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Role of Beta-Endorphin in the Skin



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Abstract

Beta-endorphin is a peptide neurotransmitter that is mainly produced in the central nerve system where it causes an analgesic effect and a feeling of euphoria after binding to opiate receptors. During the last years several research groups confirmed the presence of a fully functional beta-endorphin/mu-opiate receptor system in a variety of cutaneous cell types. The beta-endorphin/mu-opiate receptor system was shown to modulate migration of keratinocytes and to be involved in wound healing. Chaste tree, a medicinal plant indigenous to the Mediterranean region and Asia, was shown to produce lipophilic substances that bind to the mu-opiate receptor and to stimulate beta-endorphin production *in vivo*. Topical application of a preparation of the lipophilic fraction of chaste tree berries was found to exert a positive effect on skin hydration, firmness and wrinkle depth.

■ Endorphins: Structure and Function

Morphin, a substance found in *Papaver somniferum*, has an analgesic effect. Our body produces compounds with a similar effect and this is why they are called endogenous opioids. This is a group of peptide hormones comprising beta-endorphin, enkephalin and dynorphin. They share the N-terminal amino acid sequence Tyr-Gly-Gly-Phe-X (X = Met or Leu). This is the binding sequence to the opioid receptor. Each of these peptide hormones is produced out of a separate precursor peptide. Beta-endorphin is a cleavage product of proopiomelanocortin (POMC), a protein with 267 amino acid residues. Processing of POMC leads to several peptide hormones with different functions (Fig. 1): the adrenocorticotropic hormone (ACTH), also known as corticotrophin, that stimulates the adrenal cortex to secrete the anti-inflammatory and anti-allergic

hormone cortisol, the melanocyte-stimulating hormone (MSH) that is involved in skin pigmentation and beta-endorphin that comprises the 31 C-terminal amino acids. POMC and its cleavage products are produced mainly in the hypothalamus and in the anterior lobe of the pituitary gland. There are several functions for beta-endorphin described. Binding with its N-terminus to the three opioid receptors mu, kappa and delta (preference for mu) leads to morphine-like effects. Beta-endorphin produces analgesia by acting on both, central and peripheral opioid receptors which inhibits the transmission of the signal along nerve cells from the source of the pain (nociceptor) to the spinal cord. Beta-endorphin was also found to bind to receptors on cells of the immune system. It seems to be involved in the fine tuning of the immune response. Finally there is strong evidence that endorphins are connected with »pleasure centres« in the brain.

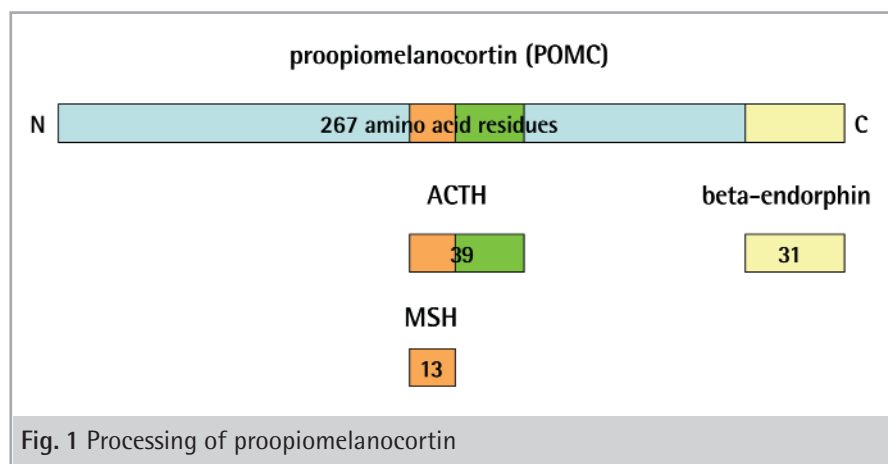


Fig. 1 Processing of proopiomelanocortin

■ Existence of the Beta-Endorphin / mu-Opiate Receptor System in the Skin

Our skin is a target for the POMC-derived hormone MSH, which regulates skin pigmentation. Recently the *in situ* production of POMC and its products ACTH, MSH and beta-endorphin and their corresponding receptors in skin cells has been demonstrated (1). It has been proposed that a cutaneous POMC system acts in an autocrine manner in response to external or internal stresses. POMC processing in melanocytes and a MSH / melanocortin 1 receptor / cAMP cascade in control of pigmentation is well documented. Recent data have demonstrated the existence of a functionally active beta-endorphin / mu-opiate receptor system in melanocytes, keratinocytes and fibroblasts. Regarding epidermal and hair follicle melanocytes, it was shown that beta-endorphin can regulate melanogenesis, dendricity and proliferation (2). *Bigliardi* et al. 2002 observed for beta-endorphin a stimulation of the migration of cultured human keratinocytes (3). They proposed for beta-endorphin a key role in the final reepithelialization and tissue regeneration in wound healing. Supporting this theory is the fact that expression of mu-opiate receptors on keratinocytes close to the wound margin of chronic wounds was indeed reduced compared

to acute wounds (4). The group of *Bigliardi* showed also a possible role of skin beta-endorphin in the communication with peripheral nerve endings (5). They found that keratinocytes positive for beta-endorphin staining are clustered around the terminal ends of afferent C-fibres, which signal the sensations of warmth, cold or pain to the central nervous system. Further, they showed that the mu-opiate receptor was expressed on these nerve fibres in the dermis and epidermis. It was hypothesized that keratinocytes can communicate directly with the nervous system through the opiate receptor system and that this might open potential therapies of skin diseases like atopic dermatitis and psoriasis.

■ Monk's Pepper Produces Substances with Beta-Endorphin Activity

Chaste tree (*Vitex agnus-castus*), also known as monk's pepper, is a large shrub native to the Mediterranean area that produces aromatic berries with a bitter taste. Dried chaste tree berries have been used as a pepper substitute and as herbal medicine until now to treat disorders of the female reproductive system. Nowadays it is especially recommended for the treatment of premenstrual syndrome

(PMS). The term refers to symptoms such as irritability, tension, anxiety and physical changes that some women experience in the two weeks before the period starts. High levels of the hormone prolactin are thought to play a role in PMS. Chaste tree was found to reduce the release of prolactin, probably through its dopaminergic action. Binding of lipophilic compounds of chaste tree to the dopamine receptor is well documented (6). *Meier* et al. showed also binding to the opiate receptors, especially to the mu and kappa type (7). Since anxiety, depression and sleeping problems are important symptoms of PMS and beta-endorphins are known to induce feelings of pleasure and euphoria, the beta-endorphin-like activity might be also involved in the beneficial effect of chaste tree in the treatment of PMS. Binding to the mu and kappa opiate receptor was more pronounced in the lipophilic fraction of an ethanol extract, but the exact molecular nature of the active compounds is not known yet. *Samochowiec* et al. also showed a possible role of beta-endorphin in the therapeutic effect of chaste tree against PMS (8). When they fed rats over 4 days with a chaste tree extract, they found an increase in the beta-endorphin level in the blood of 105%. It implies that chaste tree contains substances that stimulate the body's own production of beta-endorphin.

■ Topical Application of a Monk's Pepper Berries Extract

Dried monk's pepper berries were extracted in ethanol, glycerine and beta cyclodextrin. For standardisation the lipophilic flavonoid casticin was measured by HPLC-analysis. Casticin is a chemotaxonomic marker of the genus *Vitex* and the most dominant substance in the fingerprint chromatogram of the monk's pepper berries (9). Extraction of 5% dried berries yielded in a solution of 15 mg / l casticin. The final cosmetic ingredient (Happybelle-PE) consisted of monk's pepper berries extract, lecithin, tocopherol, ascorbyl tetraisopalmitate and beta cyclodextrin. Combination of beta cyclodextrin and lecithin resulted in a double vector system (Fig. 2). Casticin

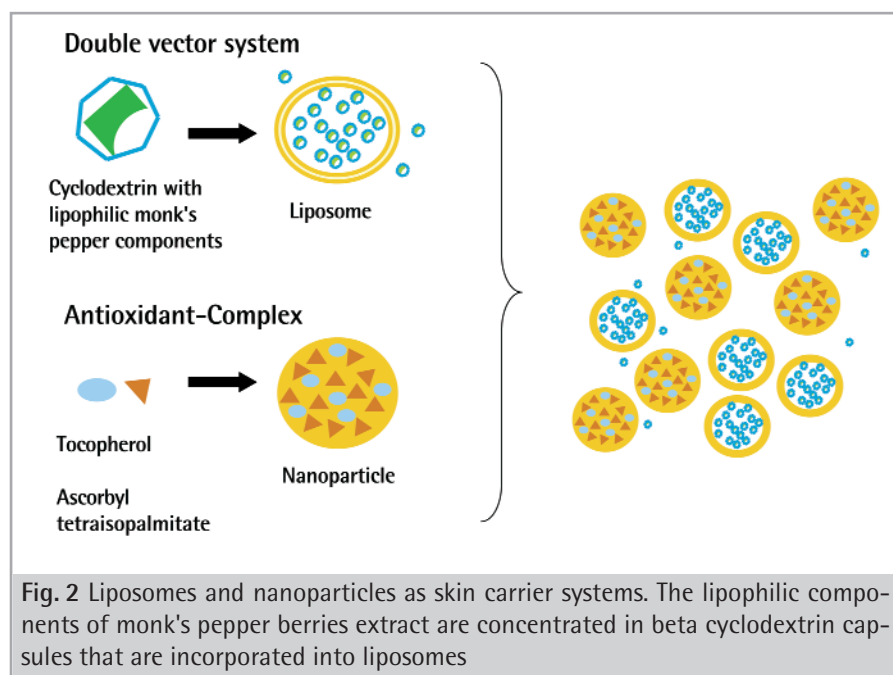


Fig. 2 Liposomes and nanoparticles as skin carrier systems. The lipophilic components of monk's pepper berries extract are concentrated in beta cyclodextrin capsules that are incorporated into liposomes

and other lipophilic monk's pepper compounds are enriched in the hydrophobic pocket of beta cyclodextrin and these complexes are enclosed in the lecithin liposomes. The lipophilic vitamins were encapsulated in a nanoemulsion, stabilized with lecithin. The double vector system increases the stability of the monk's pepper compounds and enhances their penetration into the skin. In an *in vitro* assay with cell cultures of human keratinocytes the cosmetic ingredient Happybelle-PE was found to clearly stimulate the activity of the mitochondrial succinate dehydrogenase indicating increased cell proliferation. Already 0.0625% monk's pepper ingredient was significantly increasing the enzyme activity (Fig. 3). For the *in vivo* efficacy a cream with 1% Happybelle-PE was tested in a study with 20 women (hydration and firmness) and 40 women (wrinkle depth) in the age of 30 to 61. The cream was applied twice daily for 28 days. Skin hydration, skin firmness and wrinkle depth were determined at the beginning of the study and 8 to 12 hours following product application after 14 and after 28 days. Skin hydration was improved by nearly 30% and skin firmness increased by 20%. A significant reduction in wrinkle depth could be observed after the treatment (Fig. 4).

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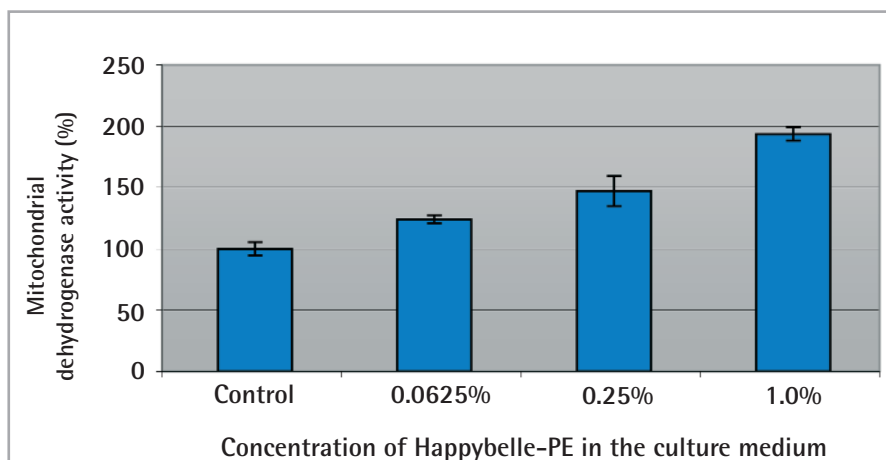


Fig. 3 Happybelle-PE stimulates cell proliferation of keratinocytes. Mitochondrial dehydrogenase activity was measured by the MTT assay. Keratinocytes (HaCaT) were preincubated at 37°C for 24 hours. Then Happybelle-PE was added, diluted in cell culture medium. The cells were incubated for another 72 hours before the MTT assay was performed

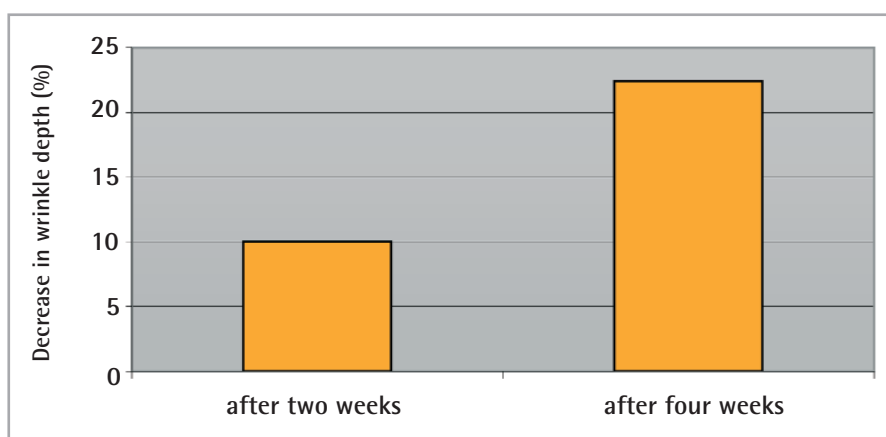


Fig. 4 Reduction of wrinkle depth compared to the beginning of the study and the untreated area. Wrinkle depth was measured by recording the crow feet area as a 3D topography using the PRIMOS system. One skin side around the eye was treated with a cream containing 1% Happybelle-PE. The other side stayed untreated as control

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