Polyamines in Psoriasis

Psoriasis is a very common, complex, inherited systemic metabolic disease having multiple etiologic factors interacting to produce characteristic cutaneous lesions. Although the most common recognizable lesions occur on the skin, other body tissues including those of the cardiovascular system, the gastrointestinal system (including liver and the skeletal system are very often involved. Probably because of the variability and multiplicity of etiologic factors, there is no other common skin disease that taxes one’s therapeutic abilities as does the disease, psoriasis. The enormous number of therapeutic agents and regimens that have been developed and devised are testimony to the lack of sustained efficacy and/or unwanted toxicity experienced with many.

In recent years, considerable research has produced a large body of information offering clues to the etiology and pathogenesis of psoriasis. If we examine closely the morphologic picture presented by a typical psoriasis plaque, we find that it occurs as the end result of hyperproliferation and inflammation. Epidermal disease is characterized by increased cellular proliferation. In the typical cutaneous plaque of psoriasis, the number of proliferating cells within the epidermis is increased up to 12-fold greater than in normal skin. Even in the uninvolved skin of patients with psoriasis, the number of proliferating cells within the epidermis is increased up to two and one-half times greater than in the skin of nonpsoratics. The mitotic index of the epidermis in involved skin is increased up to 1000 times greater than in normal skin. In the dermis of the psoriasis plaque, inflammation and vascular injury predominate. Of importance in the pathogenesis of epidermal and dermal disease are abnormalities of cyclic nucleotide, polyamine and of the by-products of arachidonic acid metabolism principally prostaglandins and leukotrienes [1-5]. It appears that in the presence of increased quantities of polyamines, prostaglandins, and leukotrienes, epidermal cell nuclear acid synthesis (DNA) and epidermal cell proliferation are increased. In the dermis, increased quantities of these substances are associated with increased vascular permeability, dispersion of polymorphonuclear leukocytes (both epidermal and dermal), and dermal accumulation of fluid.

In this issue of the Journal, McCullough et al report some very interesting and potentially significant findings on polyamine levels in injury-stimulated epidermis and on inhibitors of polyamine synthesis. Their findings, which may eventually be applicable in the treatment of psoriasis, extend and corroborate the observations of other investigators [6,7]. Before considering the significance of McCullough's findings, it is most appropriate to summarize the present state of our knowledge of polyamines and their role as growth promoters, particularly in psoriasis.

Polyamines, spermidine and spermine, are rather ubiquitous and are found in significant amounts in virtually all mammalian cells, as well as in bacteria, parasitic protozoa and the like. They are also probably required for intracellular viral replication. The chemical structure of the polyamines, putrescine, diamine, as well as the precursor diamine, putrescine, are shown in Fig 1. The principle pathway of polyamine synthesis in mammalian cells is demonstrated in Fig 2. Although the exact physiologic function of the polyamines remains elusive and is not well understood at the molecular level, it is generally acknowledged that normal cellular growth and differentiation require polyamines [8]. In this discussion, our attention will be focused on the significance of these substances on cellular growth rather than differentiation.

Tissue and cellular quantities of polyamines and their precursor, putrescine, have been found substantially elevated in liver regenerating after partial hepanectomy; in skin and leukemic cells after the application of tumor promoters, such as the phorbol esters; in skin following UVB irradiation; and in skin stimulated by hair plucking [8-10]. Russell et al have found polyamine levels to be higher in involved skin of patients with psoriasis than in uninvolved skin [11]. Polyamine levels were also found to be higher in the uninvolved skin of psoriasis patients than in the normal skin of individuals without psoriasis. These data correlate well with information previously cited on the nature of cell proliferation in psoriasis in involved and noninvolved skin. Urinary polyamine levels are also higher in patients with psoriasis than in normal individuals.

Increased cellular levels of polyamines have been previously associated with increased levels of DNA synthesis and increased cellular replication [12]. Topical spermine and putrescine hydrochloride increased DNA synthesis in hairless mouse epidermis [13]. In psoriasis, increased polyamine synthesis and DNA synthesis precede the state of hyperproliferation and disturbed keratinization. Increased levels of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis, have been demonstrated in states of hyperproliferation as in psoriasis.

Polyamine synthesis and cell replication, most research in psoriasis therapeutics has centered around the development of specific inhibitors of nucleic acid synthesis [14]. Probably because of their relative availability as cancer chemotherapeutic agents, most antipsorias drugs have tended to come from groups of nonselective cytotoxics, and have required systemic administration. Among the most efficacious agents are methotrexate, hydroxyurea, triacetyl-6-azauridine, mycophenolic acid, 2-mercaptopurine, and 5-fluorouracil. Unfortunately, with the exception of mycophenolic acid, these agents are nonselective in their effects; they are cytotoxic to all tissues in which rapid cellular replication is taking place, and have severe and, at times, life-threatening adverse effects in organ systems other than the skin.

Numerous attempts at formulating topically applicable and effective forms of the presently available nucleic acid inhibitors have been most unsuccessful. With few exceptions, topical formulations have shown little or no effect on psoriasis plaques when applied directly to the skin. Lack of effect in these circumstances probably relates to a number of ill-defined factors such as poor percutaneous penetration (inability of the formulation to penetrate the epidermal barrier layer); drug instability when applied to the skin; absence of specific drug-activating enzymes in the epidermis; inappropriate vehicle and many more. Some agents such as topical nitrogen mustard and 5-fluorouracil, although active in topical form, have proved too toxic and irritating when applied over prolonged periods directly to the skin. In a series of earlier experiments designed to identify a group of agents which may prove of some use when applied to active psoriasis plaques, Weinstein, McCullough, and others observed that MGBG, an inhibitor of polyamine biosynthesis, was moderately effective in controlling the cutaneous lesions of psoriasis [14]. Grosshans and others demonstrated a marked inhibition in dinitrogen mustard treatment of psoriatic skin with difluoromethylornithine, an irreversible inhibitor of ornithine decarboxylase [5]. In their most recent report, McCullough and Weinstein, as have other investigators, have shown that topicaly applied MGBG can, in fact, reduce polyamine synthesis and ultimately epidermal DNA synthesis (Fig 3) and epidermal cell
replication. Topically applied glucocorticoids and anthralin, PUVA, and retinoids have also been found to reduce epidermal polyamine synthesis and cell replication. Although these findings do not ultimately answer the questions relative to the specific role of polyamines in the regulation of growth in psoriatic tissue, they do take us a step further along in the development of a group of topical agents which may prove to be effective and revolutionary in the control of cutaneous psoriasis. Some newer polyamine antagonists such as DFMO, α-methylornithine, α-ethylornithine, α-hydrazono-δ-aminvaleric acid, and 5-hexynyl-4-diamine may singly or in combination, exert an even more profound effect on polyamine synthesis and cell replication in psoriasis. There is no question that the safest method of treating a skin disease is via the application of effective and nontoxic topical substances to the skin. In psoriasis therapy, effective topical agents would relieve the therapist of the need to use toxic systemic agents, reserving their use only for those individuals found to have significant systemic disease.

REFERENCES


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