγRs by flow cytometry.

Immunofluorescence capping experiments were performed to examine the effects of in vivo-administered androgens and antiandrogens on the membrane mobility of FcγR1,2 and FcγR2. We considered whether highly lipophilic androgen or antiandrogen molecules might alter the mobility of surface membrane receptors, thus contributing to the inhibitory effects observed on FcγR1,2 and FcγR2 expression. We performed in vitro capping experiments comparing splenic macrophages isolated from treated animals to those from sham-treated controls. DHT (5, 10, and 50 mg/kg), MT (1, 5, and 15 mg/kg), and D (5, 25, and 50 mg/kg) were the androgens chosen. Four antiandrogens were examined: NL, CA, S, and FN (50 mg/kg per day in all cases). Cells incubated at 0°C to prevent membrane movement showed a uniform, diffuse ring pattern when stained for either FcγR1,2 or FcγR2. When incubated at 37°C,

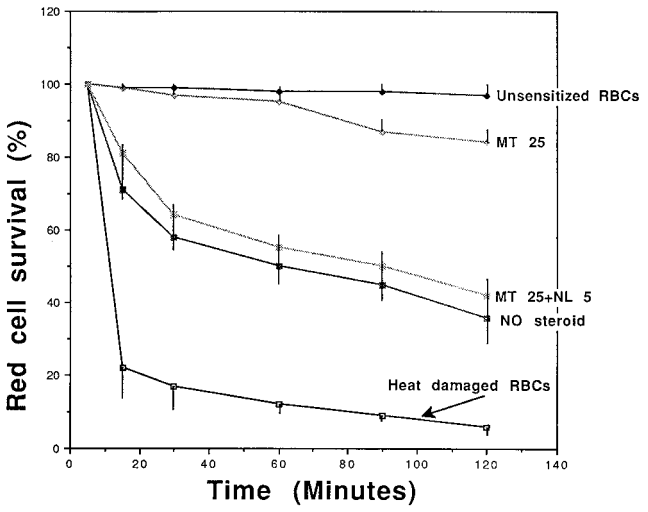

FIG. 3. Treatment with the antiandrogen NL counteracts the decreased in vivo clearance of IgG-sensitized RBCs induced by treatment with the androgen MT. Numbers beside abbreviations represent the doses of NL and MT used (milligrams per kilogram per day). Red cell survival represents the percentage of ^{51}Cr-labeled, IgG-sensitized RBCs (mean ± SEM) remaining in the circulation at each time point. Survival of heat-damaged RBCs (mean ± SEM) was not significantly different in androgen- or androgen-treated animals compared to that in sham-treated controls.

the majority of cells displayed aggregates or patches of membrane fluorescence, with some cells showing an intense polar distribution of staining for both FcγRs similar to that reported for the ligand-induced capping of lymphocyte surface immunoglobulin (47). No significant differences were observed between sham- and androgen-treated animals for either FcγR1,2 or FcγR2 staining intensity or distribution. Androgens and antiandrogens do not appear to have a major effect on the membrane mobility of these receptors.

Coadministration of any of the antiandrogens used counteracted the decreased expression of macrophage FcγRs induced by androgens. Figure 3 shows the blocking effect of NL (5 mg/kg per day) on the decreased clearance of IgG-sensitized RBCs by treatment with MT (25 mg/kg per day).

Our data indicate that treatment with androgens impairs the clearance of IgG-sensitized cells by inhibiting the cell surface expression of splenic macrophage FcγRs (Fig. 4).

DISCUSSION

Macrophage FcγRs play an important role in the regulation of the immune response, in host defense against infection, and in the pathophysiology of immune disorders (3, 9, 18–20). Thus, the regulation of macrophage FcγR expression is a therapeutic possibility in the management of immune-mediated diseases.

Glucocorticoids are basic in the treatment of immune-mediated disorders, but substantial side effects limit their use. Progesterones, like glucocorticoids, impair the clearance of IgG-sensitized cells (7, 21). We have developed a guinea pig model that has been useful in the study of the pathophysiology of immune cytopenias, autoimmune hemolytic anemia (AIHA), and immune thrombocytopenic purpura (ITP) (19, 20) and the effects of glucocorticoids and sex hormones on macrophage FcγR expression (5, 7, 8, 17, 21).

We studied the effect of treatment with androgens on macrophage FcγR expression. Four androgens (T, DHT, MT, and D) and five antiandrogens (FL, NL, CA, S, and FN) were studied. Animals were treated with androgens or antiandrogens for 7 days. The function of splenic macrophage FcγRs was assessed in vivo by measuring the clearance of IgG-sensitized RBCs and in vitro by measuring the binding of IgG-sensitized RBCs by macrophages isolated from the spleen. The cell surface expression of both guinea pig macrophage FcγR1,2 and FcγR2 was studied by flow cytometry using specific MAbs for each FcγR class.

Androgens impaired the clearance of IgG-sensitized cells by inhibiting the expression of both splenic macrophage FcγR1,2 and FcγR2. DHT and MT were more effective than T or D. Treatment with antiandrogens had no significant effects on macrophage FcγR expression. However, coadministration of antiandrogens counteracted the effects of androgens on macrophage FcγR expression.

Decreased function of macrophage FcγRs is one of the mechanisms by which immune-mediated diseases such as ITP and AIHA improve after medical therapy (2–4, 6, 13). Several studies have shown that intravenously administered immunoglobulin produces a mononuclear phagocyte system FcγR blockade (2–4, 6, 13), a decrease in the number of available FcγRs, an impairment of the affinity of receptor-ligand interaction, and an alteration of the phagocytic capacity of mononuclear phagocytes (13). Similarly, we found androgens to impair splenic macrophage FcγR function. Therefore, androgens other than D are potential therapeutic agents for immune-mediated disorders that may benefit from delayed immune complex clearance.

Two FcγR types, FcγR2 and FcγR1,2 have been identified in guinea pig macrophages (26). Our data suggest that both receptors are expressed on essentially all splenic macrophages and participate in the binding of IgG-sensitized erythrocytes (7, 8, 17). Immunofluorescence capping experiments were performed to examine any possible effects of in vivo-administered androgens or antiandrogens on the membrane mobility of FcγR1,2 and FcγR2 (23). Androgens or antiandrogens do not appear to have a major effect on the membrane mobility of these receptors, suggesting that their inhibitory effects are likely at the level of surface receptor expression.

There is substantial similarity between humans and guinea pigs in their response to steroids. Both species are steroid

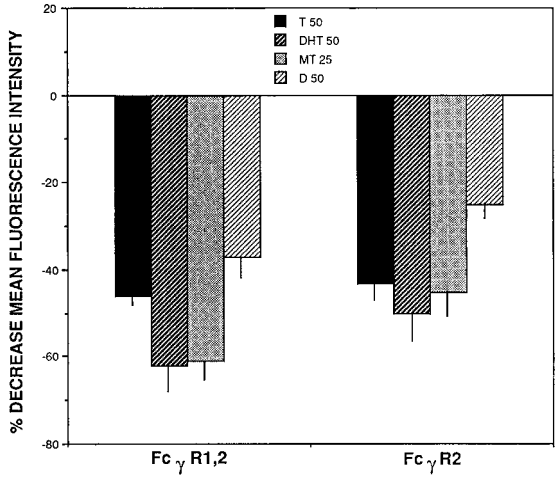

FIG. 4. Inhibition of cell surface expression of macrophage FcγR1,2 and FcγR2 isolated from the spleens of guinea pigs treated for 7 days with T, DHT, MT, and D at the indicated dosages (milligrams per kilogram per day). Percent inhibition of MFI (mean ± SEM) over sham-treated controls is indicated.

resistant and are similar in their steroid metabolism (28). We have previously measured the circulating levels of steroid hormones in guinea pigs and observed that they correlate with the administered in vivo dose and with the steroid levels observed during hormonal state changes in humans (5, 7, 8, 17, 21). Guinea pig macrophage FcγR1,2, in our experiments, appeared to be more responsive to such modulatory signals than did the other macrophage FcγR, FcγR2. The precise homology between the guinea pig and human macrophage FcγRs has not been established.

Antiandrogens are substances that counteract exogenous androgens in castrated animals (24). We have used four androgen receptor antagonists that block the action of both T and DHT: FL, NL, S, and CA. FL and NL are nonsteroidal antiandrogens (16, 24). S and CA are steroidal antiandrogens. FN is a 5α-reductase inhibitor that interferes with the conversion of T to DHT (16).

Our results indicate that treatment with the androgens T, DHT, MT, and D decreases the clearance of IgG-sensitized cells by inhibiting the expression of splenic macrophage FcγRs. Guinea pig macrophage FcγR1,2 appears to be more responsive to inhibition than the other macrophage FcγR, FcγR2. Androgens decrease splenic macrophage FcγR expression and the clearance of IgG-sensitizing immune complexes. Thus, androgens are candidate drugs for the management of immune disorders.

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