

Ornithine Decarboxylase in Skin

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Ornithine decarboxylase (ODC) was discovered in animal tissues in 1968 [1,2] and interest in its activity and regulation has led to a rapidly and still expanding literature on the enzyme. Several comprehensive reviews have already appeared [3-6]. This article emphasizes our current knowledge of ODC in mammalian skin. The involvement of ODC in tumor promotion will be discussed only briefly, since several recent monographs review this subject [7]. The extensive literature on ODC in tissue culture systems will be omitted for the sake of brevity.

Ornithine decarboxylase is the first enzyme in the biosynthetic pathway for the polyamines, putrescine, spermidine and spermine (Fig. 1). Putrescine is the immediate product of ODC; and spermidine and spermine are synthesized from putrescine by the addition of aminopropyl groups generated by the enzyme S-adenosyl-L-methionine decarboxylase. The polyamines spermidine and spermine are polycationic molecules which interact strongly with nucleic acids. Polyamines stabilize the structure of both DNA and RNA and also participate in many enzymatic reactions involving nucleic acids, such as transfer RNA aminoacylation, protein synthesis and RNA transcription [4,5]. Intracellular levels of polyamines and their biosynthetic enzymes are generally found to correlate with growth, though a cause and effect relationship has not been proven. Since ODC is the rate-limiting enzyme for polyamine synthesis, its control has been of primary interest and importance in most studies.

BIOCHEMISTRY

L-ornithine is synthesized in skin from arginine by the enzyme arginase. Determinations in the rat, guinea pig and man show that it represents 0.25 to 6.42 mole % of the free amino acids in skin [8]. ODC is a cytosol enzyme that enzymatically removes CO₂ at the 1 position of L-ornithine to yield putrescine. Putrescine and CO₂ are formed with a 1:1 stoichiometry [1,9]. ODC activity is generally assayed by measuring the release of ¹⁴CO₂ from [1-¹⁴C]-ornithine. The enzyme does not require metal ions and has an optimum pH of 7.0-7.3 depending on the buffer. The K_m for L-ornithine varies from 0.026-0.19 mM, depending on the source and purity of the enzyme [1,10,11]. ODC activity is inhibited by its product, putrescine, and by a variety of product and substrate analogues including spermidine

The research on ODC in this laboratory was supported in part by NIH grants AM-17253 and AM-17977 while JL was a trainee supported by NIH grant 5T32-AM07093 and LG was a recipient of RCD AM-00008.

This is publication number 81 of the Dermatology Research Laboratory at Duke University Medical Center.

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Abbreviations:

MIX: 1-methyl-3-isobutylxanthine

ODC: ornithine decarboxylase

TPA: 12-0-tetradecanoyl phorbol-13-acetate

and spermine. Low concentrations of putrescine (2 μM) result in competitive inhibition [1], but at higher concentrations (10 mM) inhibition becomes noncompetitive [11].

Pyridoxal phosphate is required for enzymatic activity, with an apparent K_m of 0.1 mM [11]. Inhibitors of pyridoxal-requiring enzymes (e.g. isonicotinic acid hydrazide and 4-bromo-3-hydroxybenzoxamine) inhibit mammalian ODC activity [1]. Binding of the L-ornithine substrate to the active site takes place through Schiff base formation with enzyme-bound pyridoxal phosphate. The irreversible inhibition of ODC activity seen with certain substrate analogues requires Schiff base complexing of the inhibitor with pyridoxal phosphate in the enzyme's active site [12]. The noncompetitive inhibition of ODC activity seen at high concentrations of putrescine or its analogues appears to result from competition for pyridoxyl phosphate by the enzyme and the polyamine.

Dithiothreitol, at a concentration of 5 mM, is also required for optimal ODC enzymatic activity. Monothiol reducing agents, including reduced glutathione, a major reducing agent in skin, are considerably less effective. In the absence of added thiols, ODC appears to undergo polymerization to larger, often inactive forms [10]. When isolated and chromatographed in the presence of 0.1 mM pyridoxal phosphate and 5.0 mM dithiothreitol, ODC from rat skin elutes from a calibrated Biogel-P100 column with an estimated molecular weight of 52,000 (J. Lesiewicz and L. A. Goldsmith, unpublished observations).

ODC IN NORMAL SKIN

The activity of ornithine decarboxylase is generally high in rapidly proliferating cells. Fetal tissues and organs possess high ODC activity, which then decreases postnatally [4]. No data is yet available on ODC levels in fetal periderm, epidermis or whole skin. ODC activity is generally reported as specific activity per mg protein and has not been correlated with cell numbers or the number of cells in particular cell layers. Studies in rat dorsal whole skin indicate that basal ODC activity decreases progressively as the animals grow from pre-weanling to young adult [9]. Pre-weanling mice are found to exhibit a transient increase in skin ODC in response to subcutaneous injection of epidermal growth factor [13].

Basal ODC activity (per mg soluble protein) is higher in the dermis than in the epidermis [9]; presumably most of the dermal ODC is follicular in origin. In hair follicles, ODC activity correlates positively with the cyclic growth of hair, with minimal activity found during the resting phase [14]. Both follicular and interfollicular epidermal ODC activities are stimulated by plucking of telogen hairs. ODC activity decreases initially, then rises to peak levels 4 hr after hair plucking. A high level of activity is maintained for at least 12 hr after plucking [9,14,15].

As reported for other mammalian organs, ODC from skin has an unusually short biological half-life. In unstimulated whole dorsal rat skin extracts, ODC exhibits a half-life of 29.5 min. Stimulation of skin ODC activity by hair plucking results in an approximate doubling of the enzyme's half-life to 54.0 min [15].

The response of rat skin ornithine decarboxylase to nutri-

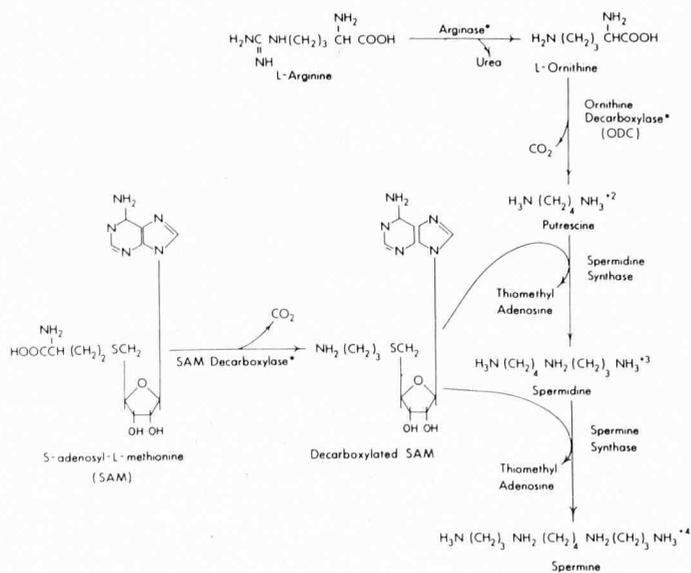


FIG 1. Biosynthetic pathway for the polyamines. Enzymes indicated by an asterisk (*) have been reported in mammalian skin.

tional alterations has been studied. When rats are fed diets containing from 2 to 24% protein for 4 or 8 days, the level of ODC activity in both unstimulated and plucked skin is found to increase with increasing dietary protein. Rehabilitation with 16% protein diet after 7 days of a 2% protein diet indicates that ODC enzyme activity increases over 5 days to levels near or slightly higher than control 16% protein diet levels [9]. Further experiments have determined that both unstimulated and plucked skin ODC activity levels are maintained for up to 24 hr of starvation, followed by significant decreases below fed controls. Under these conditions the half-life of unstimulated ODC is reduced to 13.2 min. Following 24 hr of starvation, refeeding of complete diet for 12 or 24 hr restores ODC enzyme activity to fed control levels (J. Chain, J. Lesiewicz and L. A. Goldsmith, unpublished observations). Refeeding of protein deficient diets for up to 24 hr does not restore unstimulated or stimulated ODC activity to control levels, and stimulated ODC activity appears to correlate with dietary protein levels (J. Lesiewicz, D. Morrison and L. A. Goldsmith, unpublished observations).

Skin ODC activity is stimulated by wounding. In rat whole skin wounded by punch biopsy, ODC activity levels rise rapidly to a maximum 12 hr later. Enzyme activity returns to basal levels by 48 hr [16]. Similar results are seen in mouse epidermis wounded by either multiple cuts or abrasion. Maximal ODC activity is detected 20–26 hr after wounding and a secondary rise occurs at 72 hr [17]. Administration of the synthetic glucocorticoid, betamethasone, delays the rise in ODC activity in wounded skin [16]. The delay of wound healing produced by topical treatment of skin with the drug Furacin, may result from inhibition of ODC induction [18].

ODC IN HYPERPLASIA AND DISEASE

Irradiation of hairless mice with ultraviolet light of wavelengths 290 to 320 nm (UVB) produces thickening of the epidermis within 48 hr. ODC activity in UVB-irradiated epidermis begins to increase within 2 hr after irradiation and reaches a peak 250 to 350-fold greater than unirradiated controls after 28 hr. Enzyme activity declines to near control levels after 48 hr. The increase in ODC activity resulting from UVB exposure is dose dependent and is inhibited by both cycloheximide and 5-azacytidine, indicating a requirement for *de novo* protein and RNA synthesis [19]. The anti-inflammatory glucocorticoids triamcinolone acetonide, and fluocinolone acetonide and the prostaglandin cyclooxygenase inhibitor, indomethacin, are effective inhibitors of UVB induction of ODC activity in mouse

epidermis. Inhibitions of 50% or greater are seen at doses between 0.05% and 2.5%, as compared to irradiated, vehicle-treated controls [20]. Irradiation of skin with longwave ultraviolet light (UVA) is known to potentiate UVB-induced erythema in humans and rabbits. Photoaugmentation of epidermal ODC activity by UVA irradiation either before or after UVB treatment does not appear to occur [21].

A major clinical characteristic of psoriasis is increased epidermal proliferation in both involved and uninvolved skin as compared to normal. Polyamine levels in psoriatic epidermis have been reported to be decreased as compared to normal skin based on nmoles of spermidine or spermine per gram tissue [22]. More recent determinations have shown putrescine, spermidine and spermine levels to be increased in involved vs. uninvolved and uninvolved vs. normal skin [23]. This data is expressed as nmoles per μg DNA, which should more accurately reflect cell numbers in the tissue samples. The ODC activity of involved psoriatic skin is significantly higher than that found in uninvolved or normal skin. Uninvolved skin has a somewhat higher ODC activity than normal skin. Treatment of psoriatic lesions with the glucocorticoid, diflorasone diacetate, reduced the activity of ODC by 81% [23].

The effects of UVA and psoralen have been studied in a model system. In the hairless mouse, UVA alone or topical treatment with 8-methoxypsoralen (8-MOP) plus UVA at 0.9 J/cm², does not increase epidermal ODC activity. However, 8-MOP plus UVA at 3.6 J/cm² results in a 4-fold increase in ODC activity 16 to 72 hr posttreatment. Similar treatment using anthracene plus UVA at 3.1 J/cm² also induces ODC, but maximal enzyme activity is seen at 4 hr and declines to control levels by 48 hr [24].

In skin tumors ODC and S-adenosylmethionine decarboxylase activities are increased; squamous cell carcinomas have higher levels than basal cell carcinomas [25]. High levels of ODC activity are also induced in mouse epidermis by application of tumor promoters, such as croton oil or its active component 12-O-tetradecanoyl phorbol-13-acetate (TPA). A single topical application of TPA results in a several hundred fold increase in ODC activity 4 to 5 hr later. The degree of stimulation of ODC is generally found to correlate closely with the promotional ability of various phorbol esters when compared on an equimolar basis [26]. This correlation has led to the proposal that the induction of ornithine decarboxylase may be an obligatory event in skin carcinogenesis [27]. Experiments with TPA and vitamin A analogs have also determined that the order of retinoid potency for the inhibition of skin tumor promotion, or for suppression of ODC induction is identical [28,29].

More recent evidence has indicated that the relationship of ODC induction to tumor promotion is not as clear-cut as is suggested above. Mezerein, an antileukemic agent with structural similarities to TPA, induces epidermal ODC activity to the same extent and with the same time course as TPA. However, mezerein is a very weak tumor promoter with 2% or less the potency of TPA [30]. When weak or nonpromoting phorbol esters are applied to mouse epidermis in doses which stimulate ³H-thymidine labeling of DNA equally with TPA, comparable inductions of ODC enzyme activity are also seen [31]. This suggests that the induction of ODC may more accurately reflect the degree of epidermal hyperplasia rather than tumor promotion per se. TPA has also been observed to stimulate ODC activity in rat epidermis, a tissue for which it is not known to be a tumor promoter [15].

Similarities between TPA-treated epidermis and psoriatic epidermis led to investigation of the effects of the anti-psoriatic drug anthralin in this system. Anthralin alone is a weak tumor promoter and stimulator of ODC activity [26]. Treatment of mouse skin with anthralin prior to TPA however, results in substantial inhibition of both tumor formation and ODC induction [32,33]. Information on the effects of the clinically used

crude coal tar would be of great interest but are not currently available.

REGULATION OF ODC

A number of mechanisms for the regulation of ODC have been proposed. Most of the research in this area has been done in organs other than skin, and will only be briefly discussed.

In vivo administration of polyamines at the time of partial hepatectomy, blocks the induction of ODC during liver regeneration in the rat [3-5]. These data suggest regulation of ODC activity at the level of gene transcription. Administration of diamine inhibitors subsequent to the induction of ODC in regenerating liver also results in substantial inhibition of ODC activity. This inhibition of ODC is associated with a decrease in the amount of immuno-reactive enzyme protein, and the authors propose a direct inhibition of enzyme synthesis [34]. Other evidence indicates that prolonged treatment of liver with the putrescine analog, 1,3-diaminopropane, leads to the formation of a nondialyzable, macromolecular inhibitor (antizyme) of ODC in liver [34,35].

Possible involvement of cyclic nucleotides in the regulation of ODC has also been investigated. Alterations in the levels of cyclic AMP (cAMP), cAMP-dependent protein kinase and ODC have been found to occur in a close temporal sequence in regenerating rat liver [36]. Direct evidence of phosphorylation or dephosphorylation of ODC enzyme has not been reported. Administration of dibutyryl cAMP or the potent phosphodiesterase inhibitor, 1-methyl-3-isobutylxanthine (MIX) does result in an increase in hepatic ODC. This increase can be abolished, however, by prior hypophysectomy. No increase in ODC activity is detected in livers perfused with dibutyryl cAMP or MIX [37]. These data indicate that the apparent induction of ODC by cAMP is mediated through pituitary and/or adrenal hormones in the intact animal.

The isolation of multiple, active and inactive forms of ODC from various tissues has raised the possibility of their participation in the regulation of enzyme activity. However, this research has all been conducted with ODC enzyme prepared in buffers containing no, inappropriate, or suboptimal concentrations of thiols. The appearance of multiple forms of the enzyme may then be an artifact of such conditions (see "Biochemistry" section).

The relatively short biological half-life of ODC allows this enzyme to rapidly reflect changes in rates of protein synthesis and degradation. Alterations of the half-life of ODC have been reported under several conditions of stimulation or inhibition (references 3,5,34, see "Normal Skin" section). However, little or no research has been directed toward elucidating the mechanisms by which ODC is degraded. The group-specific proteases for pyridoxal-requiring enzymes may be involved. These proteases catalyze limited proteolysis of the apo form of pyridoxal enzymes. It has been proposed that their function involves inactivation and initiation of degradation of most, but possibly not all, pyridoxal enzymes [38]. Modulation of such a protease could specifically alter ODC activity levels in the absence of effects on total cellular protein. Proteases for pyridoxal enzymes have been reported in several types of endothelial tissue [38] and are likely to be present in skin.

Several studies have now indicated that ODC induction by different agents may occur via different mechanisms. Pösö, Guha and Jänne [39] found that the half-life of liver ODC is lengthened in thioacetamide- or carbon tetrachloride-treated rats, but not in growth hormone-treated animals. Canellakis and Theoharides [40] reported that the induction of ODC in cultured rat hepatoma cells by dibutyryl cyclic AMP or dexamethasone differed in time course, inhibition by polyamines and inhibition by Actinomycin D. Our own studies on the response of rat skin ODC to either hair plucking or TPA has also revealed differences in time course and sensitivity to inhi-

bition by either Actinomycin D or indomethacin [15]. These data strongly support the conclusion that different inducers may affect different aspects of the control of ODC activity.

SUMMARY, SPECULATIONS AND PROSPECTIVES FOR FUTURE RESEARCH

Ornithine decarboxylase and the polyamines are central to normal and abnormal growth. The basic characteristics of the biochemistry of ODC seem similar in skin and other tissues—special advantages of skin have not yet been exploited, and i.e. ODC and the polyamines have not been localized to particular cell layers or portions of the cell. The cellular localization and compartmentalization of the polyamines and their transport between the cell membrane, cytoplasm and nucleus are no doubt important and have not been studied in any tissues. Diseases have not been studied extensively; studies of diseases will have to be controlled for disease type and should emphasize combined studies of polyamines and ODC. Various stimuli will increase skin ODC, but more than one mechanism has already been found in skin and studies showing increases in ODC should be interpreted with that caveat. Many studies have emphasized transcriptional control of ODC and the antizyme concept. Studies with enucleated cells produced by cytochalasin B have shown that cytoplasts (cytoplasm freed of nuclei) can respond to stimuli for growth with an increase in ODC [41]. This event in a non-nucleated cell must be controlled at a translational level and opens many previous ODC experiments to alternate interpretations. Since the polyamine pathway is influenced at many levels by structural analogues of the substrate or cofactor, modification of the pathway with both topical and systemic drugs is to be expected and those results should be of great interest.

We would like to thank those colleagues who so kindly provided us with current abstracts, manuscripts in press, and discussions of their unpublished work in progress.

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