Molecular and clinical pharmacology of psoriasis

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Psoriasis appears in most cases to be a genetic disease[8] in which stratified squamous epithelium (epidermis) of skin in involved versus normal-appearing uninvolved areas has the following prototypic features: (1) excessive cell proliferation and an accelerated cell cycle of the proliferating cells[21]; (2) incomplete epidermal specialization (keratinization) for tissue function; and (3) marked increase in glycogen content.[7] It has been widely held that the relative lack of epidermal specialization is due to the rapid transit of cells through the epidermis (i.e., the cells are shed from the patient without sufficient time for normal keratinization to occur). However, an alternate explanation is that the excessive cell proliferation is the result of an inability of differentiated basal cells to make the commitment of specialization. For this reason we have listed incomplete specialization as one of the three characteristic findings in psoriasis lesions.

We developed the concept that increased proliferation, decreased specialization, and increased glycogen content in psoriasis lesions might be associated with diminished levels of epidermal cyclic adenosine monophosphate (cAMP).[10] This concept was derived from earlier observations that epinephrine inhibits epidermal mitosis in vitro and in vivo[3] and also promotes glycogenolysis in most tissues.[11] Epinephrine elevates the levels of cAMP in the tissue, which then initiates glycogenolysis.[12] Using the four criteria of Sutherland, a series of experiments[4, 15-17] were conducted showing that epinephrine inhibited the $G_2 \rightarrow M$ phase of the epidermal cell cycle via a rise in the cellular levels of cAMP.

The concept that deficient cAMP was possibly central to the prototypic features of the psoriasis lesion was further supported by observations of Pastan and his coworkers[9] on malignant cells in culture. Lowered steady-state levels of cAMP could be found in rapidly dividing cells exhibiting "malignant" growth characteristics. When such cells are grown in the presence of exogenous cAMP, differentiation appears to be promoted since their morphology quite closely resembles that of benign cells and there is also a slowing of their growth rate. It seemed to us that these findings in malignant cells in culture might have relevance to psoriasis (i.e., both are characterized by rapid growth and lack of cell specialization).

Thus arose the hypothesis that cAMP was responsible for the coordinate regulation of normal epidermal morphogenesis (proliferation-specialization) and glycogen content. The corollary of this hypothesis was that in the presence of low steady-state epidermal levels of cAMP one might expect to find the coordinate misregulation of

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epidermal morphogenesis and glycogen metabolism (i.e., the three prototypic features of the psoriasis lesion).

To test this postulate we compared cAMP levels in involved versus uninvolved epidermis from 50 patients using two different assays and three data bases—deoxyribonucleic acid (DNA), protein, and wet weight.[14, 18] Depending on the assay and denominator selected, the decrease in cAMP levels in involved areas was between 55% and 17%. All decreases were statistically significant except the 17% that was based on wet weight. In our hands DNA is the most reliable denominator,[18] and in our view the Gilman assay[5] for cAMP is superior to the method of Brooker, Thomas, and Appleman[2] since smaller quantities of tissue are required. Using this data base and the Gilman assay, a 36% ($p < 0.005$) decrease in cAMP levels was found in involved versus uninvolved areas.[18] However, due to inherent problems in the biologic material, any decrease might best be viewed as strongly suggestive rather than as conclusive.[18]

Since the cAMP level is probably decreased in the involved areas, the cause of this decrease has been investigated. Contrary to the findings of Wright and associates,[22] we have not been able to detect a defect in the biosynthesis of cAMP[17] if saturating concentrations of substrate and hormone are utilized. Preliminary results also indicate that excessive release of cAMP from the involved areas into the culture medium in vitro[19] does not occur. Lastly, preliminary results have been obtained indicating that the catalytic activity of cAMP phosphodiesterase may be increased in involved areas.[20] Although additional experiments are required to establish this increase with certainty, such an abnormality if present could explain the decreased cAMP levels.

Recently, another cyclic nucleotide, cyclic guanosine monophosphate (cGMP), has been implicated in the control of proliferation. For example, cyclic GMP had been found to be strikingly elevated in lymphocytes that have been stimulated to proliferate with mitogens.[6] In collaboration with Dr. Nelson Goldberg at the University of Minnesota, we measured cGMP levels in psoriasis areas with increased proliferation versus uninvolved areas with normal proliferation. Cellular levels of cGMP were significantly ($p < 0.02$) increased by all three data bases.[18] Since cGMP can stimulate the hydrolysis of cAMP in vitro,[1] the elevated levels of cGMP observed in psoriasis tissue could also account for the decreased levels of cAMP in the lesion.

If decreased cAMP is central to the morphogenetic abnormality of the psoriasis lesion, it should be possible to reverse or prevent the lesion by raising the epidermal cAMP levels. Because cAMP and its derivatives are relatively impermeable to cell membranes, we chose to elevate cAMP by the use of a known phosphodiesterase inhibitor papaverine. Papaverine has been demonstrated to raise intraepidermal cAMP 160% in our laboratory in epidermal slices.[13] In a double-blind study with a 1% papaverine cream in which 45 patients participated, a statistically significant ($p < 0.05$) improvement was found.[13] However, the clinical potency of this particular formulation of papaverine is approximately that of 0.5% to 1% hydrocortisone cream and is therefore inferior to certain of the fluorinated glucocorticoid creams. Nonetheless, the fact that a cAMP elevating agent improved psoriasis suggests that this type of therapy holds promise. The reasons for this view have been discussed elsewhere.[20] Additional clinical trials of other cAMP elevating agents are in progress with others scheduled for the near future.

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