Review Article

Nicotinic acid/niacinamide and the skin

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Summary

Nicotinic acid (also generally known as niacin) and niacinamide (also known as nicotinamide) are similarly effective as a vitamin because they can be converted into each other within the organism. The blanket term vitamin B_3 is used for both.

Niacinamide is a component of important coenzymes involved in hydrogen transfer. Here, the two codehydrogenases, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) are of central importance. Topical application of niacinamide has a stabilizing effect on epidermal barrier function, seen as a reduction in transepidermal water loss and an improvement in the moisture content of the horny layer. Niacinamide leads to an increase in protein synthesis (e.g. keratin), has a stimulating effect on ceramide synthesis, speeds up the differentiation of keratinocytes, and raises intracellular NADP levels. In ageing skin, topical application of niacinamide improves the surface structure, smoothes out wrinkles and inhibits photocarcinogenesis. It is possible to demonstrate anti-inflammatory effects in acne, rosacea and nitrogen mustard-induced irritation.

Because of its verifiable beneficial effects, niacinamide would be a suitable component in cosmetic products for use in disorders of epidermal barrier function, for ageing skin, for improving pigmentary disorders and for use on skin prone to acne.

Keywords: niacin, niacinamide, nicotinamide, nicotinic acid, topical application, vitamin B_3

Introduction

Nicotinic acid and niacinamide are similarly effective as vitamins because they can be converted into each other within the organism. The blanket term vitamin B_3 is used for both. Nicotinic acid and niacinamide are water-soluble vitamins (vitamin B_3). Offal, meat and fish are particularly rich in niacinamide, although less is present in vegetables. Of the cereal crops, wheat has the highest content, whereas the content in corn is very low. Nicotinic acid and niacinamide can be taken up in the free form or produced during the digestive process by enzymatic action. Reabsorption then occurs in the upper section of the small intestine.

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Functions

Niacin is a component of important coenzymes involved in hydrogen transfer. Here, the two codehydrogenases nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) are of central importance. NADP is produced from NAD by phosphorylation by means of an NAD-kinase and ATP (Fig. 1).

There are three ways in which biosynthesis of NAD from niacin occurs:

- starting with nicotinic acid;
- from niacinamide;
- biosynthesis from L-tryptophan via quinoline acid.

NAD and NADP are the coenzymes of countless dehydrogenases. NAD-dependent dehydrogenases are found mainly in the mitochondria. Their main function is to supply hydrogen to the respiratory chain for oxidation and energy production. NADP-dependent dehydrogenases are mainly localized in the cytosol. The most important

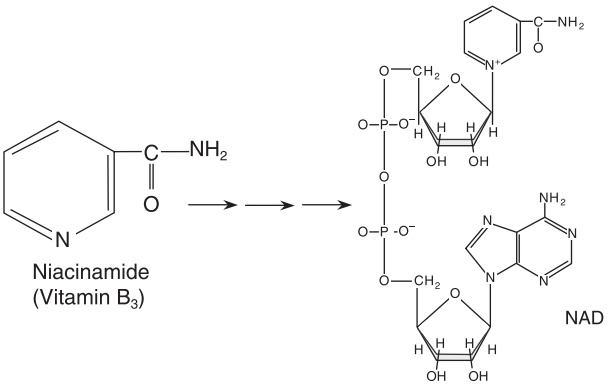

Figure 1 Niacinamide is a precursor to energy co-factors.

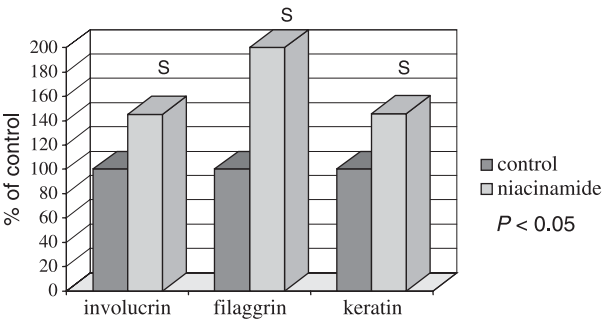

Figure 2 Niacinamide increases barrier layer proteins.[24]

function of the NADP system is to provide hydrogen for reductive biosyntheses such as in fatty acid synthesis, cholesterol synthesis and hydroxylations. The lipid-reducing effect of niacinamide is explained by its direct influence on adipocytes and spleen cells via a G-protein-coupled receptor. This results in the inhibition of lipolysis.[1] At pharmacological concentrations, niacinamide can lead to modification of the various lipoprotein fractions. This, in turn, leads to an increase in HDL and simultaneous reduction of LDL and triglycerides.

Daily requirements

The daily requirement of niacin/niacinamide depends on the intake of tryptophan because L-tryptophan is an important precursor for the coenzyme form of niacinamide. In NAD synthesis, 60 mg of tryptophan is equivalent to 1 mg of niacin. The German Nutrition Society[2] gives recommendations for daily intake of niacin (see Table 1).[2]

Table 1 German Nutrition Society recommendations for daily intake of niacin (mg).

Age	Female	Male
0–4 months	2	2
4–12 months	5	5
1–4 years	7	7
4–7 years	10	10
7–10 years	12	12
10–13 years	15	13
13–15 years	18	15
15–25 years	17	13
25–51 years	16	13
51–65 years	15	13
65 years and older	13	13
Pregnant women from the 4th month	15	
Breast-feeding mothers	17	

Symptoms of deficiency

The symptoms of a deficiency in niacin/niacinamide are evident in the gastrointestinal tract, in the nervous system and, above all, in the skin. Gastrointestinal problems as a result of niacinamide deficiency are accompanied by glossitis, stomatitis, diarrhoea and vomiting. Neurological effects may be pain and dysaesthesiae of the extremities, tremor, spastic and atactical movement disorders with peripheral neuritis, psychological effects with depression, hallucinations, confusion and electroencephalogram changes. On the skin, the symptoms of pellagra become apparent. Pellagra is characterized by diarrhoea, dermatitis and dementia. Untreated, the disease is fatal. The skin effects are concentrated on areas exposed to light. To begin with they resemble sunburn, in the later course of the disease there is a thickening of the skin with flaking. There is a strong itching sensation, the skin takes on a brown–blue shade and blisters may appear.

Classic pellagra as a symptom of deficiency occurs mainly in some regions of Africa and the Far East where the diet consists mainly of corn. In America, the first case of pellagra was described in 1902. However, it is not usually purely a result of niacin deficiency. Generally, there is also a deficiency of other B-group vitamins and proteins. However, sporadic outbreaks of pellegra do occur even in the West. There have been reports in America,[3] Denmark,[4] the Netherlands[5] and the Mediterranean.[6]

Even where there is sufficient dietary intake, it is possible for niacin deficiency to occur.[7] Deficiency can arise from interactions with various medications; for example:

- cytostatic agents (mercaptopurine);
- psychotropic drugs (diazepam);
- tuberculostatic drugs (isoniazid);

- antiepileptic drugs (phenytoin, phenobarbital);
- analgesics and antiphlogistics (salicylamide, ethenzamide, paracetamol, morazone).

In Hartnup syndrome, in addition to metabolic changes, there is also disruption to the renal and intestinal transport of tryptophan, resulting in the occurrence of pellagra-like symptoms.

In carcinoid syndrome, most tryptophan is used up in serotonin synthesis. This means that the biosynthesis of niacin from L-tryptophan is substantially impaired.

Malabsorption leads to niacin deficiency. Besides chronic diarrhoea, particular mention should be made of chronic alcoholism and liver damage.

Because folic acid and vitamin B_6 are involved in the synthesis of NAD from tryptophan, a lack of these vitamins can also lead to secondary niacin deficiency.

Pellagra has been seen in cases of chronic dialysis treatment and long-term parenteral nutrition without appropriate niacin substitution.

Uses of niacinamide

The systemic and topical use of niacinamide in the case of medical and cosmetic problems has proved effective, not only where there are signs of a deficiency. There are also repeated references in the literature to beneficial effects that have mainly been attributed to the significance of niacinamide for the codehydrogenases NAD and NADP.

Feldmann and Maibach[8] highlighted the possibilities for the topical application of niacinamide because they were able to prove sufficient percutaneous penetration of human skin. In a quantitative analysis of barrier penetration on the forearms of healthy test subjects, they found a good penetration rate for niacinamide. However, nicotinic acid is able to overcome the epidermal barrier function only with difficulty. Franz[9] investigated the penetration rate of niacinamide *in vitro* on full-thickness skin products and underlined the significance of the vehicle for penetration. With ether as the vehicle, 28.8% penetrated; in emulsions, which are standard in cosmetic formulations, 10% of the niacinamide content penetrated.

Topical application of niacinamide in isoniazid-induced pellagra

The tuberculostatic agent isoniazid can lead to pellagra-like symptoms on the skin, which can be traced back to a breakdown in the metabolic conversion of tryptophan. The conversion of tryptophan to nicotinic acid is linked to the enzyme kynureninase and its cofactor pyridoxal phosphate. The complex formation between isoniazid and pyridoxal phosphate can then lead to inhibition of the synthesis of nicotinic acid from tryptophan.[10] Comaish *et al.*[11] were able to observe complete remission of an isoniazid-induced pellagra following topical treatment with niacinamide.[11] One per cent niacinamide was used in a macrogol ointment. To our knowledge, there have been no reports in the literature of beneficial effects as a result of the systemic use of niacinamide in the case of isoniazid-induced pellagra.

Significance of niacinamide for epidermal barrier function

For the current views on the structure and function of the epidermal barrier lipids, the studies of Elias are decisive.[12] The intercellular spaces of the horny layer contain mainly apolar lipids represented by free fatty acids, cholesterol and ceramides.[13] In addition to their composition, the structure of the epidermal barrier lipids is also significant. In the intercellular space of the stratum corneum, the lipids are formed into multilayer, bilamellar structures separated by a hydrophilic phase. An intact bilamellar barrier lipid structure is decisive for the hydration of the stratum corneum. Ceramides are mot significant in the formation of the bilamellar structure and subsequent epidermal barrier function. There is a deficiency and related restriction of the epidermal barrier function, which for measuring purposes can be presented as an increase in transepidermal water loss and horny layer moisture deficiency, in atopic dermatitis,[14] ageing skin[15] and weather-induced xerosis of the skin in winter.[16]

Using cell cultures of human keratinocytes, Tanno *et al.*[17] established that niacinamide led to improved differentiation of keratinocytes and increased synthesis of ceramides, free fatty acids and cholesterol.[18] When these results were transferred to conditions *in vivo*, Tanno *et al.* demonstrated, by the topical application of niacinamide in the context of a vehicle-controlled study in the case of winter xerosis, an improvement in epidermal barrier function, which can be presented as a reduction of transepidermal water loss and an improvement in horny layer moisture.[18] In this study, 2% niacinamide was used in polyoxyethylene[20] sorbitan monolaurate. Similar results were observed by Ertel *et al.*,[19] who also showed improvement in horny layer moisture in combination with a reduction in transepidermal water loss after the topical application of 2% niacinamide.

Niacinamide and keratinocyte differentiation

In cell cultures, Tanno *et al.*[17] established more rapid keratinocyte differentiation following treatment with niacinamide. In particular, it was possible to determine an influence on keratin K1. Keratin K1 is a basic keratin

synthesized mainly in the lowest layers of the stratum spinosum. In the case of psoriasis vulgaris, there is a pathological time reduction in the differentiation of keratinocytes which has led to discussion concerning a possible stimulation of cell proliferation through niacinamide.[20] Herschel and Zackheim healed psoriasis vulgaris by topical treatment with 6-aminonicotinamide.[20,21] 6-Aminonicotinamide is the most important antagonist of niacinamide and seems to have an inhibiting effect on the proliferation stimulation of niacinamide in the case of psoriasis vulgaris.

Niacinamide and wound healing

Myczkowski[22] has shown, by split skin removal, that niacinamide induces an improvement in wound healing. Three groups were compared, one of which was treated with an ointment dressing. In the second group, a dry viscose dressing was used. The third group were given infusions with Complamin® in addition to the viscose dressing. This is a nicotinic acid salt with a xanthine corpus (xanthinol nicotinate). Using the infusion treatment, it was possible to reduce the time to wound healing from 15–17 days to 7–10 days.[22]

Collins *et al*. investigated the postoperative healing of wounds caused by reconstructive plastic surgery and established better wound healing in the case of parenteral administration of niacinamide.[23] In the case of monotherapy with saline solution, the skin flaps were 45.67% (± 31.14) vital. Niacinamide increased the vitality rate to 85.30% (± 9.24). The results are statistically highly significant ($P < 0.01$).

Niacinamide and skin ageing

Skin ageing involves morphological and functional changes. The external appearance changes through atrophy and the development of wrinkles as a result of the decrease in epidermal cell layers and, as dermal components, from a reduction in protein and collagen synthesis. Reduced protein synthesis is reflected in keratin, filaggrin and involucrin. Keratin deficiency has an effect on the epidermal cell structure and its water-binding capacity. Filaggrin is an antecedent of natural moisturizing factor (NMF). Involucrin is seen as significant for the cell envelope and structure of the stratum corneum. In sum, the effects of reduced protein synthesis are poorer structure and reduced skin elasticity, as well as a decrease in the efficiency of the epidermal barrier function with a reduction in horny layer moisture. The functional limitations of ageing skin include reduced 'turnover' of the epidermis (slower epidermal cell cycle), which results from a deficiency of NADP in ageing cells.[24]

In studies on cell cultures, Oblong *et al*.[24] found that in ageing cells, niacinamide enabled NADP content to be increased to a level comparable with that of young cells. It was also possible to prove that niacinamide, as a precursor of NAD / NADP, had a stimulatory effect on collagen synthesis, epidermal biopolymers (proteins) keratin, filaggrin and involucrin (Fig. 2).[24] In general, niacinamide enabled improved dermal and epidermal cell growth. Thus, niacinamide is a therapeutic option in the case of age-related skin changes.

Effect of niacinamide on the surface structure of the skin

Using a multiple-angle reflectance spectrophotometer and *in vivo* tests of the back of the hand, Matts and Solechnik established a beneficial effect for the topical application of niacinamide in smoothing the surface structure of the skin.[25] Using long-term application of an emulsion containing 2.5% niacinamide, it was possible to correct the damage to the surface of the skin as a result of ageing. The results were statistically significant compared with the influence of the vehicle ($P < 0.05$).

Matts and Solechnik confirmed the results of two clinical studies carried out by Bissett *et al*. In the context of a vehicle-controlled study, it was possible to show a smoothing of the skin surface structure and a reduction in wrinkle depth on the facial skin of women following 12 weeks topical treatment with niacinamide, results which differed statistically significantly from the influence of the vehicle.[26] The studies were carried out with 5 and 2% niacinamide. The results demonstrated that the effect of niacinamide was dose-dependent.

Niacinamide and light damage to the skin

UV radiation leads to the formation of reactive oxygen species (ROS) which are responsible for the creation of free radicals that lead to direct damage to DNA, lipids and proteins, i.e. mainly damage to membranes, and which are held responsible for photocarcinogenesis. All oxygen compounds that have a reactivity greater than that of molecular oxygen are termed ROS. These include singlet oxygen (O_2), hydrogen superperoxide (H_2O_2), the superoxide anion (O_2^-) and the hydroxyl radical (OH).

Shen *et al*.[27] treated cell cultures with H_2O_2 and irradiated cells with UVC; both treatments led to cell death. Morphologically, there were signs of apoptosis, which is a typical finding in photocarcinogenesis. By adding various concentrations of niacin, the morphological changes to the cells could be substantially reduced. Gensler[28], in an *in vivo* study in mice, inhibited photocarcinogenesis by the nutritive administration of niacinamide. There was a

clear dose/effect ratio between the quantity of niacinamide administered and per cent light-provoked carcinoma development. Gensler noted that it was also possible to inhibit both photo-immunosuppression and photocarcinogenesis by the topical application of niacinamide. There are no fixed ideas on the mechanism by which niacinamide exerts its beneficial effects.

Niacinamide in cases of hyperpigmentation

In two studies, Hakozaki[30] has shown a reduction in pigment disorders as a result of niacinamide. In the first study, facial pigment disorders in 18 Japanese women were treated on one side with 5% niacinamide and on the other side with vehicle only. The pigment disorders were evaluated qualitatively and quantitatively using high-resolution digital images and subjective judgements. In both evaluation procedures, it was found that after 8 weeks of treatment there was a significant lightening of hyperpigmentation as a result of niacinamide compared with the effect of the vehicle ($P < 0.05$). In a second study on 120 Japanese women, in the context of a three-part study using the same evaluation parameters as in the first study, comparisons were made among an SPF 15 sun protection cream with and without 2% niacinamide and the relevant vehicle. As a result of niacinamide treatment, there was a lightening of the skin after 4 and 6 weeks, which was significantly better than with either the sun cream without niacinamide or the vehicle. In their study on the topical application of niacinamide on ageing skin, in addition to a stabilizing effect on the epidermal barrier function, Bissett *et al.*[26] were able to establish a lightening of pigment disorders. One possible explanation for this effect is given by Boissy *et al.*[31] who established that melanosome transfer from melanocytes to keratinocytes was inhibited as a result of niacinamide treatment. These results justify the use of niacinamide both as a prophylactic and for the treatment of pigment disorders.

Sebo-suppressive effect of niacinamide

Facial skin obtained from face-lift surgery was used to obtain cell cultures of sebocytes.[32] By incubating with niacinamide it was possible to prove a dose-dependent sebo-suppressive effect. These results support the topical use of niacinamide in the treatment of acne vulgaris.

Anti-inflammatory effects of niacinamide

In the treatment of acne vulgaris with a commercial product containing 4% niacinamide (Papulex®), Shalita *et al.*[33] found an anti-inflammatory effect which could be clinically established by the reduction of inflammatory papules. In total, 82% of those treated showed an improvement in overall disease condition after 8 weeks.[33] In the case of a comparable treatment with a clindamycin gel there was an improvement in only 68% of cases.

Indications of an anti-inflammatory effect as a result of topically applied niacinamide were also established in the case of rosacea.[34] In addition to an improvement in horny layer moisture, there was also a reduction in the reddening of the skin as an indication of the anti-inflammatory effect.

The topical use of nitrogen mustard represents a form of treatment for cutaneous lymphoma.[35] An early indication for cutaneous irritation is the development of erythema. Yourik *et al.*[36] established that niacinamide has an anti-inflammatory effect on erythema in guinea pigs as a result of nitrogen mustard exposure.[36]

Conclusion

Niacinamide is beneficial because it results in the increased synthesis of proteins and keratin, stimulation of ceramide synthesis and acceleration of the differentiation of keratinocytes. These provide a stabilizing influence on epidermal barrier function and an improvement in horny layer moisture content. On ageing skin, niacinamide improves the surface structure of the skin, shows a wrinkle-smoothing effect and has an inhibitory effect on photocarcinogenesis.

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