SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: (U)	1b. RESTRICTIVE MARKINGS: NA
2a. SECURITY CLASSIFICATION AUTHORITY: NA	3. DISTRIBUTION/AVAILABILITY OF REPORT: Unlimited Distribution
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE: NA	
4. PERFORMING ORGANIZATION REPORT NUMBER(S): The Medical College of Pennsylvania	5. MONITORING ORGANIZATION REPORT NUMBER(S): Office Of Naval Research
6a. NAME OF PERFORMING ORGANIZATION: The Medical College of PA; 6b. OFFICE SYMBOL (If applicable): NA	7a. NAME OF MONITORING ORGANIZATION: Office of Naval Research
6c. ADDRESS (City, State, and ZIP Code): 3300 Henry Ave, Philadelphia, PA 19129	7b. ADDRESS (City, State, and ZIP Code): 800 N. Quincy St., Arlington, VA 22217-5000
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: Office of Naval Research; 8b. OFFICE SYMBOL (If applicable): ONR	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: N00014-87-0386
8c. ADDRESS (City, State, and ZIP Code): 800 N. Quincy St., Arlington, VA 22217-5000	10. SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO. 6115N; PROJECT NO. RR04108; TASK NO.; WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)
Effect of Glucocorticoids and Catecholamines on Macrophage Antimicrobial Activity.

12. PERSONAL AUTHOR(S)
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13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual	FROM 5/87 TO 5/88	June 10, 1988	10

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
08			macrophages; glucocorticoids; hydrocortisone; dexamethasone; herpes simplex virus; ectoenzymes; methylprednisolone;

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

The effects of glucocorticoids on resident peritoneal macrophages (MO) were determined. First a serum-free, chemically defined medium which supported resident peritoneal MO in culture for 72 hours was selected HL-1 (Ventrex, Inc.) supported MO adherence, cell number, ectoenzyme phenotype, and allowed determination of intrinsic antiviral activity of MO. Neither hydrocortisone nor dexamethasone altered the alkaline phosphodiesterase activity of the MO; however, dexamethasone (10^{-9} M) resulted in depressed 5'Nucleotidase activity of resident MO after 24 hours in culture. Hydrocortisone (10^{-6}M) resulted in a transient depression in 5'N activity. Neither dexamethasone nor methylprednisolone altered MO intrinsic resistance to herpes simplex virus type I .

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	(U)
22a. NAME OF RESPONSIBLE INDIVIDUAL: Dr. J.A. Majde	22b. TELEPHONE (Include Area Code): 202/696-4055; 22c. OFFICE SYMBOL: ONR

DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY CLASSIFICATION OF THIS PAGE

June 10, 1988

PROGRESS REPORT ON CONTRACT N-00014-87-0386

PRINCIPAL INVESTIGATOR: Walla L. Dempsey

CONTRACTOR: J.A. Majde

START DATE: MAY 1, 1988

RESEARCH OBJECTIVE: The overall objective of this project is to establish whether glucocorticoids and catecholamines can directly modulate macrophage (MO) antimicrobial activity.

PROGRESS (Year 1):

Specific aim 1: Develop an in vitro system using a defined medium for assay of MO intrinsic antiviral and bactericidal functions.

a. Selection of optimal defined medium.

Since July, 1988, upon receipt of ONR funding, we have compared three serum free, chemically defined media for their ability to support resident peritoneal MO in culture. MO were cultured up to 72 hours in one of the media listed in Table 1 or in Eagles minimal essential medium (EMEM, GIBCO) supplemented with 10% fetal bovine serum, a standard medium for short term culture of resident peritoneal MO. The percentage of cells adhering after two hours in culture (which is indicative of selection of MO), the percentage adhered cells which had extended processes (spread), and the ectoenzyme phenotype (5' Nucleotidase and Alkaline phosphodiesterase-I, cell surface markers of MO activation or priming) of the isolated MO were determined. Nonadherent cells were removed from duplicate cultures, and these MO were incubated for 24, 48 or 72 hours. The number and the ectoenzyme phenotype of adherent MO remaining after the culture periods were measured.

Table 1. SERUM-FREE, CHEMICALLY DEFINED MEDIA[1]

HL-1:	(Ventrex) DME:F12 base, Hepes buffer, insulin, transferrin, testosterone, sodium selenite, ethanolamine, saturated and unsaturated fatty acids, stabilizing proteins (<30 ug/ml). Endotoxin levels < 0.05 ng/ml.
PC-1:	(Ventrex) DME:F12 base, Hepes buffer, insulin, transferrin, fatty acids, stabilizing proteins (<530 ug/ml)
HB102:	(Hana Biologics) Completely defined medium. Specific content not listed in product data sheets. Protein concentration = 750ug/ml. Endotoxin levels^R (<0.05 ng/ml)

[1] Data listed on product information

Fewer cells (45%) adhered initially (2 hr) in PC-1 medium (Table 2); whereas, approximately, 55-60% of recovered peritoneal cells adhered in EMEM, HL-1 and

HB102 media. HL-1 and HB102 each supported greater spreading of the adhered MO after 2 hours than did PC-1 or EMEM. Although approximately 25% of the MO were lost in 24 hours, HL-1 supported MO cultures somewhat better than EMEM or HB102, with only 30% lost after 48 hr and 48% lost after 72 hours. In contrast by 48 hours in culture, only 40-50% of the initial MO population remained attached in EMEM and HB-102 (Table 3). PC-1 medium appeared to support MO cultures well until 72 hours, however, fewer MO adhered initially in PC-1 (Table 3).

Table 2. MEDIA EFFECTS ON MACROPHAGE ISOLATION[1]

MEDIA	% ADHERED	% SPREAD
EMEM (10% FBS)	54.9% [2] (39-71%) [3]	5-20%
HL-1	58.8% (55-65%)	30-50%
PC-1	44.9% (33-57%)	10-30%
HB102	57.2% (46-68%)	30-50%

[1]Peritoneal cells were cultured for 2 hours at 37°C, in 5% CO_2
[2]Represents the average from 2-3 experiments
[3]Represents the range from 2-3 experiments.

Table 3 EFFECTS OF SERUM FREE MEDIA ON MACROPHAGE CULTURE

MEDIA	% REDUCTION IN MACROPHAGE NUMBER[1]		
	24 hr[2]	48 hr	72 hr
EMEM (10% FBS)	0%	59.5%[3] (59-60%)[4]	80.6% (79-82%)
HL--1	25.6%	30.9% (14-47%)	47.7% (40-55%)
PC-1	0%	9.2% (0-13%)	54.9% (54-55%)
HB-102	0%	50.3% (48-52%)	54.7% (50-59%)

[1]Represents the percent reduction in MO isolated by adherence after 2 hours in culture.
[2]Results from one experiment are depicted at 24 hr.
[3]Data are presented as the mean from 2 experiments.
[4]Represents the range in data from 2 experiments.

None of the defined media induced a change in MO ectoenzyme phenotype after 2 or 24 hours in culture (Tables 4, 5). However, MO which had been cultured in EMEM or HB102 increased in 5'nucleotidase (5'N) after 48 and 72 hours in culture, while MO which had been cultured in PC-1 for 72 hours decreased in 5'N. In contrast, culturing the MO in HL-1 had no significant effect on 5'N activity (Table 4). Alkaline phosphodiesterase-I (APD-I) activity was essentially unaffected in MO which had been cultured in HB102, HL-1, or EMEM, but was increased significantly in those MO which had been cultured in PC-1 for 48 and 72 hours (Table 5).

Table 4. EFFECTS OF CULTURING IN SERUM FREE MEDIA ON MACROPHAGE 5'N ACTIVITY

MEDIA	5'N ACTIVITY[1,2] (Hours in Culture)			
	(2)	(24)	(48)	(72)
EMEM (10% FBS)	37.2 ± 8.5	29.9 ± 20.2	54.6 ± 25.2	64.5 ± 0.7
HL-1	48.6 ± 7.8	21.7 ± 16.8	35.0 ± 8.4	55.4 ± 9.7
PC-1	32.0 ± 4.4	17.8 ± 7.7	21.9 ± 4.9	18.1 ± 2.7
HB-102	45.6 ± 6.1	24.4 ± 9.4	84.9 ± 22.8	92.0 ±22.8

[1]Data are presented as specific activity/mg protein.
[2]Represents the mean ± 1 SEM from 2 experiments, 1-3 samples /experiment.

Table 5. EFFECT OF MACROPHAGE CULTURE IN SERUM FREE MEDIA ON APD-I ACTIVITY

MEDIA	APD-I ACTIVITY[1,2] (Hours in Culture)			
	(2)	(24)	(48)	(72)
EMEM (10% FBS)	15.0 ± 1.8	13.2 ± 3.9	24.2 ± 4.7	29.3 ± 8.5
HL-1	11.6 ± 1.4	13.6 ± 1.6	23.7 ± 0.5	22.3 ± 5.0
PC-1	11.9 ± 1.4	23.5 ± 6.0	30.9 ± 8.2	38.7 ± 6.3
HB-102	12.9 ± 0.9	8.8 ± 1.4	15.5 ± 0.4	11.4 ± 1.7

[1] Data are present as specific activity/mg protein.
[2] Represents the mean ± 1 SEM from 2 experiments, 1-3 samples/experiment.

These results indicate that resident peritoneal MO which had been cultured in HL-1 were maintained better in culture over a 72 hour period. A lower percentage of MO were supported for at least 48 hours in HL-1 than in PC1, EMEM

or HB102. In addition, the ectoenzyme phenotype of MO cultured in HL-1 did not change appreciably over the culture period, indicative of the lack of activation of HL-1 cultured MO. In contrast, MO cultured in HB102 or PC-1 showed some signs of activation or priming.

b. Establish the intrinsic MO antiviral assay in a defined medium.

The effect of serum free media on MO intrinsic resistance to herpes simplex virus type 1 (HSV-1) was determined. Resident peritoneal MO (after isolation by adherence) were cultured for 24 hours in either EMEM, HL-1, or HB102. Each culture well (24 well plate) was infected with 2-3 multiplicities of infection (MOI). Virus was allowed to adsorb for one hour. Unadsorbed virus was removed by washing the cultures extensively in PBS. Triplicate cultures were disrupted by scraping the MO in the culture medium overlay, and the resultant lysates were titered for infectious virus. A cell line (VERO) which is permissive for HSV-1 growth was infected, and treated similarly, as a control.

MO which had been cultured in the serum free media exhibited the typical resistance pattern to HSV-1. Recoverable infectious virus decreased over the culture period (Table 6), regardless of the medium in which the MO were cultured. By 48 hours, MO, which had been cultured in any of the media, contained neglible infectious virus and contained no detectable infectious virus by 72 hours. In contrast, VERO cells, which are permissive for HSV-1, increased in viral titer over the same period. MO, which had been cultured in serum free medium, exhibited significantly lower titers throughout the culture period than did MO cultured in serum containing medium. This is probably due to less virus actually adsorbing because the titers were signficantly lower after only two hours in culture. Experiments to test this hypothesis are underway.

Table 6. EFFECT OF SERUM FREE MEDIA ON MACROPHAGE INTRINSIC RESISTANCE TO HSV-I

CELL TYPE Media	VIRUS CONCENTRATIONS[1] (Hours post infection) (2)	(24)	(48)	(72)
RESIDENT MACROPHAGES (Non-permissive)		(PFU x 10^4 / 10^6 CELLS)		
EMEM (10% FBS	2.40 ± 0.38	0.28 ± 0.04	0.07 ± 0.01	0
HL-1	0.52 ± 0.13[2]	0.14 ± 0.03[2]	0.01 ± 0.01[2]	0
HB102	0.66 ± 0.17[2]	0.10 ± 0.11[2]	0[2]	0
VERO CELLS (Permissive)		(PFU x 107 / 10^6 CELLS)		
EMEM (10% FBS)	0	5.66 ± 1.06	ND	1.40 ± 0.5

[1] Represents the mean ± SEM from 2 separate experiments.
[2] $p < 0.05$, ANOVA.

2. Establish the effects of exposure of MO to the neuroendocrine mediators of stress, glucocorticoids and catecholamines, on MO antiviral and antibacterial

functions in the defined medium system.

a. Establish the effects on general MO functions.

The effects of the glucocorticoids (dexamethasone, methylprednisolone, and hydrocorticortisone) on the ability to isolate and maintain resident peritoneal MO in culture were determined. Resident peritoneal MO were cultured as before in HL-1 medium which contained vrious concentrations of one of the glucocorticoids tested. The number of MO isolated by adherence (2 hr), the number of MO remaining after 24, 48 and 72 hours in culture, the percent of MO which had extended processes (spread), and the ectoenzyme phenotype of the MO were determined. None of the glucocorticoids tested had any effect on the number of MO isolated or on the number of MO remaining at each time point tested. MO cultured in 10^{-3} M concentrations of any of the glucocorticoids exhibited less spreading in culture (Table 7). Lesser concentrations of the drugs had no effect on MO spreading.

Table 7. EFFECTS OF GLUCOCORTICOIDS ON MACROPHAGE CULTURES

GLUCOCORTICOID (Molar Concentration)	% SPREAD[1] (Hours in culture) (2)	(24)	(48)	(72)
Dexamethasone				
(0)	30-40%	50-60%	50-60%	50-60%
(10^{-3})	10-20%	10-20%	10-20%	10-20%
(10^{-6})	30-40%	30-50%	40-50%	40-50%
(10^{-9})	30-40%	50-60%	50-60%	50-60%
Methyprednisolone				
(0)	30-50%	30-50%	30-50%	30-50%
(10^{-3})	10-20%	10-20%	20-30%	20-30%
(10^{-6})	30-40%	30-40%	30-40%	30-40%
(10^{-9})	40-50%	50-60%	50-60%	50-60%
Hydrocortisone				
(0)	30-40%	50-60%	50-60%	50-60%
(10^{-3})	20-30%	20-30%	10-30%	10-30%
(10^{-6})	30-50%	40-50%	40-50%	40-50%
(10^{-9})	30-40%	50-60%	50-60%	50-60%

[1]Represents the range from 2-3 experiments.

APD-I activity was not altered significantly in MO cultured in any of the concentration of dexamethasone or hydrocortisone tested (Tables 11,12). However, additional culture times and additional drug concentrations need to be completed for the hydrocortisone studies.

Table 8. EFFECTS OF DEXAMETHASONE ON MACROPHAGE APD-I ACTIVITY

CONCENTRATION	SPECIFIC ACTIVITY[1,2] (Hours in culture)			
	(2)	(24)	(48)	(72)
0	20.4 ± 3.4	17.2 ± 4.2	11.0 ± 2.4	25.3 ± 7.6
10^{-3} M	18.8 ± 4.6	20.5 ± 0.3	21.6 ± 7.5	ND
10^{-5} M	20.4 ± 4.9	25.2 ± 10.6	24.0 ± 0.9	19.3 ± 1.9
10^{-6} M	14.7 ± 2.0	22.0 ± 10.0	32.3 ± 14.9	6.2 ± 0.7
10^{-7} M	20.8 ± 8.7	12.9 ± 4.8	14.9 ± 3.7	8.9 ± 0.8
10^{-8} M	11.7 ± 4.5	12.3 ± 5.6	14.5 ± 0.4	14.8 ± 4.1
10^{-9} M	16.4 ± 5.6	7.3 ± 3.8	12.3 ± 0.4	14.0 ± 1.0

1 Represents the specific activity/mg protein.
2 Data are presented as the mean ± 1 SEM.

Table 9. EFFECT OF HYDROCORTISONE ON MACROPHAGE APD-1 ACTIVITY

CONCENTRATION	SPECIFIC ACTIVITY[1,2] (Hours in culture)			
	(2)	(24)	(48)	(72)
0	24.0	34.1 ± 1.9	31.4 ± 5.4	39.1
10^{-3}	21.2 ± 6.5	12.6 ± 11.8	41.3 ± 5.5	25.6 ± 13.8
10^{-6}	22.8 ± 12.8	28.9 ± 14.4	23.0	37.2 ± 0.6
10^{-9}	15.4 ± 9.0	35.5	ND	ND

1 Represents the specific activity/mg protein.
2 Data are expressed as the mean ± 1 SEM.

5'N was consistently depressed in MO which had been cultured for 24, 48 or 72 hours in 10^{-9}M dexamethasone (Table 10). Some transient depression in 5'N was observed in MO cultured for 24 hours in 10^{-7}M dexamethasone; however, the 5'N levels at 48 hours and 72 hours were not significantly different from the control at those times. MO cultured in hydrocortisone (10^{-6}M) demonstrated a transient decrease in 5'N activity (Table 11). As before, addtional time points and drug

concentrations must be completed before conclusions can be determined.

Table 10. EFFECTS OF DEXAMETHASONE ON MACROPHAGE 5'NUCLEOTIDASE ACTIVITY

CONCENTRATION	SPECIFIC ACTIVITY[1,2] (Hours in culture) (2)	(24)	(48)	(72)
0	30.1 ± 2.9	17.2 ± 4.2	11.0 ± 2.4	25.3 ± 7.6
10^{-3} M	36.2 ± 1.2	27.5 ± 7.8	26.7 ± 10.8	42.2 ± 8.5
10^{-5} M	31.6 ± 5.2	17.4 ± 6.1	14.9 ± 0.5	15.0 ± 0.2
10^{-6} M	29.5 ± 4.3	20.1 ± 6.1	ND	13.4 ± 5.6
10^{-7} M	27.1 ± 6.1	6.8 ± 1.0	24.7 ± 1.8	10.8 ± 2.4
10^{-8} M	26.7 ± 2.4	23.8 ±15.5	41.5 ± 8.6	17.6 ± 6.2
10^{-9} M	25.8 ± 2.3	9.4 ± 3.8[3]	9.8 ± 1.3[3]	6.8 ± 1.5[3]

[1]Represents the specific activity/mg protein.
[2]Data are presented as the mean ± 1 SEM from 2 experiments.
[3]Represents a signficant difference from the control (0) value.

Table 11. EFFECT OF HYDROCORTISONE ON MACROPHAGE 5'NUCLEOTIDASE ACTIVITY

TREATMENT	SPECIFIC ACTIVITY[1] (Hours in culture) (2)	(24)	(48)	(72)
0	34.4	43.2 ± 14.9	13.3 ± 5.0	39.5
10^{-3}	54.2 ± 6.1	3.3 ± 1.6	18.0 ± 6.0	25.2 ± 2.5
10^{-6}	50.6 ± 9.9	4.2 ± 1.7	1.5 ± 0.8	25.1 ± 9.0
10^{-9}	49.4 ± 7.1	26.0± 6.5	ND	ND

[1]Data are expressed as the specific activity/mg of protein. Results are listed as the mean ± 1 SEM from 2 experiments.

b. Establish the effects of glucocorticoids on MO intrinsic antiviral activity.

The effect of dexamethasone and methylprednisolone on the ability of MO to restrict growth and replication of HSV-1 was determined. As previously described, MO were isolated by adherence and cultured for 24 hours in HL-1 medium

containing various amounts of one of the glucocorticoids. The MO were washed in PBS, and HSV-1 was allowed to adsorb for 1 hour in the absence of the glucorticoids. Subsequently, the unadsorbed virus was removed, and fresh medium containing the glucocorticoids was added. The MO were cultured for an additional 2, 24, 48, or 72 hours. At these time points, the MO were lysed by scraping, and the recoverable infectious virus was titered.

MO which had been cultured with dexamethasone or methylprednisolone (at all concentrations) exhibited the typical resistance pattern to HSV-1 (Tables 12, 13). The infectious virus decreased over the culture period, with little to no virus detectable by plaque assay at 48 or 72 hours. In contrast, viral titer increased in HSV-1 permissive VERO cells increased over the culture period.

Table 12. EFFECTS OF DEXAMETHASONE ON MACROPHAGE INTRINSIC RESISTANCE TO HSV-I

CELL TYPE [dexamethasone]	PFU/10^6 CELLS (Hours post infection) (2)	(24)	(48)	(72)
MACROPHAGES				
0	1.60×10^4	0.09×10^4	0	0
10^{-3} M	2.42×10^4	0.12×10^4	0	0
10^{-5} M	0.97×10^4	0.19×10^4	0	0
10^{-6} M	1.77×10^4	0.04×10^4	0	0
10^{-7} M	2.16×10^4	0.04×10^4	0	0
10^{-8} M	1.95×10^4	0.09×10^4	0	0
10^{-9} M	0.97×10^4	0.10×10^4	0	0
VERO				
0	1.54×10^4	6.05×10^7	8.3×10^7	3.75×10^7

Table 13. EFFECT OF METHYLPREDNISOLONE ON MACROPHAGE RESISTANCE TO HSV-I

CELL TYPE [methylprednisolone]	PFU / 10^6 CELLS (Hours post infection) (2)	(24)	(48)	(72)
MACROPHAGES				
0	3.60×10^4	0.48×10^4	0	0
10^{-3}M	0.54×10^4	0.14×10^4	0	0
10^{-5}M	1.86×10^4	0.37×10^4	0	0
10^{-6}M	1.66×10^4	0.11×10^4	0	0
10^{-7}M	3.11×10^4	0.37×10^4	0.005×10^4	0
10^{-8}M	5.82×10^4	0.39×10^4	0	0
10^{-9}M	1.62×10^4	0.55×10^4	0	0
VERO				
0	1.47×10^4	5.92×10^7	4.34×10^7	3.95×10^7

WORK PLAN (YEAR 2): The objectives of year 2 are to : 1) Expand the studies on the effects of glucocorticoids on general MO characteristics, 2) expand the studies on the effects of glucocorticoids on MO antiviral activity, 3) measure the effects of catecholamines on MO characteristics and antiviral activity, and 4) determine whether the glucocorticoids or catecholamines have any affect on MO resistant to the bacterium Listeria monocytogenes.

We are currently finishing the studies on the effects of glucocorticoids on MO characteristics. In addition to completing some of the dose effects of hydrocortisone and methylprednisolone on MO cultures, we will also determine the effects of corticosterone on the selected MO parameters. These studies should be completed by August.

We are also completing the studies on the effects of co-culturing MO with glucocorticoids on MO intrinsic resistance to HSV-1. We have some preliminary data on the effects of hydrocortisone on MO antiviral activity, and we will examine the effects of corticosterone on the same system. Because MO are reportedly slow in upregulating receptors for glucocorticoids, we will also determine the effect of longer exposure of MO to the glucocorticoids prior to infection with HSV-1. These studies should be completed by December.

We will begin studies on the effects of catecholamines in experiments

similar to the ones described in the progress section . These studies will begin in September. We will also begin studies on the effects of glucocorticoids and catecholamines on in vitro resistance to L. monocytogenes. These studies also will begin in September.

TRAINING ACTIVITIES: One graduate student assisted on the studies reported in the progress section. She and another graduate student will begin work on the experiments outlined in the work plan section in July. Both are women and are U.S. citizens.

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