EFFECT OF GLUCOCORTICOSTEROIDS ON EPIDERMAL LANGERHANS CELLS*

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Epidermal Langerhans cells (LC) play a key role in the presentation of antigen to lymphocytes during the induction of delayed contact hypersensitivity (1-5). Normal functioning of the epidermal LC therefore may be a prerequisite for the induction and elicitation of contact allergic reactions. Recently, UVB light (10 mJ/cm² once daily for 4 consecutive d) has been reported to diminish the density of murine epidermal LC as determined by staining for membrane ATPase (6, 7) and to prevent the induction of contact sensitization to dinitrofluorobenzene (6). Furthermore, when such irradiation is administered in higher doses (720 mJ/cm² thrice weekly for 4 consecutive wk) even spleen cells from such UVB irradiated mice are unable to present antigens effectively (8). It was therefore of great interest to ascertain whether other physicochemical agents also have an effect on the number or functions of epidermal LC.

Glucocorticosteroids are the agents most commonly used for the treatment of skin diseases. We therefore investigated the effect of these agents on the LC. Burrows and Stoughton (9) reported inhibition of the induction of contact sensitivity to dinitrochlorobenzene (DNCB) in human skin by the simultaneous application of topical glucocorticoids; however, the possible role of epidermal LC in mediating this effect was not examined.

The present study was undertaken to determine the effect of repeated topical and systemic administration of glucocorticoids on the density of epidermal LC of guinea pigs, as assessed by staining for cell membrane ATPase activity and Ia antigens, and by electron microscopy (EM). It will be shown that glucocorticoids of high anti-inflammatory activity such as betamethasone dipropionate and betamethasone valerate cause a marked decrease in LC demonstrable by these methods in guinea pig skin.

Materials and Methods

Animals. Inbred strain 13 guinea pigs were used throughout the experiments involving the topical applications of glucocorticoids. Outbred Hartley strain guinea pigs (Camm Research
Lab Animals, Wayne, N. J.) were used in the studies on the effects of systemically administered glucocorticoids.

**Topical and Systemic Glucocorticoid Administration.** Guinea pigs were locally treated with 0.1% and 0.5% concentrations of betamethasone dipropionate (BD), betamethasone valerate (BV), cortisol (CL), and cortisone (CN). The drugs were prepared by dissolving the pure steroid compounds (Schering Corp., Kennilworth, N. J.) in absolute ethanol. Four 3 cm² areas separated by 2 cm were mapped out on the dorsal surface of each guinea pig and marked with suture material. Twice daily, for either 14 or 21 d, one of these areas was treated with 0.05 ml of either one of the above steroid solutions, ethanol, or saline; the fourth area was left untreated. During the treatment period, two 6 mm punch biopsies were performed from each treatment and control area on days 0, 2, 4, 7, 10, and 14, and where applicable, on days 17 and 21. Biopsies were likewise obtained on days 2, 4, and 7 after treatment had been discontinued. Periodically, during and after treatment, biopsies were taken for EM. At the beginning of each experiment and at the time of each biopsy, the guinea pigs were shaved with an electric clipper. The remaining hair was then removed with Neet (Whitehall Laboratories Inc., New York).

Systemic glucocorticoid treatment was accomplished by intraperitoneal injections once daily for 5 consecutive d of 100 mg/kg, 10 mg/kg, or 1 mg/kg of either triamcinolone acetonide suspension (TAC) (E. R. Squibb & Sons, Inc., Princeton, N. J.) or methylprednisolone sodium succinate (MP) (The Upjohn Co., Kalamazoo, Mich.) in saline. Control animals received the same volume of normal saline (NS) instead of the drug. Biopsies were performed on the dorsal skin of all animals before the first injection and on days 0, 1, 2, 4, 9, 14, and 18 on the TAC-treated animals. MP-treated animals were biopsied on days 0, 1, 2, 3, 4, 7, 9, and 11. Peripheral blood for blood counts was also obtained from the latter group by retro-orbital sinus puncture.

**Light Microscopic Enumeration of LC.** Each biopsy was immersed in 1 M NaBr for 3-4 h at room temperature. The epidermal sheets were then easily separated from the underlying dermis. The epidermis was then fixed in 5% neutral formalin at 20°C for 20 min and stained for ATPase activity or for the presence of Ia antigen as described below. The stained specimens were then allowed to air-dry (dermal side up) on cover slips and then mounted with Permount (Fisher Scientific Co., Pittsburgh, Pa.). The density of LC within each epidermal sheet was determined using a light microscope with a calibrated eyepiece (Zeiss Kpl W125 × 20, Carl Zeiss Inc., New York). The number of LC per mm² in one central and four peripheral areas of each epidermal sheet was determined; epidermal areas about the hair follicles were excluded. The reported LC density for each sheet represents the arithmetic average of the five counts ± standard error per mm² of skin surface.

**ATPase and Ia Staining.** Stains for ATPase activity were performed as described by Wolff and Winkelmann (10). Staining for Ia-bearing epidermal cells was performed using an anti-Ia antiserum. This antiserum was prepared by immunizing inbred strain 13 animals with spleen cells from inbred strain 13 animals according to the method of Shevach, et al. (11). Fixed epidermal samples were washed in 0.05 M Tris buffer in normal saline (pH 7.6) and incubated for 60 min at 37°C with anti-Ia antiserum. The tissue was then washed three times in the Tris buffer and incubated for 60 minutes at 37°C with 0.1 mg of protein A conjugated to horseradish peroxidase (Zymed Laboratories, Burlingame, Calif.) per ml of Tris buffer. The epidermal sheets were then washed three times with Tris buffer and stained with 0.1 ml of a solution containing 0.075 g of 3,3'-diaminobenzidine tetrachloride plus 0.1 ml of 3% H₂O₂/100 ml Tris buffer. The stained sheets were washed three more times with Tris buffer and allowed to air dry on cover slips.

**Electron Microscopy.** Biopsies taken for EM were fixed according to the method of Karnovsky (12) and post-fixed in OsO₄. They were then embedded in Epon and cut in 700 Å sections, stained with a uranyl acetate-lead citrate mixture, and studied under a Zeiss electron microscope 10 (Carl Zeiss Inc.).

**White Blood Count.** Counts were done using a standard hemocytometer dilution technique. Differential counts were performed on blood smears stained with Wright’s stain.

**Statistics.** All probabilities were determined using a two- or three-way analysis of variance.

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**Results**

**Topically Applied Glucocorticosteroids**

**ATPase and Ia Stain.** Both the 0.1 and 0.5% concentrations of BD and BV
produced a significant ($P < 0.01$) decrease in LC density as determined by the number of ATPase positive cells, as well as by staining for Ia antigen (Figs. 1–3). The observed decrement appeared to be an "all or nothing" phenomenon: there was no evidence that cells possessed intermediate densities of surface markers. This decrease became evident as early as 2 d after initiation of treatment with 0.5% BD. It was more readily demonstrated at this time with staining for ATPase rather than for Ia. By day 7, in both 0.1% and 0.5% BD-treated areas, the decrease in ATPase and Ia positive cells had become statistically significant ($P < 0.01$). The decrease in LC caused by BV

![Graphs showing the effect of topical BD on epidermal LC.](image)

Fig. 1. Effect of topical BD on epidermal LC. Guinea pigs were treated twice daily for 21 d with either 0.5% (top) or 0.1% (bottom) solutions of BD in absolute ethanol. Duplicate biopsies were obtained from dorsal skin on day 0 before treatment and on days 2, 4, 7, 10, 14, 17, and 21, as well as 7 d after discontinuation of treatments. Epidermal sheets were obtained and stained for ATPase activity ($\bullet$, left) and Ia antigen ($\bigcirc$, right). Control values ($\bullet$) represent the arithmetic mean of the untreated controls, NS-treated controls, and ethanol-treated controls ± standard error (SE).
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Fig. 2. Effect of topical BV on epidermal LC. Guinea pigs were treated with either 0.5% (top) or 0.1% (bottom) solutions of BV in absolute ethanol. Biopsies were performed as described in Fig. 1. Epidermal sheets were obtained and stained for ATPase activity (○, left) and Ia antigen (○, right). Control values (○) represent the arithmetic mean of the untreated controls, NS-treated controls, and ethanol treated controls ± SE.

developed somewhat slower and became significant only after day 7 (0.5%) or day 10 (0.1%). In each case, a near maximal decrease of 37–62% in the density of LC was noted with both staining procedures to occur by day 14 (Figs. 1 and 2; Table I). Treatment twice daily with either drug for an additional wk produced only a minimal further decline in LC density. It was noted, however, that in the animals treated for 21 d with 0.5% BD or BV, there was a significant decrease (P < 0.01) in LC in the control sites, suggesting that by this time sufficient systemic absorption of the drugs had occurred to affect untreated sites in these animals. Increased absorption of
glucocorticoids via the biopsy-damaged skin areas could have added to this effect. Upon discontinuation of local treatment, the LC density in both treated and control sites returned to pretreatment levels within 7 d as measured by both criteria (Figs. 1, 2 and 4). Double blind studies (Table II, guinea pigs 1 and 2) reaffirmed these findings for animals treated with a 0.1% BD solution.

Application of 0.5% CL and 0.5% CN produced a slight decline (30 and 22%, respectively) in LC density (Tables I and III) as determined by ATPase stain; however, these decrements were barely significant ($P < 0.05$). No diminution of cells by Ia staining was noted with either drug (Tables I and III). In double blind studies using 0.5% CL, the previously found decrement in LC density was not observed (Table II, guinea pigs 3 and 4). Topical application of CL, 0.1%, and CN, 0.1%, solutions had no effect (data not shown).

EM STUDIES. Ultrastructural examination of the skin from animals treated topically with BD in either 0.5 or 0.1% concentrations showed alterations in the LC starting on day 4 that became maximal by day 7. These changes affected ~50% of the clearly recognizable LC in any given biopsy. Alterations noted included clumping of nuclear chromatin, dilatation of endoplasmic reticulum, swelling and condensation of mitochondria with flocculent densities, and myelin figures (Fig. 5). No alterations
TABLE I
Effect of Topical Glucocorticoids on Epidermal LC Membrane Markers

| Applied drug | Drug concentration | Percent decrease in LC density on day 14 of treatment |
|--------------|--------------------|----------------------------------------------------|
|              |                    | By ATPase staining  | By staining for la antigen |
| BD           | 0.5%               | 62*                               | 48*                        |
|              | 0.1%               | 52*                               | 44*                        |
| BV           | 0.5%               | 53*                               | 40*                        |
|              | 0.1%               | 40*                               | 37*                        |
| CL           | 0.5%               | 30†                               | 0                           |
|              | 0.1%               | 0                                 | 0                           |
| CN           | 0.5%               | 22‡                               | 0                           |
|              | 0.1%               | 0                                 | 0                           |

* P vs. control < 0.01.
† P vs. control < 0.05.
‡ P vs. control < 0.05.

Fig. 4. Effect of topical BD on la-bearing epidermal LC. Guinea pigs were treated twice daily for 7 d with either 0.5% (□) or 0.1% (□) BD. Punch biopsies were obtained before beginning treatment on day 0 and on day 7 of treatment as well as days 4 and 7 after treatments were discontinued. Epidermal sheets were obtained and stained for la antigen. Controls (○) represent the arithmetic mean of untreated and ethanol treated animals ± SE.

were noted in the keratinocytes. By day 7 after cessation of topical steroids these changes could no longer be seen. The findings were similar to those seen in other forms of cell injury, such as those caused by ischemia (13).

Systemically Administered Steroids. Guinea pigs were given five daily intraperitoneal injections of TAC at 10 mg/kg and 100 mg/kg (Fig. 6). 5 d after discontinuation of treatment, there was a 49% (100 mg/kg, P < 0.01) and a 28% (10 mg/kg, P < 0.05) decrease in LC density. The cell density returned to baseline values within 9 d after its nadir. When TAC was injected at 1 mg/kg, it did not produce any effect on the number of LC per mm² (Fig. 6).

MP, 100 mg/kg, administered intraperitoneally, produced a significant decline in the LC density by the last day of treatment (P < 0.01, Fig. 7). Within 7 d after treatment was discontinued, the LC density had returned to control values. Neither MP at 10 mg/kg (Fig. 7), 1 mg/kg, nor NS (data not shown) had any noticeable effect on LC density. None of the MP dosage used had any significant effect on
### Table II

**Decrease and Recovery of ATPase Positive LC in Epidermis of Guinea Pigs during and after Topical Treatment with 0.1% BD and 0.5% CL**

| Day of Treatment | ATPase positive epidermal LC/mm² ± SE | ATPase | Ia antigen |
|------------------|-------------------------------|--------|------------|
|                  | Guinea pig 1 | Guinea pig 2 | Guinea pig 3 | Guinea pig 4 |
| Day              | Ethanol 0.1% BD | Ethanol 0.1% BD | Ethanol 0.5% CL | Ethanol 0.5% CL |
| 0                | 1205 ± 35 ND§ | 1514 ± 59 ND | 1152 ± 21 ND | 1410 ± 45 ND |
| 7                | 1232 ± 41 586 ± 34 | 1346 ± 157 729 ± 36 | 1114 ± 39 971 ± 38 | 1310 ± 111 1438 ± 49 |
| 10               | 1124 ± 60 500 ± 31 | 1348 ± 47 590 ± 20 | 1019 ± 21 924 ± 48 | 1038 ± 55 1338 ± 45 |
| 14*              | 1124 ± 80 500 ± 27 | 1286 ± 79 352 ± 25 | 990 ± 42 1071 ± 85 | 1143 ± 110 1257 ± 90 |
| 18               | 1000 ± 46 667 ± 20 | 1143 ± 54 643 ± 27 | 1090 ± 44 1106 ± 94 | 1229 ± 44 1190 ± 43 |
| 21               | 1086 ± 74 1143 ± 23 | 1052 ± 23 955 ± 31 | 967 ± 34 1019 ± 46 | 1271 ± 80 1510 ± 104 |

* Double blind studies.  
§ Guinea pigs were treated topically twice daily for 14 d with the indicated drug dissolved in absolute ethanol. Control sites were painted with equal amounts of absolute ethanol or were left untreated. Untreated controls did not differ from the ethanol treated controls.  
¶ Not done.

### Table III

**Effect of Topically Administered CL and CN on Epidermal LC**

| Day of Treatment | Number of LC/mm² ± SE as assessed by staining for ATPase | Number of LC/mm² ± SE as assessed by staining for Ia antigen |
|------------------|---------------------------------|----------------------------|
|                  | Control* 0.5% CL§ 0.5% CN‡ | Control* 0.5% CL§ 0.5% CN‡ |
| 0                | 1290 ± 33 ND§ | 1404 ± 44 ND | 1604 ± 44 ND |
| 4                | 1230 ± 37 1467 ± 100 1438 ± 39 | 1434 ± 27 1376 ± 37 1366 ± 42 |
| 10               | 1124 ± 29 881 ± 51 976 ± 20 | 1472 ± 29 1195 ± 20 1414 ± 53 |
| 14               | 1152 ± 28 962 ± 50 1124 ± 64 | 1469 ± 43 1461 ± 65 1585 ± 53 |
| 21               | 1046 ± 25 886 ± 30 1024 ± 31 | 1403 ± 27 1395 ± 46 1528 ± 50 |

* Average of all counts for that day on the untreated controls as well as the NS and ethanol treated controls.  
§ Guinea pigs were treated topically twice daily for 21 d with the indicated drug dissolved in absolute ethanol. Control sites were painted with equal amounts of NS or absolute ethanol, or were left untreated.  
¶ Not done.

leukocyte (WBC) counts (Fig. 7) or lymphocyte counts, which ranged from 55–70% of the total WBC count.

### Discussion

Both topical and systemic administration of potent glucocorticosteroids resulted in a decreased density of LC as assessed by staining for ATPase and Ia antigen. Furthermore, the decreases obtained in LC density correlated with the concentration and known vasoconstrictive potency of the drugs used. Topically, BD proved to be more rapid-acting and to result in a greater decrease in LC density than the other drugs; BV, CL, and CN followed in decreasing order. Systemically, at doses of 100 mg/kg, TAC and MP each caused an ~40% decrease in LC density. The delayed action of TAC as compared with MP was to be expected in view of the relatively low water solubility of this drug.

The exact mechanism for the observed decrease in LC density is not clear, but at least three different possibilities should be considered. First, there may have been
irreversible damage and an actual decrease in number through cellular death. A second possibility is that the cells were affected functionally as a result of alterations in membrane surface antigen and enzyme expression. Although no direct enumeration of LC was attempted by EM, the type of damage seen ultrastructurally did not
Fig. 6. Effect of systemic TAC on epidermal LC. Animals were injected intraperitoneally once daily for 5 consecutive d with either 1 mg/kg (left), 10 mg/kg (center), or 100 mg/kg (right) of the drug. Biopsies were taken from the dorsal skin of each animal before the first injection on day 0 and on days 2, 4, 9, 14, and 18. Epidermal sheets were obtained and stained for ATPase activity.

Fig. 7. Effect of systemic MP on epidermal LC and peripheral WBC counts. Guinea pigs were injected intraperitoneally once daily for 5 consecutive d with either 10 mg/kg (left) or 100 mg/kg (right) of the drug. Biopsies were taken from the dorsal skin before the first injection on day 0 and on days 2, 4, 7, 9, and 11. Epidermal sheets were obtained and stained for ATPase activity (○). Blood for WBC counts (▲) was obtained on days 0, 2, 4, and 7.

exclude reversibility of the damage (13). Changes in function without clear cytolytic effect have been described in guinea pig macrophages in the presence of glucocorticosteroids: both macrophage inhibition factor (14) and macrophage aggregation factor (15) are inhibited from acting on the macrophages. Furthermore, human monocytes have been found to express reduced rosette formation with erythrocytes coated with C3 or IgG, although phagocytosis of latex particles was unimpaired (16). In view of the similarities previously summarized between LC and macrophages (17), a functional rather than killing effect of glucocorticosteroids on LC is a distinct possibility. The recently reported studies of Lynch et al. (18) on the effects of topical glucocorticoids on the induction of contact sensitivity in mice suggest that the effect on LC is accompanied by functional impairment. Finally, it is possible that such a functional effect could also be the result of an enhanced migration of LC from the
epidermis, similar to what has been observed during contact sensitivity reactions (19, 20). The observation that the epidermis was repopulated with LC 7 d after the peak effect of local and systemic treatments does not help to clarify this issue; therefore, further studies are being conducted.

It was somewhat puzzling that the rapid decrease in LC seen over the first 10 d of topically applied glucocorticoids was followed by a relative plateau on LC density during which no further major decrease was observed over the ensuing 10 d of treatment. Several possibilities, although not mutually exclusive, should be considered. A continuous influx of LC from the bone marrow (21) could establish an equilibrium with the damage inflicted by the steroids. It is also possible that two distinct LC populations exist in relation to steroid sensitivity. One of these cell populations might include the indeterminate dendritic cells that are thought to represent immature LC containing few or no characteristic Birbeck granules (22, 23). It has been shown that mouse macrophages express low and high affinity receptors for glucocorticoids, although there is no evidence that such receptors are expressed differently on different cell populations (24). Finally, the possibility that the observed equilibrium is a result of the kinetics of drug accumulation in the skin cannot be excluded at this time.

As in man, lymphoid cells in guinea pigs are known to be relatively resistant to systemic steroid administration, although a decrease in circulating mononuclear cells can be obtained (25–27). In our experiments, the glucocorticosteroid doses that produced a marked decrease in LC did not affect the peripheral WBC count, suggesting that in this system the LC is more sensitive to glucocorticosteroids than is the lymphocyte.

Early reports on the effect of glucocorticoids on the immune response have suggested that their major effect is on the presentation of antigen rather than on antibody production (28). LC have been shown to serve as antigen-presenting cells in the induction of antigen-specific proliferation (1–5). The effect of glucocorticosteroids on LC shown in this report is therefore in agreement with the conclusions of previous investigators. The observations that such disparate therapeutic modalities of treatment as ultraviolet light and glucocorticoids can prevent the induction of contact sensitivity, together with the fact that both agents have a negative effect on LC activity, strengthen the hypothesis that the LC is essential for the induction of contact sensitivity to environmental agents. Furthermore, these data suggest that the anti-inflammatory action of glucocorticosteroids in dermatologic disorders may, at least in part, be through the drug's ability to alter epidermal LC.

Summary

The effects of topical and systemic administration of various glucocorticoids on the density of epidermal Langerhans cells (LC) were studied in guinea pigs. Glucocorticoids, such as betamethasone dipropionate and valerate, caused a marked decrease in LC demonstrable by staining for cell membrane ATPase activity and Ia antigens. By electronmicroscopy, LC also showed morphologic alterations. The observed decrements in LC density correlated with the concentration and known vasoconstrictive potency of the glucocorticoids administered. The anti-inflammatory action of glucocorticoids in skin disorders may, at least in part, be through their ability to alter epidermal LC, thus interfering with the antigen-presenting functions of these cells.
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