REVIEW ARTICLE

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The Role of Dimethylaminoethanol in Cosmetic Dermatology

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Contents

Abstract

Skincare formulations for the improvement of aging skin are increasingly important consumer products. Here, we review available data on one such agent – 2-dimethylaminoethanol (DMAE) or deanol – that has recently been evaluated in a placebo-controlled trial. DMAE is an analog of the B vitamin choline and is a precursor of acetylcholine. Although the role of acetylcholine as a neurotransmitter is well known, growing evidence points to acetylcholine as a ubiquitous cytokine-like molecule that regulates basic cellular processes such as proliferation, differentiation, locomotion, and secretion in a paracrine and autocrine fashion. Indeed, this modulatory role may contribute to the cutaneous activity of DMAE.

In a randomized clinical study, 3% DMAE facial gel applied daily for 16 weeks has been shown to be safe and efficacious ($p < 0.05$) in the mitigation of forehead lines and periorbital fine wrinkles, and in improving lip shape and fullness and the overall appearance of aging skin. These effects did not regress during a 2-week cessation of application. Beneficial trends ($p > 0.05$ but ≤ 0.1) were noted in the appearance of coarse wrinkles, under-eye dark circles, nasolabial folds, sagging neck skin, and neck firmness. Application was found to be well tolerated, with no differences in the incidence of erythema, peeling, dryness, itching, burning, or stinging between the DMAE and placebo groups. An open-label extension of the trial showed that the long-term application of DMAE gel for up to 1 year was associated with a good safety profile. The acute skin-firming effects of DMAE have been confirmed by quantitative measures of cutaneous tensile strength. *In vitro* studies in peripheral blood lymphocytes indicate that DMAE is a moderately active anti-inflammatory agent. Although its mechanisms of action in the skin remain to be elucidated, evidence suggests that the skin is an active site of acetylcholine synthesis, storage, secretion, metabolism, and receptivity. Muscarinic acetylcholine receptors have been localized to keratinocytes, melanocytes and dermal fibroblasts, whereas nicotinic acetylcholine receptors have been found in

keratinocytes. The role of acetylcholine and the role of DMAE as a modulator of acetylcholine-mediated functions in the skin remain to be elucidated.

Thus, the benefits of DMAE in dermatology include a potential anti-inflammatory effect and a documented increase in skin firmness with possible improvement in underlying facial muscle tone. Studies are needed to evaluate the relative efficacy of DMAE compared with other skin-care regimens (e.g., topical antioxidant creams, α-hydroxy acids).

Deanol or 2-dimethylaminoethanol (DMAE) is a relatively new skin-care ingredient that is gaining popularity as an antiwrinkle and skin-firming agent. An analog of the B vitamin choline, DMAE is found naturally in high concentrations in salmon, anchovies and sardines, and is believed to contribute to the beneficial effects of these foods. Described as an 'instant antiaging facelift' and 'wrinkle cure', it is the latest entrant into the arena of skin rejuvenation products.[1] Although relatively new to dermatology, the compound has a long history of investigation in the treatment of mood and hyperkinetic disorders,[2] enhancement of memory,[3] and improvement in children with learning and behavior disorders.[4,5] These investigations were based on early reports of DMAE as a precursor of choline and the cholinergic neurotransmitter acetylcholine.[2,6] Originally marketed in the US for the treatment of hyperactivity in children, DMAE is no longer available for that indication. However, it continues to be available as a nutritional supplement, being used largely for memory enhancement and potential antiaging effects.

Recent evidence suggests a more ubiquitous or non-neuronal role for DMAE, since acetylcholine has been shown to act as an autocrine and paracrine factor, regulating basic cellular functions such as mitosis, differentiation, cell-cell contact, cytoskeletal organization, secretion, absorption, trophic and locomotor functions, as well as barrier and immune functions.[7,8] Indeed, the history of DMAE can be delineated along two lines of evidence or ideas: the classic evidence of DMAE as a precursor of acetylcholine in the neuromuscular system, and the relatively newer evidence of acetylcholine as a local transmitter or cytokine in non-neuronal tissues. Whereas the former has led to studies of neuromuscular applications, the latter is becoming important to dermatologic investigations. This article reviews the experimental and clinical evidence of DMAE activity in the skin and present thoughts on the potential mechanisms of action of this compound in the skin. Although much work remains to be done, available clinical data support the efficacy and safety of DMAE as a skin-firming and antiwrinkle agent with potential utility in antiaging topical formulations.

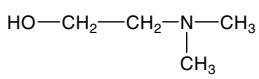
1. Chemistry

DMAE is a simple amine base [$C_4H_{11}NO/(CH_3)_2NCH_2CH_2OH$] with structural similarity to choline (figure 1). Considering its alkalinity, pure DMAE is neutralized by acid to form DMAE salts that are used in various formulations. DMAE salts have been formulated as oral tablets for studies of neurologic applications and as topical preparations for dermatologic applications.

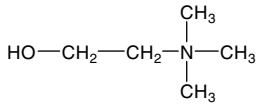
2. Pharmacologic Actions

Known pharmacologic actions of DMAE may be classified under three major types of activity: acetylcholine-enhancing, anti-inflammatory, and antiaging activity. These actions have generally not been specifically demonstrated in the skin and must remain speculative at present. The role of DMAE as a cytokine modulator and regulator of cellular function, growth, and differentiation in the skin also remains to be elucidated, although the identification of the enzymatic machinery and receptor proteins for acetylcholine in this organ suggest the molecular existence of a framework for such actions (see section 4).

Dimethylaminoethanol (DMAE/deanol)



Choline



Acetylcholine

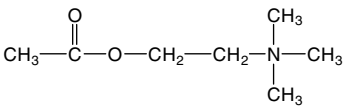


Fig. 1. Chemical structure of 2-dimethylaminoethanol (DMAE): comparison with the structures of choline and acetylcholine.

2.1 Acetylcholine-Enhancing Activity of 2-Dimethylaminoethanol (DMAE)

Evidence suggests that DMAE can increase choline concentrations in the blood by inhibiting its metabolism in peripheral tissues such as the kidney and liver.[9] In mice, intravenous administration of DMAE has been shown to increase both the concentration and the rate of turnover of free choline in the blood.[9] In this study, DMAE was administered intraperitoneally at a dose of 3 mmol/kg (267.3 mg/kg) and caused an increase in the concentration of choline as well as an inhibition of the oxidation and phosphorylation of [^{3}H]methylcholine in the kidneys. In the liver DMAE inhibited the rate of phosphorylation of [^{3}H]methylcholine but did not affect its oxidation or increase its level in this tissue. The direct addition of DMAE *in vitro* did not appear to affect the concentration of free choline or choline metabolism to phosphorylcholine in the blood, suggesting that increases in serum choline were due to the inhibitory effects of DMAE in peripheral tissues and not due to direct serum effects of DMAE. The accumulating choline can conceivably feed the acetylcholine synthesis pathway in tissues containing choline acetyltransferase (ChAT), the enzyme required for catalyzing the conversion of choline to acetylcholine. The acetylcholine content of brain tissue, for example, has been shown to increase following intraperitoneal administration of 2.4 mmol/kg (213.8 mg/kg) DMAE or 2.2 mmol/kg (196 mg/kg) of its acetamidobenzoate salt in rats.[10] Although the cutaneous influx of choline or an increase in the levels of acetylcholine in skin following topical application of DMAE have not yet been documented, ChAT activity has been localized to the epidermis, indicating that acetylcholine synthesis can occur in the skin.[11] As in other muscles, acetylcholine is the neurotransmitter that signals contraction of the facial muscles. Additional effects modulated via acetylcholine receptors in other skin components, such as keratinocytes, melanocytes, dermal fibroblasts and endothelial cells, may occur and are open to investigation.

2.2 Anti-Inflammatory Activity of DMAE

DMAE appears to have moderate anti-inflammatory activity as documented in a peripheral blood lymphocyte (PBL) assay.[12] Human PBLs were stimulated with phytohemagglutinin *in vitro* to induce the clonal expression and secretion of cytokines by T cells. The addition of DMAE to this assay system was shown to strongly inhibit interleukin (IL)-2 secretion and to moderately inhibit IL-6 and IL-10 secretion by phytohemagglutinin-stimulated PBLs (table I). All three cytokines are important in the regulation of humoral immunity, antibody response and allergic reactions; IL-2 can additionally mediate macrophage activation and delayed hypersensitivity reactions. DMAE was also shown to moderately inhibit proliferation of and to exhibit stimulatory activity against tumor necrosis factor-α. No activity was documented against the remaining cytokines tested (IL-1α, IL-4, IL-12 and interferon-γ). The cutaneous anti-inflammatory activity of DMAE remains to be documented.

Table I. Effect of 2-dimethylaminoethanol (DMAE) on cytokine secretion in stimulated peripheral blood lymphocytes *in vitro*[12]

Cytokine	DMAE IC_{50} (μg/mL)[a]
IL-1α	>1000
IL-2	19
IL-4	>1000
IL-6	450
IL-10	425
IL-12	>1000
IFNγ	>1000
TNFα	Stimulated

a The inhibitory constant for 50% inhibition (IC_{50}) of cell proliferation by DMAE in this assay was 550 μg/mL.

IFN = interferon; **IL** = interleukin; **TNF** = tumor necrosis factor.

2.3 Antiaging Activity of DMAE

In vitro studies show that DMAE decreases the extent of protein crosslinking, a characteristic of cellular aging.[13] The increase in crosslinking of proteins may be due to the formation of hydroxyl free radicals, and DMAE is hypothesized to reduce such crosslinking by acting as a free-radical scavenger.[13] Indeed, electron spin resonance spectroscopic evidence demonstrates that DMAE is a free-radical scavenger[14,15] and that polymerization of bovine serum albumin induced by hydroxyl free-radical generation *in vitro* can be inhibited by DMAE.[13] An emerging concept in gerontology is a modification of the "free-radical theory of aging" and posits that while oxygen free radicals are an inherent and essential aspect of aerobic cellular metabolism, excessive formation of such (positive) radicals during aging can have damaging effects, particularly at the cell membrane.[16] Antiaging therapies should therefore increase the number of electrons on the inside of the plasma membrane that are available to scavenge the hydroxyl free radicals and stabilize cell membranes. In addition to being such a free-radical scavenger, DMAE has long been known as a precursor of phosphatidylcholine, the primary phospholipid of cell membranes. Thus, it may also serve to stabilize cell membranes via phosphatidylcholine formation. Again, such mechanisms have not specifically been demonstrated in cutaneous cells, and further investigation is warranted to explore the cutaneous pharmacology of DMAE.

3. Clinical Perspective in Dermatology

Various properties such as skin firming, lifting, and antiaging have been attributed to DMAE. However, until recently, double-blind, placebo-controlled trials were not available to back these claims. Three recent reports have documented the efficacy of a 3% gel formulation of DMAE.[17-19] Two of these studies[17,18] have further documented the safety of DMAE facial applications for up to 1 year of use.

3.1 Efficacy Studies of DMAE

The efficacy of a 3% DMAE gel was shown recently in a multicenter, double-blind, placebo-controlled study.[17] The study included 156 patients between 35 and 60 years of age who were randomized to receive the DMAE gel or placebo gel for 16 weeks followed by a 2-week period of regression evaluation. On a scale of 0–9 (where 0 indicated none and 9 indicated severe), study patients had a score of 3–6 for the overall appearance of aging skin at baseline, indicating moderate to moderately severe photodamage. All patients were considered as candidates for daily use of facial skin-care products such as tretinoin, α- or β-hydroxy acids, and/or other products for photodamaged skin. However, all concomitant treatments for photoaging were prohibited during the trial. Following 16 weeks of application, clinician-rated overall global assessment of facial skin appearance was significantly ($p < 0.05$) better among patients who received topical DMAE gel compared with those who received placebo applications (figure 2).

Other parameters showing consistent and significant ($p \leq 0.05$) improvements with DMAE gel relative to placebo included the appearance of forehead lines, periorbital fine wrinkles, lip thickness, and lip shape (figure 3; table II). Beneficial trends ($p > 0.05$ but ≤ 0.1) were noted in the appearance of coarse wrinkles, under-eye dark circles, sagging neck skin, and neck firmness. Instrumental evaluation of skin moisturization was found to be better with active DMAE application than with vehicle at various time points and relative to baseline values. Application of DMAE gel was found to be safe, with no differences in the incidence of erythema, peeling, dryness, itching, burning or stinging between the DMAE and placebo groups. The overall incidence of adverse effects was 40% in the DMAE group and 47% in the placebo group. None of these adverse effects was considered by the investigator as definitely or probably related to the applications. No statistically significant differences were noted between the active and vehicle groups. No evidence of rebound effect was noted during the 2-week evaluation after cessation of application; the benefits of topical DMAE gel persisted after cessation of application.

At the end of 16 weeks at one center, patients were eligible to enter an open-label 8-month extension of the above study, which

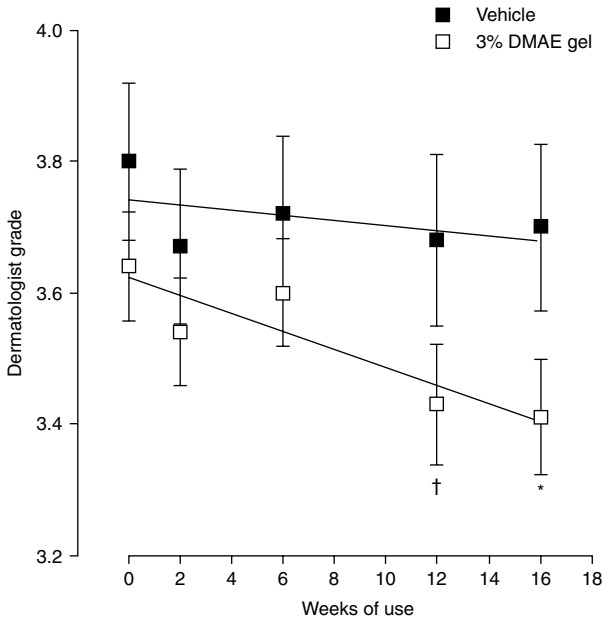


Fig. 2. Clinician-rated overall appearance of aging skin (scale: 0 [none] to 9 [severe]) for patients who applied 3% 2-dimethylaminoethanol (DMAE) facial gel (n = 105) vs the vehicle gel (n = 51) for 16 weeks.[17] * $p < 0.05$; † $p \leq 0.1$.

confirmed the skin-firming ability of 3% DMAE gel.[18] Thirty-five patients entered the open extension study. No other photoaging treatments were permitted but patients were encouraged to use sunscreen. This study showed that the beneficial effects were maintained with no further statistical differences noted. Adverse effects were limited to cutaneous effects only.[12,18] The incidence of erythema and irritation was reduced from baseline, suggesting that irritation attenuated over time.[12] Thus, DMAE facial gel is amenable for long-term use, with documented safety for up to 12 months of continuous use among patients with moderate to moderately severe photoaged skin.

With the exception of skin color and skin moisture content, all evaluations of efficacy in the two studies described were subjective evaluations. A third study sought to objectively quantify the efficacy of DMAE gel, specifically in terms of the skin-firming ability or skin tensile effect of the agent. The study was a randomized, double-blind, split-face trial that compared a 3% DMAE gel formulation with placebo vehicle.[19] The tensile properties of facial skin were measured using three different methodologies – sensorial assessment, measurements of skin distension under suction, and measurements of shear-wave propagation. The first phase of the study was a pilot phase that included 8 volunteers, 26–53 years of age. The DMAE and placebo facial gels were applied on each cheek and objective measurements were made after 10 minutes of such application. Although a trend toward decreased (improved) skin distensibility was noted in the DMAE

group, wide interindividual variations precluded the drawing of any consistent conclusion. Therefore, the researchers designed a second phase of study, during which 30 healthy women, 36–49 years of age, were enrolled and objectively evaluated 45 minutes after applying a pea-sized amount of 3% DMAE or placebo gel. The DMAE formulation was found to produce an 11% decrease in maximum resonance running time measurements (RRTM), a measure indicating significant increase ($p < 0.05$) in the firmness of the skin compared with the placebo gel formulation.[19] Mechanical anisotropy, which has previously been shown to increase progressively with age,[20] was also shown to decrease following DMAE application.[19] The use of DMAE also produced a small (4%) albeit statistically insignificant decrease in multidirectional RRTM, a measure of the average tensile strength of the skin. No change was noted in the minimum RRTM, a measure of tension along resting skin tension lines. Data also indicated that the skin-firming effect of DMAE gel was restricted to the area of skin with loose tensile characteristics. In other words, DMAE appears to firm facial skin in areas where it is needed most. The effect of DMAE on the tensile strength of skin could not be attributed to changes in hydration-related viscoelastic properties of the stratum corneum. In fact, hydration and lipid measurements were documented to be similar for both DMAE and placebo gel formulations.[19]

Taken together, data from these three studies document the skin-firming ability of DMAE gel. From a clinical and aesthetic standpoint, potential benefits of DMAE application include improvements in forehead lines, periorbital fine wrinkles, lip thickness (fullness) and shape, and overall appearance of facial skin after 4 weeks of application.

3.2 Safety of Topical DMAE

In the clinical trials described in section 3.1, DMAE gel (3%) was found to be safe for up to about 1 year of continuous application. No adverse events were related to the DMAE gel. In human modified repeated-insult patch tests (sensitization), 3% DMAE facial gel did not elicit any sensitization ($n = 382$).[21] Thus, 3% DMAE gel appears to have a good safety profile when used topically on a daily basis for up to 1 year, with no significant adverse events.

4. Potential Mechanism(s) of Action of DMAE: Evidence for the Role of Acetylcholine in the Skin

Why should DMAE have any effect on the skin? How does it bring about its skin-firming effects? Does it do so via modulation of the well-understood classic system of neurotransmitter (acetylcholine) regulation of facial muscle contraction? Is there a role for DMAE in the regulation of paracrine and autocrine functions of acetylcholine in this non-neuronal tissue? Indeed, what is the evidence for the existence of such a cytokine system in the skin? The simple answer to these questions is that much of this remains to be elucidated. DMAE-induced increases in cutaneous acetylcholine levels remain to be documented. Increased acetylcholine at neuromuscular synaptic junctions may be the driving force behind increased facial muscle tensile strength and increased firmness of the skin and should be investigated in further studies. However,

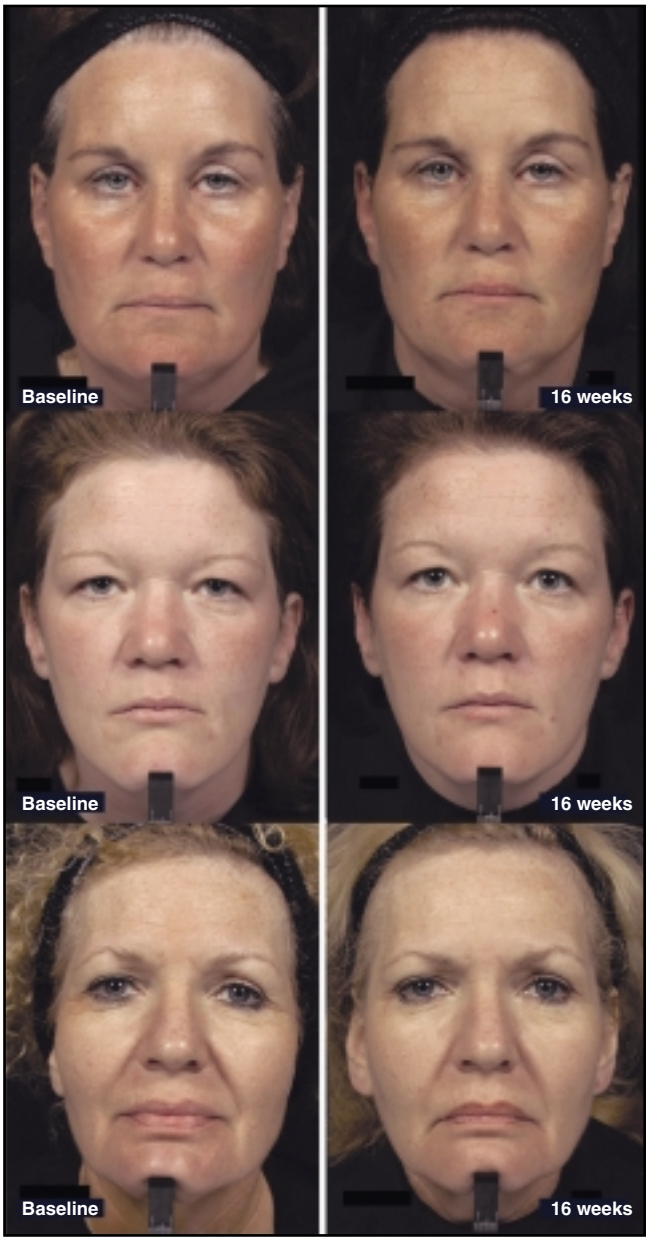


Fig. 3. Representative photographs of three patients before (left) and after (right) a 16-week application of 3% 2-dimethylaminoethanol (DMAE) facial gel.[17]

Table II. Statistical differences[a] between 2-dimethylaminoethanol (DMAE) [n = 105] and placebo (n = 51) groups in secondary efficacy parameters following 16 weeks of 3% topical DMAE facial gel application in a double-blind, placebo-controlled trial[17]

Parameter	Week 2	Week 4	Week 6	Week 12	Week 16	Week 18 (2-week regression phase)
Forehead lines	p < 0.068		**p < 0.023**	**p < 0.012**	p < 0.068	**p < 0.012**
Coarse wrinkles			p < 0.095			p < 0.077
Periorbital fine wrinkles				**p < 0.0230**		
Under-eye dark circles		p < 0.08				
Diminished nasolabial fold					p < 0.059	
Increased lip thickness	**p < 0.0340**	p < 0.058	**p < 0.021**	**p < 0.130**	**p < 0.023**	**p < 0.024**
Increased lip shape		**p < 0.05**	**p < 0.05**	**p < 0.050**		p < 0.073
Improved sagging neck skin						p < 0.088
Improved neck firmness		p < 0.092				

a Values of $p \leq 0.05$ appear in **bold** and indicate statistically significant differences in the DMAE group compared with the placebo group; values of $p > 0.05$ but ≤ 0.1 indicate trends in improvement with DMAE facial gel application compared with placebo gel application.

the lack of change in resting skin tension lines in the study of the tensile properties of skin following DMAE gel application described in section 3.1[19] indicates that mechanisms other than classic neurotransmitter regulation of facial muscle contraction contribute to the increased firmness and other benefits noted with DMAE treatment.

There is growing evidence for the role of a non-neuronal signaling network or communication system in human skin in which acetylcholine acts as a local hormone or cytokine.[22,23] Enzymes and receptors involved in acetylcholine synthesis, catabolism and action have been documented in various layers of the skin. It appears highly likely that DMAE mediates its benefits via this cholinergic system.

4.1 Epidermis

Acetylcholine appears to work in the epidermis as a local hormone with autocrine and paracrine functions. Both ChAT (synthesizing enzyme) and acetylcholinesterase (metabolizing enzyme) activities have been immunohistochemically visualized near the nuclei and in or near cell membranes, respectively.[11] Further, newly synthesized acetylcholine has been detected in cell homogenates and culture supernatants.[24] More recently, human keratinocytes in culture were shown to express a Na^+-dependent, saturable, high-affinity choline transporter system similar to that reported in intestinal epithelial cells and endothelial cells of the blood-brain barrier.[25] Thus, acetylcholine can be synthesized, stored, secreted and metabolized by human epidermal keratinocytes.[11]

Besides the enzymatic machinery, the epidermis also contains both muscarinic and nicotinic receptor types for acetylcholine. Muscarinic receptors are transmembrane glycoprotein molecules with highly conserved coding sequences.[26] Activation of these receptors following acetylcholine binding is responsible for bringing about metabolic changes in target cells and in mediating signal transduction by coupling with G proteins and altering the levels of second messengers. Overall, five molecular subtypes of muscarinic receptors are known.[27,28] These include the m1 through m5 receptors. The odd-numbered muscarinic receptors – m1, m3 and m5 – activate phospholipase C, which triggers the release of the second messenger inositol 1,4,5-triphosphate, resulting in the mobilization of intracellular calcium (Ca_i). The even-numbered muscarinic receptors – m2 and m4 – inhibit adenyl cyclase, thereby increasing intracellular cyclic adenosine monophosphate. Keratinocytes express a heterogeneous population of muscarinic acetylcholine receptors (mAChRs).[29] Receptor subtypes m1 and m3 have been identified in the granular and basal cells, respectively, while both m4 and m5 receptors have been shown to be present in the prickle cell layer.[30] Confocal microscopy data indicate that these receptors are present on the keratinocyte cell surface[29] and accumulate at sites of cell-to-cell contact.[30] The profile of mAChRs changes during different stages of keratinocyte turnover,[30] indicating that these muscarinic receptors are involved in the intrinsic changes of epidermal growth and differentiation.

Human keratinocytes also express nicotinic acetylcholine receptors (nAChRs). These receptors are acetylcholine-gated ion channels or ionotropic receptors, mediating the influx of Na^+ and Ca^{2+} ions and the efflux of K^+ ions.[31,32] Activation of nicotinic receptors results in the release of a variety of second and third messengers such as Ca^{2+}, nitric oxide, prostacyclin, cytokines, and growth factors. The receptor channels are composed of α- and β-subunits. At least nine different α-subunits, named α_2 to α_{10}, and

three β-subunits, named β_2 to β_4, have been identified in non-muscle cells. The differences in subunit composition determine the functional characteristics of the channel.[32] Activation of nAChRs regulates cell differentiation[33] and cell adhesion and motility.[31] Specifically, activation of α_7 and α_9 nAChRs expressed at the latest stage of keratinocyte differentiation in the epidermis causes an increase in filaggrin, a prohumectant substance that may be responsible for skin softness.[34] It will be interesting to evaluate the role of these receptors and of acetylcholine in the manifestation of skin appearance, particularly during aging and following application of DMAE.

Normal human skin melanocytes express m1–5 subtypes of mAChRs on their surface membranes.[35] Activation of these receptors has been shown to result in a transient mobilization of Cai.[35]

4.2 Dermis

In the dermis, human skin fibroblasts have been shown to express m2, m4 and m5 receptor subtypes.[36] Acetylcholine action via these receptors has also been shown to be mediated following mobilization of Ca_i stores.[36] Additionally, immunohistochemical studies have shown ChAT activity in the endothelial cells of dermal blood cells.[37] Such endothelial cells express a vesicular acetylcholine transporter system *in vitro*, indicating a developed endothelial cholinergic system in the dermal vasculature.

Overall, these data reflect an exquisite control of cellular processes by a single molecule – acetylcholine. The molecule appears to regulate different biologic processes by differentially activating cholinergic receptors at specific stages of growth and differentiation.[38] It is conceivable that DMAE mediates its cutaneous effects, at least partially, via increasing acetylcholine levels and modulating acetylcholine receptors much like endogenous steroid hormones and retinoids[39] or growth factors.[40] Depending on the timing and specificity of receptor interaction, multiple effects on skin strength, elasticity, and the appearance of wrinkles and fine lines, could be affected.

5. Potential Role of DMAE in Aging Skin: An Overview

The aging skin is a complex and dynamic system that undergoes chronologic aging as well as photoaging. The latter is caused by environmental effects, specifically UV irradiation, and superimposes on changes of chronologic aging. In addition, climacteric aging caused by hormonal changes in postmenopausal women has also been recognized and may additionally impact the skin. Thus, the manifestations and appearance of facial skin can be highly variable between individuals, depending on age, lifestyle, hormonal status and genetic predisposition.

UV irradiation results in the photochemical generation of reactive oxygen species such as superoxide anion, peroxide and singlet oxygen that cause deleterious chemical modifications of cellular components such as DNA, proteins and lipids.[41] Additionally, the oxidative stress induces signal transduction pathways that mediate damage to connective tissue, largely because of an increase in the expression of the nuclear transcription factor, activator protein factor-1 (AP-1), which stimulates transcription of genes for matrix degrading enzymes such as metalloproteinases. Consequently, photoaging results in a degradation of skin collagen. In addition, ongoing collagen production is impaired by downregulation of type I and type II procollagen gene expression. Impairment of collagen synthesis also occurs during chronologic aging as a result of decreasing numbers of fibroblasts and their capacity to produce type I procollagen in aging skin compared with young skin.[42] Photoaged skin shows an accumulation of degraded and disorganized collagen fibrils and is characterized by the appearance of wrinkles, mottled pigmentation, rough skin, and loss of skin tone.[43] Sun-protected aged skin appears thinner, more evenly pigmented, laxer, and more finely lined.[41] Elastin fibrils are also altered during aging, with decreases in protected aged skin and increases in photodamaged skin, with the increase being due to abnormal elastin.[44] Much like photoaging and chronologic aging, climacteric aging has been shown to be characterized by increased skin distensibility and viscosity and a decrease in elasticity.[45]

Considering the overall changes in aging skin, any formulation developed to improve its appearance should provide some combination of the following benefits:

- free-radical scavenging capacity;
- decrease in oxidative stress;
- inhibition of AP-1 expression;
- inhibition of metalloproteinase induction;
- inhibition of collagen degradation and/or promotion of collagen synthesis, which should result in an increase in skin elasticity and skin thickness or firmness; and
- decrease in appearance of coarse and fine wrinkles or lines.

Currently, the only US FDA-approved product for photodamaged skin is topical tretinoin. Topical tretinoin has been approved as an adjunctive agent for the mitigation of fine facial wrinkles (0.02% tretinoin cream, 0.05% tretinoin emollient cream) and for the mitigation of mottled pigmentation and rough skin in patients using comprehensive skin-care and sun-avoidance programs. Besides retinoids, other agents used in skin-rejuvenation programs include α-hydroxy acids and antioxidants (e.g. vitamin C ester).[46,47] In addition, nonpharmacologic procedures such as

microdermabrasion, α-hydroxy acid peels, and laser resurfacing are common practices aimed at rejuvenating photodamaged skin. For improvement in frown lines associated with aging, Botox® [1] Cosmetic (Allergan, Inc.) – a sterile, vacuum-dried, purified botulinum toxin type A neurotoxin complex – received FDA approval in 2002.[24] It is indicated in the US for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≥65 years of age. Improvement in facial appearance following botulinum toxin injection occurs because of the blockade of neuromuscular transmission (acetylcholine) to the facial muscles involved in frown formation. Since reinnervation of muscles or development of extrajunctional acetylcholine receptors may occur with time, the effects of botulinum toxin can slowly reverse. Thus, treatment with Botox® Cosmetic requires intramuscular injections at repeated intervals by skilled healthcare providers to maintain its effect and the search for more easily used, long-lasting skin-care products continues.

A novel agent, DMAE has been described here as a safe and efficacious agent for the mitigation of forehead lines and periorbital fine wrinkles, improved lip shape and fullness, and overall improvement in the appearance of aging skin. These effects have been documented in a randomized, placebo-controlled trial of 16 weeks following daily application of a 3% facial gel formulation.[17] Further, long-term safety has been documented in an open-label extension of this study for a total treatment duration of 1 year.[18] The acute skin-firming effects of 3% DMAE gel have been confirmed by quantitative measures of cutaneous tensile effect.[19] The benefits of topical DMAE gel include lack of sensitization,[21] anti-inflammatory potential,[12] and overall safety.[17,18] Further, DMAE may mediate its benefits via multiple effects, including an increase in skin firmness and possible improvement in underlying facial muscle tone and anti-inflammatory effects. Other modes of action that remain to be investigated include prevention of free-radical damage, compensation of age-related loss of acetylcholine receptors, autocrine and paracrine modulation of local cytokines, and regulation of growth, differentiation, and locomotion.

6. Future Considerations

As indicated throughout this article, much work remains to be done on the elucidation of the mechanism(s) of action of DMAE in the skin. An acetylcholine-mediated action that modulates facial muscle contraction and muscle tone does not appear to explain completely the observed clinical effects of DMAE on the skin. For the future, controlled studies with objective evaluations are also needed to compare DMAE with other anti-aging formulations/therapies, including head-to-head comparisons and combination regimens that may have the potential for synergistic efficacy.

7. Conclusions

DMAE is a relatively new skin-care ingredient. Clinical data regarding its efficacy and safety in improving the appearance of aged facial skin are emerging and show that the use of facial DMAE gel can improve skin firmness and reduce wrinkles safely at a concentration of 3%. The exact mechanism(s) by which DMAE mediates these effects on the skin has not been clarified. Indeed, it appears that it may do so via multiple actions. Thus, for example and similar to neuromuscular tissue, it may improve muscle tone by increasing the supply of acetylcholine at the neuromuscular junction. Additionally, it may mediate some of its actions, particularly proliferation and differentiation, via increasing cutaneous acetylcholine availability for paracrine and autocrine functions. There is now considerable evidence for the skin as an active site of acetylcholine synthesis, metabolism and receptivity. Other potential mechanisms of action of DMAE in the skin include free-radical removal, inhibition of age-associated increases in protein crosslinking, membrane stabilization, and anti-inflammation. More studies are needed to elucidate the actions of DMAE in the skin and to assess its clinical benefits relative to other available antiwrinkle and/or anti-photoaging treatments. Because of its multiple actions, DMAE may also have utility in combination regimens that can provide a more comprehensive approach to skin care for aging skin.

Acknowledgments

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