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MODULATION OF MACROPHAGE MANNOSE RECEPTOR AFFECTS THE UPTAKE OF VIRULENT AND AVIRULENT *LEISHMANIA DONOVANI* PROMASTIGOTES

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ABSTRACT: The effect of oxidants and the anti-inflammatory steroid dexamethasone on the attachment and internalization of virulent and avirulent *Leishmania donovani* promastigotes by the macrophage mannosyl fucosyl receptor was examined. Oxidants and dexamethasone are known to down- and upregulate the expression of the mannose receptor. Macrophages, when treated with 500 μM H_2O_2 at 37 C for 30 min, stimulate about 45% inhibition in uptake of an avirulent strain (UR6), and 30 and 25% inhibition for virulent strains AG-83 and GE-I, respectively. Treatment of macrophages with dexamethasone for 20 hr resulted in a stimulation in uptake of the parasite. When UR6 was used, a 3-fold increase in uptake was observed compared with the controls. Parasite uptake was also inhibited by the H_2O_2-generating system, glucose/glucose oxidase; inhibition was blocked by catalase. Treatment of macrophages either with H_2O_2 or dexamethasone did not affect the binding of the advanced glycosylation end product–bovine serum albumin (AGE-BSA), the ligand for AGE receptor of macrophages. Similarly, indirect evidence also shows that both types 1 and 3 complement receptors (CR1, CR3) are not affected by these treatments, indicating that, besides the mannosyl fucosyl receptor, other receptors are minimally altered in the identified condition. These results suggest that the up- and downregulation of the mannose receptor of macrophages may play a role in affecting *L. donovani* infection.

The mannose receptor is well-characterized on the surface of mature macrophages and is thought to play an important role in the recognition of mannose-containing glycoconjugates and in clearing lysosomal enzymes from the extracellular space (Shepherd et al., 1985). Expression of this receptor on the cell surface can be modulated by a variety of agents. Receptor expression is increased by treatment with dexamethasone (Shepherd et al., 1985) and vitamin D (Clohisy et al., 1987), whereas treatment with swainsonine (Chung, et al., 1984), interferon (IFN)-γ (Mokoena and Gordon, 1985), and H_2O_2 (Bozeman et al., 1988) decreases expression. Physiological studies indicate that this receptor may participate in a variety of functions involving both up- and downregulation of expression.

Leishmania donovani, the causative agent of visceral leishmaniasis, or kala-azar, is an obligate intracellular parasite that survives within the phagolysosomes of its hosts' macrophages. Several studies conducted on intact parasites have implicated a variety of receptors that may function in the binding of the promastigote form of the parasites to macrophages. These include the mannose receptor (Wilson and Pearson, 1986), a receptor of advanced glycosylation end products (AGE) (Mosser et al., 1987), and the types 1 and 3 complement receptors (CR1, CR3) (Russell and Wright, 1988; Da Silva et al., 1989; Rosenthal et al., 1996).

Macrophages are known to play a major role in host responses at sites of inflammation. Oxidants are a prominent constituent of the inflammatory milieu, and glucocorticoids are used extensively as anti-inflammatory agents; these agents are important modulators of mannose receptor activity. The present study was undertaken to investigate whether in vitro modulation of the macrophage mannose receptor by these agents affects the attachment and internalization of virulent and avirulent *L. donovani* promastigotes.

MATERIALS AND METHODS

Media and chemicals

RPMI 1640, bovine serum (FBS, heat inactivated) were from Difco (Detroit, Michigan); M199, penicillin, streptomycin, and gentamycin were from Gibco Laboratories (Grand Island, New York). Dexamethasone, *p*-NH_2-phenyl-α-D-mannopyranoside, bovine serum albumin (BSA), catalase, and glucose oxidase were from Sigma Chemical Co. (St. Louis, Missouri). All other reagents used were of analytical grade.

Parasites

Leishmania donovani strain UR6 (MHOM/IN/1978/UR6) (Dutta et al., 1987) was isolated from an Indian patient with kala-azar. The organisms were maintained and grown in modified Ray's medium (Ray, 1932) and subcultures were made at 72-hr intervals. *L. donovani* AG83 (MHOM/IN/1983/AG83) and GE-I (MHOM/IN/89/GE-I) strains were maintained in female BALB/c mice. Parasites were recovered from the spleen of infected mice by adding spleens to culture medium (M199 supplemented with 20% FBS, 100 U/ml penicillin, and 100 μg/ml streptomycin). The cultures were kept for 5 days at 22 C to obtain the promastigotes, which were then washed and used for infection of macrophages.

Preparation of macrophages

Macrophages were prepared as previously described (Russell et al., 1992). Briefly, thioglycolate-elicited macrophages were isolated by peritoneal lavage from female Swiss albino mice. Cells were plated in 35-mm tissue culture plates for 2 hr at 37 C. The cells were washed extensively with phosphate-buffered saline (PBS) (20 mM sodium phosphate buffer containing 0.15 M NaCl, pH 7.4) to remove any nonadherent cells. Cells obtained this way were ~85% viable, as judged by trypan blue exclusion test.

Treatment of macrophages with oxidants or dexamethasone

Medium was removed from the cells on coverslips and replaced with fresh medium containing oxidant or oxidant-generating system with or without catalase (100 μg/ml) or dexamethasone, and incubated at 37 C with H_2O_2 (0.25–1.0 mM) for 30 min, glucose (10 mM) plus glucose oxidase (500 mU/ml) for 30 min, and dexamethasone; a stock solution of dexamethasone was made in absolute ethanol as described elsewhere (Shepherd et al., 1985). Dilutions were made before use in PBS and added to cultures as 0.1–0.2 μg/ml for 20 hr.

Infection of macrophages

Promastigote forms of the parasites were used to infect cultures of adherent macrophages at a ratio of 10 parasites per macrophage. Infection was allowed to proceed for 2 hr at 37 C; then all extracellular parasites were washed out. In most instances, 80% of the macrophages were infected. Infection levels were determined by microscopic examination of Giemsa-stained cells.

Preparation of mannose-BSA and AGE-BSA

Mannose-BSA (Man-BSA) was prepared according to the method previously described (Das et al., 1982). Briefly, *p*-aminophenyl-α-D-mannopyranoside was coupled to BSA through water-soluble 1-ethyl-

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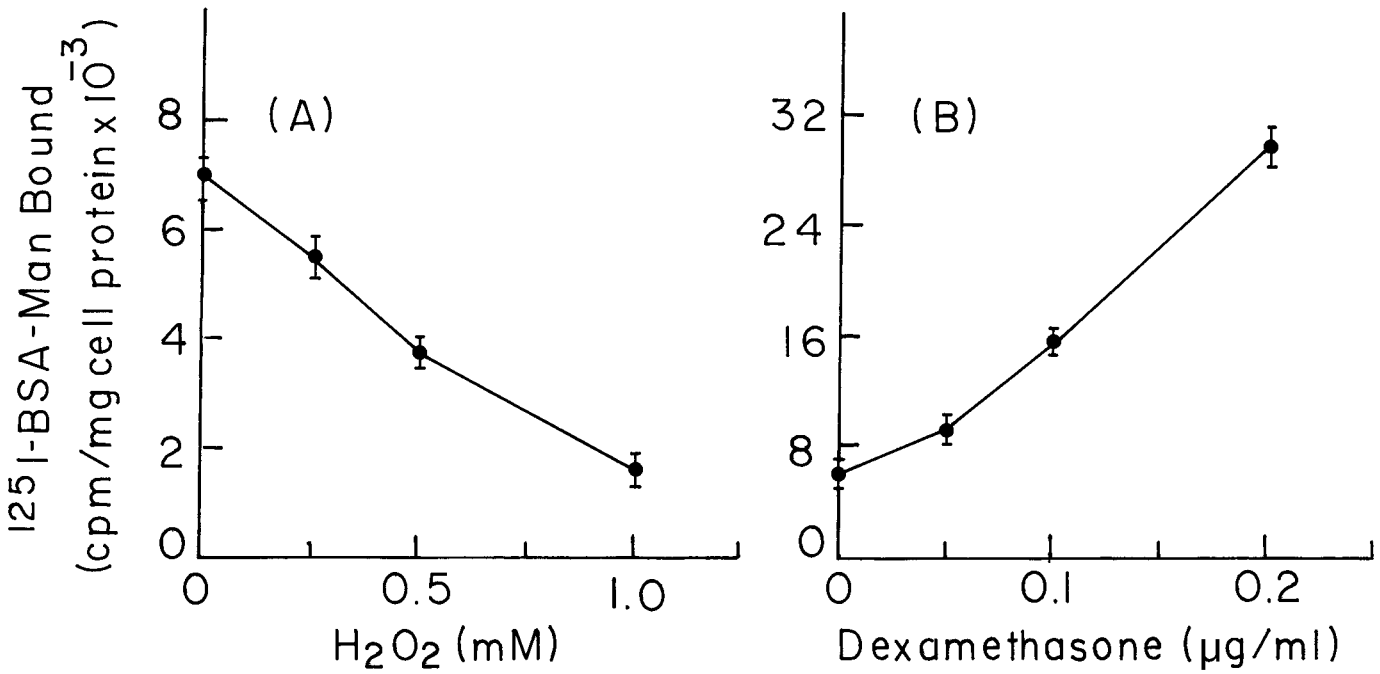

FIGURE 1. Effects of H_2O_2 or dexamethasone on binding of ^{125}mannose–bovine serum albumin (^{125}Man-BSA). **A.** Effects of H_2O_2 treatment at 37 C on binding of ^{125}I-Man-BSA. Mouse peritoneal macrophages were incubated in the presence or absence of H_2O_2 at 37 C for 30 min, cooled, washed, and resuspended in assay medium at 10^7 cells/ml. Control and H_2O_2-treated cells were incubated at 4 C with 5×10^5 counts per minute of ^{125}I-Man-BSA for 2 hr. Cells were collected and radioactivity quantified. **B.** Effect of dexamethasone on binding of ^{125}I-Man-BSA. Macrophages were cultured and dexamethasone was added at the concentrations indicated. At the end of the incubation, the cells were washed and ^{125}I-Man-BSA was added. Cells were collected and radioactivity quantified as in **A**.

3-(3-dimethyl aminopropyl)-carbodiimide hydrochloride at pH 4.75. After coupling, sugar and protein were estimated by phenol–sulfuric acid (Dubois et al., 1956) and Lowry methods (Lowry et al., 1951), respectively.

For the mannose receptor blocking experiment with Man-BSA, macrophages were incubated in the absence or presence of H_2O_2 (500 μM) or dexamethasone (0.1 μgm/ml) at 37 C, washed, and Man-BSA was added to both treated and untreated macrophages. Both virulent and avirulent parasites were then added and incubated at 37 C for 2 hr.

AGE-BSA was prepared by incubating protein solution (BSA, 25 mg/ml) with 0.5 M glucose in 0.15 M phosphate buffer, pH 7.3, at 37 C for 4 wk in the presence of 1.5 mM phenylmethylsulfonyl fluoride (PMSF), 0.5 mM EDTA, penicillin (100 U/ml), and gentamycin (40 μg/ml) under sterile conditions according to the method of Vlassara et al. (1985). After incubation, low-molecular-weight reactants were removed by dialysis against PBS. Sugar and protein were then analyzed again as described above. Both ligands were iodinated using a chloramine-T procedure (Hunter, 1978).

Binding of ^{125}I-Man-BSA, ^{125}I-AGE-BSA by mouse peritoneal macrophages

Binding studies were performed with peritoneal macrophages in α-MEM plus 10% FBS buffered with 20 mM 3-(*N*morpholino)propanesulfonic acid (MOPS), adjusted to pH 7.0. Adherent macrophage cells were first scraped with a disposable cell scraper and were suspended in the binding medium, washed twice with the medium, cooled to 4 C, and incubated for 2 hr with radioiodinated ligands (5×10^5 counts per minute) in the presence or absence of 100-fold excess of unlabeled cold ligands or mannan (2 mg/ml). After incubation, the cells were washed extensively, solubilized, and assayed for radioactivity in a γ-radiation counter. The protein was estimated by the Lowry procedure (Lowry et al., 1951).

Effect of H_2O_2 or dexamethasone treatment on attachment and uptake of parasites

Macrophages were incubated with H_2O_2 or dexamethasone for 30 min or 20 hr. The cells were washed extensively with PBS and then incubated with virulent or avirulent *L. donovani* promastigotes. After incubation, the excess promastigotes were removed and the cells were washed with PBS. Cells were then air dried, fixed, stained with Giemsa, and the number of attached and internalized parasites counted using light microscopy.

RESULTS

Effects of H_2O_2 or dexamethasone on mannose receptor activity of peritoneal macrophage cells

Binding of ^{125}I-Man-BSA (ligand) to mannose receptor of macrophages is shown in Figure 1. Macrophages were pretreated with increasing concentrations of H_2O_2 for 30 min at 37 C or with dexamethasone for 20 hr. More than half-maximal inhibition in binding was achieved with 500 μM H_2O_2, with maximal effects at 1 mM H_2O_2 (Fig. 1A). In contrast, treatment with dexamethasone shows a near 2-fold increase in cell surface binding at 0.1 μg/ml (Fig. 1B). Although it was reported that 1 mM H_2O_2 had no effect on macrophage viability (Bozeman et al., 1988), little toxicity was observed at this concentration in which 80–85% of cells excluded trypan blue.

Effect of H_2O_2 or dexamethasone on phagocytic activities of peritoneal macrophages for *L. donovani* strains

As a mannose receptor of macrophages is involved in the recognition of *L. donovani* promastigotes, an attempt was made to evaluate the contribution of this receptor after treatment with H_2O_2 or dexamethasone toward the uptake of virulent and avirulent strains of *L. donovani* promastigotes. In general, H_2O_2 exerted an inhibitory effect on the uptake of parasites (Fig. 2); the inhibition was maximum for the avirulent strain (UR6), i.e.,

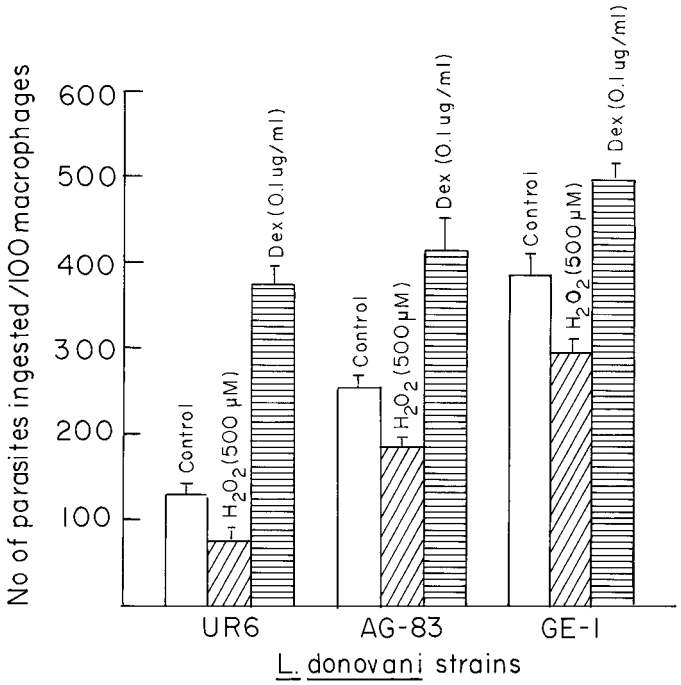

FIGURE 2. Effect of H_2O_2 or dexamethasone on mannose receptor-mediated uptake of *Leishmania donovani* strains by mouse peritoneal macrophages. Cells were incubated in absence or presence of H_2O_2 or dexamethasone and washed and promastigotes were added, washed, and counted for uptake by light microscopy.

about 45%, whereas for virulent strains (AG-83) and (GE-1), inhibition was roughly 30 and 25%, respectively. However, dexamethasone stimulated macrophages to take up the parasites. Again, for the avirulent strain, maximum stimulation in uptake was at least 3 times greater compared with the untreated control.

H_2O_2-mediated *L. donovani* promastigote uptake by mannose receptor: block by catalase

Since maximal inhibition in uptake of avirulent parasites (UR6) was observed by H_2O_2-treated macrophages, an effort was made to examine whether the actual decrease in mannose receptor, or indirectly the inhibition in uptake of UR6, was due to the effect of H_2O_2. For this, macrophages were coincubated with H_2O_2 and catalase (100 μg/ml) for 30 min at 37 C, washed, and then charged with UR6. Coincubation of H_2O_2 and catalase blocked the inhibition of uptake (data not shown).

TABLE II. Effect of H_2O_2 or dexamethasone on advanced glycosylation end product (AGE) receptor of macrophages.*

Treatment	^{125}I-Bovine serum albumin (BSA)-AGE bound to macrophages (cpm)		
	(−) Cold AGE-BSA	(+) Cold AGE-BSA	Specific binding
None	8,395 ± 148	4,275 ± 106	4,120
H_2O_2 (500 μM)	8,262 ± 88	4,415 ± 49	3,847
Dexamethasone (0.1 μg/ml)	8,712 ± 123	4,482 ± 130	4,230

* These data are representative of 3 separate experiments. Results are expressed as the mean ± SD.

Effect of artificially generated oxidant system on attachment and uptake of *L. donovani* promastigotes

Glucose plus glucose oxidase, capable of artificially generating reactive oxygen species, was examined to study their effects on the uptake of UR6 and AG83 promastigotes. It is known that 500 mU of glucose oxidase produces 100 nmol/ml of H_2O_2 per minute (Bozeman et al., 1988). When macrophages were pretreated with 500 mU of glucose oxidase, there was 40% inhibition in attachment and 42% in internalization for UR6, and 24% inhibition in attachment and 30% in internalization for AG83 (Table I).

Effect of H_2O_2 or dexamethasone on other macrophage receptors

To examine the effect of oxidant or dexamethasone treatment on other macrophage receptors, binding of another ligand by another macrophage receptor (AGE receptor) was measured. Incubation of macrophages with H_2O_2 or dexamethasone decreased or increased mannose receptor-mediated binding of ^{125}I-Man-BSA, whereas binding of ^{125}I-AGE-BSA on AGE receptor of macrophages was virtually unaffected (90% of control) (Table II). To determine indirectly that the expression of both CR1 and CR3 are not affected after the modification of macrophage surface by H_2O_2 or dexamethasone, mannose receptors of macrophages were blocked with freshly prepared Man-BSA. Macrophages were then challenged with both virulent and avirulent strains of *L. donovani* promastigotes and their uptake was studied (Table III). It is obvious that the uptake did not change before and after the treatment with H_2O_2 or dexamethasone, showing indirectly that the macrophage surface modification does not involve all the receptors.

TABLE I. Effect of artificial H_2O_2 generating system (glucose + glucose oxidase) on the attachment and uptake of *Leishmania donovani* promastigotes.*

L. donovani strains†	Control		H_2O_2		Glucose + glucose oxidase	
	Attachment	Internalization	Attachment	Internalization	Attachment	Internalization
UR6	202 ± 7	143 ± 6	130 ± 6	90 ± 3	122 ± 4	85 ± 7
AG83	78 ± 6	264 ± 9	50 ± 9	175 ± 5	59 ± 8	187 ± 10

* Data shown are the mean ± SD (n = 3).
† Macrophages were treated for 30 min with 10 mM glucose plus 500 mU of glucose oxidase.

TABLE III. Effect of H_2O_2 or dexamethasone on macrophage noncarbohydrate receptor-mediated uptake of virulent or avirulent *Leishmania donovani* promastigotes.*

Cells + treatment	No. of parasites/ 100 macrophages
Macrophage + UR6	144 ± 5
Macrophage + Man-BSA + UR6	63 ± 3
Macrophage + H_2O_2 + UR6	94 ± 3
Macrophage + H_2O_2 + Man-BSA + UR6	68 ± 6
Macrophage + dex. + UR6	361 ± 9
Macrophage + dex. + Man-BSA + UR6	73 ± 5
Macrophage + AG-83	252 ± 11
Macrophage + Man-BSA + AG-83	149 ± 6
Macrophage + H_2O_2 + AG-83	168 ± 7
Macrophage + H_2O_2 + Man-BSA + AG-83	138 ± 4
Macrophage + dex. + AG-83	411 ± 13
Macrophage + dex. + Man-BSA ± AG-83	163 ± 5
Macrophage + GE-I	376 ± 8
Macrophage + Man-BSA + GE-I	244 ± 3
Macrophage + H_2O_2 + GE-I	213 ± 3
Macrophage + H_2O_2 + Man-BSA + GE-I	236 ± 3
Macrophage + dex. + GE-I	472 ± 7
Macrophage + dex. + Man-BSA + GE-I	241 ± 8

* These data are representative of 3 separate experiments. Results are expressed as mean ± SD. Man-BSA, mannose–bovine serum albumin; dex., dexamethasone; UR6, avirulent strain; AG-83 and GE-I, virulent strains.

DISCUSSION

Macrophages have been shown to play a major role in host responses at sites of inflammation. Oxidants generated at the inflammatory sites and the anti-inflammatory agents used in vivo are known to regulate mannose receptor activity of macrophages in vitro. Mannose receptors may participate in a variety of physiologic functions involving both up- and downregulation of receptor expression, as, for example, expression of this receptor is low in macrophages that have been activated to a tumoricidal state (Ezekowitz et al., 1982; Imber et al., 1982). In the present study, an effort was made to determine whether and to what extent specific inhibition of mannose receptor activity by oxidants or upregulation of the same receptor by anti-inflammatory steroid, dexamethasone, affect the attachment and internalization of virulent and avirulent *L. donovani* promastigotes.

Macrophages have a variety of receptors on their cell surface, including the mannose receptor, which mediates the uptake of *L. donovani* promastigotes. In the present study, H_2O_2 and dexamethasone were shown to differentially affect mannose receptor-mediated attachment and internalization of virulent and avirulent strains by peritoneal macrophages. It is known that H_2O_2 downregulates and dexamethasone upregulates the expression of the mannose receptor (Shepherd et al., 1985; Bozeman et al., 1988). A similar result was seen in the binding experiment of ^{125}I-Man-BSA with H_2O_2 or dexamathasone-treated cells (Fig. 1). In H_2O_2-treated cells, inhibition in uptake was greater for avirulent strains compared with the virulent ones (Fig. 2). In contrast, in dexamethasone-treated macrophages, uptake was enhanced for avirulent strains in comparison with virulent strains. These results clearly indicate that H_2O_2 and dexamethasone have opposite effects on the uptake of parasites via the mannose receptor of macrophages and that the avirulent strain used this receptor more efficiently. This decrease or increase in uptake was probably due to a decrease or increase in the binding of promastigotes, which is in close agreement with previous results (Chakraborty et al., 1996, 1998), where it was shown that virulent strains use CR3 and avirulent strains use the mannosyl fucosyl receptor for their maximum uptake. In a similar approach, Mosser and Handman (1992) reported that IFN-γ-treated macrophages bind fewer *L. major* and *L. donovani* promastigotes than untreated cells because of downregulation of a lectinlike receptor. In addition to H_2O_2, glucose/glucose oxidase, which enzymatically generates H_2O_2, decreased the uptake of the parasites and the decrease was blocked by catalase (Table I). The above result suggests that the artificially generating oxidant system behaved similarly to H_2O_2. There was no cell death after treatment with 500 uM of H_2O_2 for 30 min or with dexamethasoene (0.1 ug/ml) for 20 hr as assessed by trypan blue exclusion and the protein content of adherent macrophages.

It might be possible that treatment of macrophages with H_2O_2 or dexamethasone would affect other macrophage receptors. Binding of ligands by the AGE receptor (Vlassara et al., 1985) was not affected by treatment with H_2O_2 or dexamethasone. The results also showed, though indirectly, that both CR1 and CR3 are not affected by these treatments. Thus, the modulation by H_2O_2 or dexamethasone at these levels appears to be selective for the mannose receptor.

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