

Effect of adrenergic compounds, aminophylline and hydrocortisone, on in vitro immunoglobulin synthesis by normal human peripheral lymphocytes

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Suspensions of normal human peripheral lymphocytes were exposed briefly to various concentrations of propranolol, isoproterenol, epinephrine, or aminophylline (both without and with added hydrocortisone) and then incubated for 72 hours at 37° C. After this incubation the amount of immunoglobulin (Ig) synthesized and secreted into the cultured supernatants was quantitated by radioimmunoassay. Significantly increased Ig formation compared to controls was observed with the following concentrations of the experimental compounds (without hydrocortisone): 10^{-9} to 10^{-7} M propranolol, 10^{-10} to 10^{-7} M isoproterenol, 10^{-8} M epinephrine, and 10^{-7} to 10^{-5} M aminophylline. When cell suspensions were exposed briefly to these same compounds but with hydrocortisone added, the following concentrations of compounds significantly increased Ig synthesis: 10^{-10} to 10^{-8} M propranolol, 10^{-10} to 10^{-8} M isoproterenol, 10^{-9} to 10^{-7} M epinephrine, and 10^{-5} to 10^{-3} M aminophylline. Of the four compounds studied, only the epinephrine data suggest that hydrocortisone enhanced the stimulation of Ig synthesis by this catecholamine.

There is recent evidence that a number of hormones and related compounds can influence the immune response in several species. Catecholamines and compounds related to adrenergic function¹⁻³ and corticosteroids⁴⁻⁸ have been shown to influence the immune response, both in vivo and in vitro. Several authors have postulated that the pituitary hormones, particularly growth hormone, play a role in thymic function.⁹⁻¹² In addition there is evidence that cyclic AMP (cAMP) and compounds that increase cAMP levels, by either enhancing its formation or inhibiting its breakdown, can stimulate both in vivo and in vitro antibody formation.¹³

Previously we studied the effect of hydrocortisone on in vitro immunoglobulin (Ig) metabolism of normal human peripheral lymphocytes and found that lymphocyte cultures briefly exposed to physiological concentrations of hydrocortisone formed significantly increase quantities of Ig during the 72 hour incubation.¹⁴ These experiments were made possible by the use of: (1) a pulse culture technique, slightly modified from that of Hadden and co-workers,¹⁵ which allows for a brief, controlled exposure of cells to experimental compounds, and (2) a sensitive, reproducible radioimmunoassay, a modification of the am-

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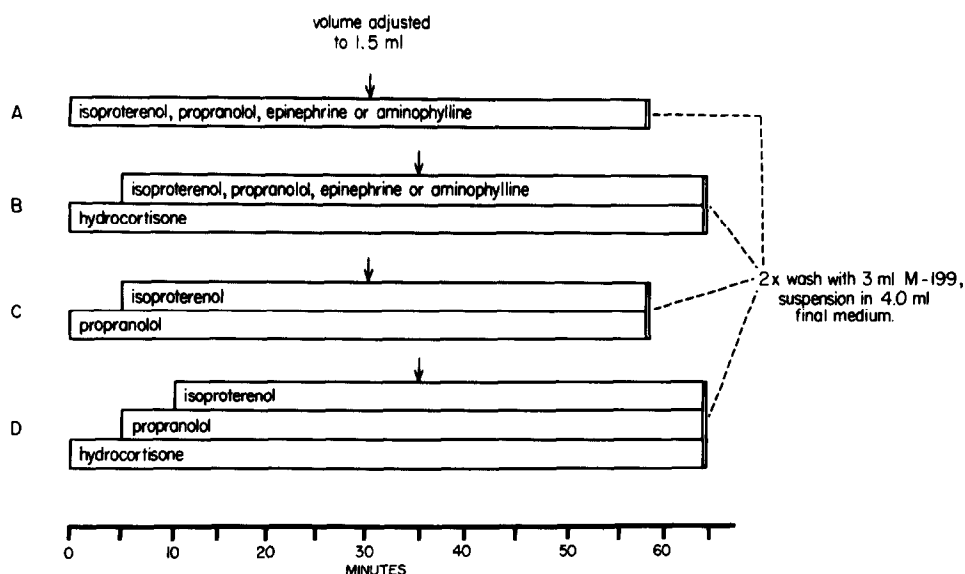


FIG. 1. Protocols for the pulse exposure of lymphocytes to the experimental compounds. At zero time all tubes contain 3.0×10^6 lymphocytes in 1.0 ml. medium. The experimental compound dilutions are added as 0.1 ml.

monium sulfate test of Farr,¹⁶ which quantitates Ig in nanogram (ng.) amounts.¹⁶ The earlier results with hydrocortisone and those reported here indicate that a controlled extracellular environment can influence in vitro Ig metabolism of normal human peripheral lymphocytes. These methods of studying in vitro metabolism provide a means for assessing the effects of a variety of compounds on Ig forming cells from normal sources as well as disease states.

MATERIALS AND METHODS

Blood donors and leukocyte preparation

Peripheral blood from normal healthy adults (male and female), taken between 8:00 and 10:00 A.M., was drawn into plastic syringes containing heparin (10 U. per milliliter of blood) and 3 per cent gelatin (Plasmagel, 1 ml. Plasmagel/4 ml. blood) and allowed to settle at room temperature. After red blood cell sedimentation, the leukocyte-rich supernatant was collected. The cells were washed twice with Tris-A buffer, pH 7.6,¹⁷ and resuspended in Tris-buffered Dulbecco's modified Eagle's medium (12.5 ml. 2.0M Tris, pH 7.4/500 ml. medium) with 20 per cent fetal calf serum (FCS). The leukocytes were counted and diluted to 3.0×10^6 lymphocytes per milliliter. One-milliliter aliquots of this suspension were pipetted into plastic culture tubes (Falcon, 16 $\times$ 125 mm.).

Experimental compounds

The experimental compounds used in these experiments were isoproterenol HCl (Mann Research Labs., New York, New York), propranolol HCl (Ayerst Labs., New York, New York), L-epinephrine bitartrate (Sigma Chemical Co., St. Louis, Missouri), aminophylline (Mann Research Labs.), and hydrocortisone (Steraloids, Pawling, New York). The initial concentrations and solvents for the above compounds were as follows: (1) isoproterenol, propranolol, and epinephrine, 1.5×10^{-3} M in normal saline; (2) aminophylline, 1.5×10^{-2} M in Tris-buffered medium 199 (M-199); and (3) hydrocortisone, either 1.5×10^{-2} M in ethanol

TABLE I. Effect of isoproterenol without and with 10^{-6} M hydrocortisone on Ig synthesis and secretion by 2 normal donors*

Donor (initials)	Control†			Isoproterenol Treatment‡		
	Preculture	72 hour control	10^{-6} M hy- drocortisone	Isoproterenol molarity	Without hydrocortisone	With 10^{-6} M hydrocortisone
N. S.	9.8	12.5	13.5	10 ⁻¹⁰ (N. S.)	15.2	17.3
L. L.	6.4	20.1	20.0	(L. L.)	21.4	25.7
				10 ⁻⁹ (N. S.)	19.5	24.3
				(L. L.)	24.6	26.7
				10 ⁻⁸ (N. S.)	20.6	25.3
				(L. L.)	25.7	33.1
				10 ⁻⁷ (N. S.)	16.0	20.5
				(L. L.)	27.8	22.5
				10 ⁻⁶ (N. S.)	14.4	16.0
				(L. L.)	24.3	24.6

*Values given as ngN IgG/10⁶ lymphocytes.

†Each control value is the mean of triplicate cultures.

‡Each treatment value is the mean of duplicate cultures.

or 1.5×10^{-4} M in M-199. These solutions were prepared just prior to use, sterilized by membrane filtration (Nalgene, 0.45 micron membrane), and serially diluted 1:10 in M-199.

Pulse culture technique

The conditions for the pulse culture technique have been described¹⁵ and have been modified by exposure of cells to experimental compounds at room temperature and by the use of Tris-buffered Dulbecco's medium containing penicillin (75 U. per milliliter), streptomycin (75 μ g per milliliter), and 20 per cent FCS as the final medium. One-tenth milliliter of the solutions of experimental compounds were added to the 1.0 ml. cell suspensions as shown in Fig. 1. Protocols A and B were followed in experiments studying the effects of isoproterenol, propranolol, epinephrine, or aminophylline (both without and with hydrocortisone). Protocols C and D were followed in experiments studying propranolol combined with isoproterenol (without and with hydrocortisone). In the isoproterenol and propranolol experiments, 1.5×10^{-6} M hydrocortisone in M-199 with 0.1 per cent ethanol (final culture tube concentration, 1.0×10^{-6} M in 0.0067 per cent ethanol) was used; with epinephrine and aminophylline, 1.5×10^{-6} M hydrocortisone in M-199 (final concentration, 1.0×10^{-7} M) was used. Thirty minutes before terminating the incubations with experimental compounds, all tube volumes were adjusted to 1.5 ml. with Tris-buffered Dulbecco's medium, with 20 per cent FCS. After the cells were washed and suspended in final medium, the cultures were incubated for 72 hours in a 37° C. humidified air incubator. After the 72 hours incubation the culture supernatants were assayed for Ig by the radioimmunoassay described below. Cell viabilities were determined on selected cultures after the 72 hour incubation using the eosin-y exclusion technique.

Quantitation of Ig synthesized in vitro

The ¹²⁵I Fab-anti-F(ab)₂ method of human Ig quantitation and its specificity have been described in detail elsewhere.^{16, 18} The unbound reference antigen, ¹²⁵I Fab, prepared from pooled human IgG, is soluble in 50 per cent saturated ammonium sulfate (SAS), while antigen-antibody complexes of ¹²⁵I-Fab-anti-F(ab)₂ are insoluble. The system was standardized so that 0.5 ml. of a dilution of rabbit antihuman F(ab)₂ precipitated 50 per cent of 20 ngN ¹²⁵I Fab when the solution was 50 per cent saturated with respect to SAS. One-half milliliter of standardized rabbit anti-F(ab)₂ was added to 0.5 ml. dilutions of culture supernatants or pooled human IgG (the standard IgG blocking curve, 50.0 to 0.8 ngN). After incubation for 24 hours at 4° C., 0.5 ml. of 20 ngN ¹²⁵I Fab was added and incubated at 4° C. for another 24 hours. At this time, 1.5 ml. of SAS was added, mixed thoroughly, centrifuged, and the

TABLE II. Effect of propranolol, without and with 10^{-6} M hydrocortisone (10^{-6} MH), on Ig synthesis and secretion by lymphocytes from 9 normal donors*

Propranolol final molarity	Without hydrocortisone % of 72 hr. control (mean % $\pm$ S.D.)	With hydrocortisone % of 10^{-6} MH control (mean % $\pm$ S.D.)
10^{-10} M	104.2 $\pm$ 16.7	115.8 $\pm$ 14.7†
10^{-9} M	123.1 $\pm$ 16.3†	124.7 $\pm$ 22.9†
10^{-8} M	122.7 $\pm$ 20.4‡	133.1 $\pm$ 19.8†
10^{-7} M	120.4 $\pm$ 17.0†	114.2 $\pm$ 22.8
10^{-6} M	104.3 $\pm$ 10.7	94.1 $\pm$ 15.0

*See "Materials and Methods" for descriptions of table headings and calculation of data.

†Significantly greater ($p < 0.01$) than control (100.0%).‡Significantly greater ($p < 0.05$) than control.**TABLE III.** Effect of isoproterenol, without and with hydrocortisone (10^{-6} MH), on Ig synthesis and secretion by human peripheral lymphocytes from 10 normal donors

Isoproterenol final molarity	Without hydrocortisone % of 72 hr. control (mean % $\pm$ S.D.)	With hydrocortisone % of 10^{-6} MH control (mean % $\pm$ S.D.)
10^{-10} M	116.3 $\pm$ 14.7*	125.2 $\pm$ 12.7†
10^{-9} M	127.8 $\pm$ 17.1†	133.0 $\pm$ 25.6†
10^{-8} M	137.6 $\pm$ 19.9†	138.4 $\pm$ 30.1†
10^{-7} M	118.5 $\pm$ 10.3†	118.2 $\pm$ 21.5*
10^{-6} M	108.4 $\pm$ 12.0	112.8 $\pm$ 13.2*

*Significantly greater ($p < 0.05$) than control (100.0%).†Significantly greater ($p < 0.01$) than control.

precipitates washed once with 1.5 ml. 50 per cent SAS. The washed precipitates were counted in a well-type gamma scintillation counter (Nuclear, Chicago, Illinois). The amount of unknown Ig in the culture supernatants was determined from the blocking curve and the results expressed as ngN IgG blocking equivalent/ 10^6 lymphocytes. The error of this technique was determined and is less than 10 per cent.¹⁹

Experimental controls

The experimental control tubes, triplicates for each control, included:

1. *Precultures*: Cells not exposed to any experimental compound and frozen after suspension in final medium. These were thawed after 72 hours, and these suspensions of lysed cells were analyzed for Ig.

2. *72 hour controls*: Cells not exposed to any experimental compound and incubated for 72 hours.

3. *Hydrocortisone controls*: Cells exposed 65 minutes to either 1.0×10^{-6} M in 0.0067 per cent thanol (isoproterenol and propranolol experiments) or 1.0×10^{-7} M in medium (epinephrine and aminophylline experiments) and incubated 72 hours.

4. *Ethanol controls, 0.0067 per cent*: Included when hydrocortisone was dissolved in ethanol.

After 72 hours of incubation, the incubated control tubes and experimental tubes (duplicates for each treatment) were centrifuged. Their supernatants and the thawed precultures were analyzed for Ig. The amount of Ig quantitated in each control and experimental tube was expressed as ngN IgG blocking equivalent/ 10^6 lymphocytes.

Analysis of data

In each experiment the mean of the duplicate Ig values for each treatment (compound concentration) was calculated. This mean treatment Ig value was expressed as a percentage of

TABLE IV. Effect of isoproterenol, without and with 10^{-7} M hydrocortisone (10^{-7} MH), on Ig synthesis and secretion by lymphocytes from 9 normal donors

Isoproterenol final molarity	Without hydrocortisone % of 72 hr. control (mean % $\pm$ S.D.)	With hydrocortisone % of 10^{-7} MH control (mean % $\pm$ S.D.)
10^{-10} M	105.9 $\pm$ 14.3	112.9 $\pm$ 12.7†
10^{-9} M	111.4 $\pm$ 24.0	116.4 $\pm$ 19.9†
10^{-8} M	127.3 $\pm$ 20.6*	130.1 $\pm$ 21.8*
10^{-7} M	115.1 $\pm$ 11.5*	116.9 $\pm$ 18.2†
10^{-6} M	112.5 $\pm$ 18.6	115.9 $\pm$ 11.7†

*Significantly greater ($p < 0.01$) than control (100.0%).†Significantly greater ($p < 0.05$) than control.‡Significantly greater ($p < 0.02$) than control.

the appropriate mean control Ig value of that experiment. By definition the mean control equals 100.0 per cent. The raw mean Ig values given in Table I can serve to demonstrate this calculation of the treatment per cent of control. Donor N. S. had a mean 72 hour control value of 12.5 ngN IgG. This donor's mean values for the five isoproterenol concentrations (without hydrocortisone) were expressed as percentages of this value: 10^{-10} isoproterenol, $(15.2 \div 12.5) \times 100 = 121.6$ per cent; 10^{-9} M isoproterenol, $(19.5 \div 12.5) \times 100 = 156.0$ per cent, etc. In the same manner the isoproterenol with 10^{-6} M hydrocortisone data were expressed as percentages*of the mean 10^{-6} M hydrocortisone control. Expressing each individual's mean treatment values as percentages of that individual's appropriate mean control values takes into account the variations among donors as to the levels of Ig attained at 72 hours in the control and treatment cultures. The t test on paired observations was used for statistical evaluation of the percentage data.

RESULTS

Raw data

The mean raw data (ngN IgG/ 10^6 lymphocytes) in Table I demonstrate several points: (1) the differences among donors as to their zero time Ig levels (precultures), (2) the differences in the amounts of Ig synthesized in 72 hours, and (3) the magnitude of responses to compound concentrations. Although space does not allow for presentation of additional raw data, these values from 2 donors are indicative of the values from the other donors. (These raw data are part of the data summarized in Table III.)

Effect of propranolol and hydrocortisone with propranolol

Data in Table II show the effect of propranolol, both without and with 10^{-6} M hydrocortisone (10^{-6} MH), on lymphocyte Ig synthesis. With propranolol alone, there was significantly increased Ig synthesis at 10^{-9} to 10^{-7} M propranolol; with 10^{-6} MH present, the trend and magnitude of stimulation did not appear to be different, with the possible exception of 10^{-6} M propranolol, with 10^{-6} MH, which may have slightly depressed Ig synthesis.

Effect of isoproterenol and hydrocortisone with isoproterenol

Table III summarizes experiments studying the Ig response of lymphocytes to isoproterenol, without and with hydrocortisone. With isoproterenol alone there was significantly increased synthesis with 10^{-10} to 10^{-7} M isoproterenol.

TABLE V. Effect of spinephrine, without and with 10^{-7} M hydrocortisone (10^{-7} MH), on Ig synthesis and secretion by lymphocytes from 7 normal donors

Epinephrine final molarity	Without hydrocortisone % of 72 hr. control (mean % $\pm$ S.D.)	With hydrocortisone % of 10^{-7} MH control (mean % $\pm$ S.D.)
10^{-10} M	102.9 $\pm$ 18.3	110.9 $\pm$ 14.8
10^{-9} M	114.6 $\pm$ 24.6	136.3 $\pm$ 32.3†
10^{-8} M	132.7 $\pm$ 7.9*	136.6 $\pm$ 25.4‡
10^{-7} M	112.7 $\pm$ 16.1	123.1 $\pm$ 16.2‡
10^{-6} M	108.0 $\pm$ 14.3	115.5 $\pm$ 16.6

*Significantly greater ($p < 0.01$) than control (100.0%).†Significantly greater ($p < 0.05$) than control.‡Significantly greater ($p < 0.02$) than control.

With 10^{-6} MH, while all five concentrations of isoproterenol gave significant stimulation, the values are similar to those of isoproterenol alone.

Adrenergic specificity of isoproterenol and propranolol

A concept of alpha and beta adrenergic receptors has been described for adrenergic function,²¹ with isoproterenol designated as a beta receptor agonist (stimulator) and propranolol, a beta receptor antagonist (blocker). In an attempt to determine if there was adrenergic specificity in regard to the Ig stimulation observed with propranolol and isoproterenol, we studied combinations of propranolol and isoproterenol, without and with 10^{-6} MH. These data are not shown. In the combinations studied, the propranolol molarity was ten times that of isoproterenol. Only one combination, 10^{-8} M propranolol plus 10^{-9} M isoproterenol (without hydrocortisone), showed what could be interpreted as adrenergic specificity, for each concentration alone significantly stimulated Ig synthesis ($p < 0.05$), but their combination was not stimulatory. The other combinations of propranolol and isoproterenol gave results similar to either compound alone.

Effect of 10^{-7} M hydrocortisone with isoproterenol

In the experiments studying the effects of 10^{-6} M hydrocortisone with propranolol, isoproterenol (Tables I, II, and III), and the combination of propranolol with isoproterenol, hydrocortisone was initially dissolved in ethanol. Concurrent experiments studying the effect of hydrocortisone dissolved in medium on lymphocyte Ig synthesis revealed that 10^{-7} M hydrocortisone was one of several concentrations that gave significantly increased Ig formation.¹⁴ Although hydrocortisone is freely soluble in ethanol and relatively insoluble in aqueous solutions, the elimination of ethanol as the initial solvent circumvented the variable responses to ethanol alone.¹⁴

We elected to use 10^{-7} M hydrocortisone (10^{-7} MH) in future experiments studying a possible synergism between hydrocortisone and compounds related to adrenergic function. We repeated experiments studying isoproterenol without and with hydrocortisone, but used 10^{-7} MH. These data are given in Table IV. A comparison of these data and those of Table III (isoproterenol with 10^{-6} MH) demonstrates that isoproterenol with 10^{-7} MH gave stimulation of the same trend and magnitude as the data in Table III.

TABLE VI. Effect of aminophylline, without and with 10^{-7} M hydrocortisone (10^{-7} MH), on Ig synthesis and secretion by lymphocytes from 9 normal donors

Aminophylline final molarity	Without hydrocortisone % of 72 hr. control (mean % $\pm$ S.D.)	With hydrocortisone % of 10^{-7} MH control (mean % $\pm$ S.D.)
10^{-9} M	99.4 $\pm$ 21.5	94.5 $\pm$ 7.4
10^{-8} M	120.3 $\pm$ 33.4	119.1 $\pm$ 21.1†
10^{-7} M	137.3 $\pm$ 23.9*	125.3 $\pm$ 27.9‡
10^{-6} M	133.4 $\pm$ 28.4†	130.1 $\pm$ 28.3†
10^{-5} M	141.4 $\pm$ 30.9*	125.7 $\pm$ 25.0*
10^{-4} M	121.6 $\pm$ 26.9	116.8 $\pm$ 21.1
10^{-3} M	108.6 $\pm$ 15.2	93.2 $\pm$ 19.7

*Significantly greater ($p < 0.01$) than control (100.0%).†Significantly greater ($p < 0.02$) than control.‡Significantly greater ($p < 0.05$) than control.

Effect of epinephrine and hydrocortisone with epinephrine

Five concentrations (10^{-10} to 10^{-6} M) of the naturally occurring catecholamine epinephrine were studied for their effect on Ig synthesis. These data in Table V demonstrate that with epinephrine alone only one concentration, 10^{-8} M, significantly stimulated Ig synthesis. However, with 10^{-7} MH, there was significant stimulation of Ig synthesis with 10^{-9} to 10^{-7} M epinephrine.

Effect of aminophylline and hydrocortisone with aminophylline

Aminophylline, (theophylline)₂-ethylenediamine, is known to favor the intracellular accumulation of cyclic AMP by inhibition of phosphodiesterase. We studied several concentrations (10^{-9} to 10^{-3} M) of this compound alone and with 10^{-7} MH. The results, shown in Table VI, demonstrate that 10^{-7} to 10^{-5} M aminophylline significantly enhanced Ig formation. The addition of 10^{-7} MH did not appear to alter this stimulation except at 10^{-3} aminophylline with 10^{-7} MH, which may have slightly depressed Ig synthesis.

Viability studies

Viability studies, performed on cultures after 72 hours incubation using the eosin-y exclusion technique, revealed a great deal of variation in lymphocyte viabilities between donors and a tendency toward loss of viability in those cultures exposed to the higher concentrations of the experimental compounds. However, there did not appear to be any correlation between viabilities and the degree of response of the cultures to the experimental compounds.

DISCUSSION

The data presented here demonstrate that a brief exposure of normal human peripheral lymphocytes to experimentally controlled extracellular environments can influence in vitro Ig synthesis and secretion by these cells during 72 hours of incubation. In contrast to other techniques in which experimental compounds are in contact with cells for a prolonged time, the pulse culture technique¹⁵ provides for brief, controlled exposure of cells to the experimental compounds. This minimizes the possibilities of in vitro cytotoxicity and of unknown effects

by metabolites from the compounds studied. Previous studies, using a modification of the ammonium sulfate test, have shown that secretion of Ig into the medium occurred over the 72 hour incubation.^{14, 22} In addition, analysis of the 72 hour cell pellets has shown the presence of little Ig or quantities below the sensitivity of the radioimmunoassay employed (< 1.0 ngN/0.5 ml. cell lysate suspension). These results suggest that the Ig quantitated is the result of active protein biosynthesis. Substantiating this are results from a radioimmuno-electrophoretic and autoradiographic study of peripheral leukocyte cultures incubated with ^{14}C -l-leucine. These results¹⁴ showed incorporation of the radiolabel into specific IgG and indicate the presence of active *de novo* protein biosynthesis of this immunoglobulin in our culture system. In the present experiments, emphasis has been placed on the Ig content of the supernatants after 72 hours of culture. Although the Ig content of the preculture lysates was determined, in the absence of information about whether or not there may be some catabolism of this Ig during the 72 hours of culture, it was thought inadvisable to subtract these preculture values from the incubated control and treatment values.

The compounds we studied have been shown to stimulate protein synthesis, as well as to influence other aspects of metabolism in other tissues and species. Ambrose⁷ and Halliday and Garvey⁸ showed that small amounts of hydrocortisone supported and enhanced *in vitro* antibody synthesis by rabbit lymphocytes. Fuller and Snoddy²³ have shown increased liver enzyme synthesis in intact rats given epinephrine or theophylline. They also observed that while only theophylline increased liver enzyme synthesis in adrenalectomized rats, hydrocortisone or hydrocortisone plus epinephrine increased synthesis in such rats.²³ In salivary glands of man and animals, isoproterenol has produced a variety of metabolic effects including increased salivary concentrations of amylase and total proteins²⁴ and stimulation of DNA^{25, 26} and RNA²⁶ synthesis. Isoproterenol and theophylline have been shown to inhibit *in vitro* target cell cytotoxicity by sensitized mouse lymphocytes, and this impaired cytotoxic reaction was correlated with the increase in lymphocyte cAMP.²⁷ Propranolol, a beta adrenergic blocker that we found to have an agonistic effect on Ig formation, has been observed to act as a mild immunologic adjuvant in the production of antidinitrophenyl egg albumin antibodies,²⁸ as well as having agonistic effects in other systems.²⁹

Although studies of other aspects of *in vitro* lymphocyte metabolism have shown that propranolol can block isoproterenol effects,^{15, 27, 30} we could not demonstrate a clear-cut antagonism by propranolol on isoproterenol stimulation of Ig synthesis. This may have been because of both compounds having similar agonistic effects in our system or may reflect the possibility that the alpha and beta receptor scheme of pharmacologic action of catecholamines on adrenergic receptors²¹ may not be as well-defined in Ig-producing cells as it is in other systems.

With our culture system we found that low concentrations of propranolol, isoproterenol, epinephrine, and aminophylline, both without and with hydrocortisone, significantly increased lymphocyte Ig formation compared to control values. Of all our data studying a possible synergism between hydrocortisone and each of these compounds, only the epinephrine data appear to support the

postulated "permissive" effect of corticosteroids on catecholamine action.³¹ Another interesting feature of the epinephrine data, compared to that of the other three compounds, is that only one concentration of epinephrine (without hydrocortisone) significantly increased Ig synthesis. These results with epinephrine may represent a more definitive effect by a naturally occurring catecholamine.

The preceding data indicate that the extracellular environment can influence the complicated and ill-defined steps in Ig protein biosynthesis.³² Isoproterenol, epinephrine, and aminophylline (theophylline), which we observed to increase Ig formation, are known to increase the intracellular accumulation of cAMP in human leukocytes,^{33, 34} human lymphocytes,³⁰ and other tissues.³⁵ This suggests that the adenyl cyclase-cAMP system may be involved in regulation of Ig metabolism, and preliminary experiments in our laboratory indicate that cAMP itself can also stimulate Ig synthesis and secretion in normal human peripheral lymphocytes.

These data on the effects of catecholamines and compounds related to adrenergic function on Ig synthesis and secretion may have important implications in the study of human disease. Indeed, data presented in an accompanying paper³⁶ demonstrate that peripheral blood lymphocytes from patients with bronchial asthma respond differently to hydrocortisone and isoproterenol.

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