

Biomimetic proopiomelanocortin suppresses capsaicin-induced sensory irritation in humans

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Abstract

Sensitive skin is a frequently mentioned cosmetic complaint. Addition of a biomimetic of neuromediator has recently appeared as a promising new way to cure skin care product problems. This study was aimed to assess the inhibitory effect of a biomimetic lipopeptide derived from proopiomelanocortin (bPOMC) on capsaicin-induced sensory irritation in human volunteers and also to compare its protective effect with that of the well-known anti irritant strontium chloride. The effect of each test compound was studied on 28 selected healthy volunteers with sensitive skin in accordance with a double-blind vehicle-controlled protocol. From day 1 to day 13 each group was applied the test compound (bPOMC or strontium chloride) to one wing of the nose and the corresponding placebo (vehicle) to the other side twice daily. On days 0 and 14, acute skin irritation was induced by capsaicin solution and quantified using clinical stinging test assessments. Following the application of capsaicin solution, sensory irritation was evaluated using a 4-point numeric scale. The sensations perceived before and after treatment (on days 0 and 14) was calculated for the two zones (test materials and vehicle). Ultimately the percentage of variation between each sample and the placebo and also the inhibitory effect of bPOMC compared to that of strontium chloride were reported. Clinical results showed that after two weeks treatment, the levels of skin comfort reported in the group treated with bPOMC were significantly higher than those obtained in the placebo group and the inhibitory effect of bPOMC was about 47% higher than that of strontium chloride. The results of the present study support the hypothesis that biomimetic peptides may be effective on sensitive skin.

Keywords: Sensitive skin; Anti irritation; Contact dermatitis; Proopiomelanocortin; Biomimetic peptides; Neurocosmetics

INTRODUCTION

The term sensitive skin generally assigns an excessive and undesirable sensitivity of the skin to usual or prolonged use of typical products such as health and beauty products (1). Management of sensitive skin is usually burdensome for both the physician and the patient. It is required to find a composition of skin care products that does not cause discomfort (2).

During recent years, manufacturers of personal care products have introduced a large diversity of formulations which are created for individuals with sensitive skin. These commercially available products contain different active ingredients such as various

vitamins, minerals, antioxidants, anti-inflammatory agents, traditional herbs, and a variety of peptides (3). Peptide cosmeceuticals are one of the new popular achievements to treat skin inflammation and pigmentation angiogenesis (4,5). Synthetic biomimetic peptides replicate a small, active amino acid sequence of neuromodulators and make them available in the dermis (6). Neuropeptides produced by nerve cells in addition to skin and immune cells constitute preferred messengers to maintain skin balance (7). Cosmetics containing synthetically produced neuropeptides are commonly indicated as neurocosmetics.

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This new approach is based on the interrelation between the nerve system and the skin through special mediators. Neurocosmetic actives can play an important role in skin homeostasis by activating or inhibiting these messengers (8). Skin responses to environmental changes assigned by biological, chemical, physical or electromagnetic factors are regulated by a skin neuroendocrine system that is able to initiate adaptation mechanisms through rapid (neural) or slow (humoral) pathways acting at local or systemic levels (9-11).

The role of hormones in the development of human skin and its importance to produce and release hormones are well known. Human skin cells produce insulin-like growth factors and binding proteins, proopiomelanocortin (POMC) derivatives, catecholamines, steroid hormones and vitamin D from cholesterol, eicosanoids from fatty acids, and retinoids from diet carotenoids. Hormones perform their biological effects on the skin via interaction with receptors for peptide hormones, neurotransmitters, steroid hormones and thyroid hormones (12-14). The skin has established an independent and fully functional peripheral local stress response system equivalent to the hypothalamic–pituitary–adrenal axis (15).

POMC peptides, at first detected as pituitary hormones, have been discovered in various tissues as well as the skin and are expressed by melanocytes, keratinocytes, microvascular endothelial cells, adnexal epithelial cells, mast cells, Langerhans cells, fibroblasts and also by immune cells such as monocytes and macrophages (16,17). POMC is a precursor protein produces many biologically active peptides through a series of enzymatic steps in a tissue-specific manner, resulting the melanocyte-stimulating hormones (MSHs), corticotrophin (ACTH) and β -endorphin (18,19).

All of the melanocortins (α , β , and γ -melanocyte-stimulating hormone and adrenocorticotropin) have melanotropic activity but can have many other effects on skin cells. Based on *in vitro* and *in vivo* findings melanocortins have been demonstrated to regulate immune and inflammatory responses, hair growth, exocrine

gland activity and extracellular matrix composition (20-23).

Biomimetic POMC (bPOMC) is derived from POMC which is a natural precursor of different neuromediators with important roles in skin physiology. *In vitro*, POMC binds and activates the melanocortin-1 receptor (MC1-R) to cause a reduction in production of inflammatory cytokines such as interleukin-8 (IL-8), without influencing melanogenesis (24). IL-8 is known to be a pro-inflammatory and chemotactic cytokines recently termed chemokines. IL-8 has been involved in the pathogenesis of some inflammatory skin diseases (25,26). Interleukin-6 (IL-6) regulates POMC expression and ACTH production in normal pituitary cells (27,28).

Capsaicin is the prominent pungent component in red chili peppers, which has been observed to cause release of neuropeptides from sensory nerve fibers in skin. Application of capsaicin to the skin causes an enhanced sensitivity to noxious stimuli. Capsaicin binds to a receptor called the vanilloid receptor subtype 1 (TRPV1) and activates the C nerve fibers and then causes the peripheral depletion of substance P, calcitonin gene related protein (CGRP) and vasoactive intestinal peptide, thereby resulting in some redness and local swelling (29,30). Strontium salts have been demonstrated to inhibit irritation and inflammation when applied topically. So In the present study, we applied strontium chloride as positive control (31). The objective of this study was to identify and assess the inhibitory effect of bPOMC on capsaicin-induced sensory irritation in humans.

MATERIALS AND METHODS

Subjects

This study was designed in accordance with a double-blind, vehicle-controlled protocols. A total of 56 healthy human volunteers (36 men and 20 women, aged 26-44 years) in 2 groups of 28 volunteers each were recruited and written consent was obtained from all subjects. Volunteers were factory workers recruited from the Goltash Company with a self-reported history of “sensitive skin” and were

sensitive to a prescreening lactic acid facial challenge (32). The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (ID No: IR.MUI.REC.93.3.378).

Materials

The following chemicals were used: bPOMC (NeutrazenTM, Lucas Meyer Cosmetics Co., France), Capsaicin (Ferndale Laboratories, USA), Strontium chloride hexahydrate (Sigma Chemicals Co., USA). Two test samples, a 2.5% bPOMC and 5% strontium salt formulations were prepared using methylcellulose viscoelastic gel. The percentage of test materials was assigned in accordance to similar studies (5,8).

Protocol summary

Volunteers came to the laboratory without applying any face cream and signed a consent form and an information sheet.

Induction of sensory irritation

Hydroalcoholic solution of capsaicin at 3×10^{-4} % was applied to both cheek sites for 10 s and then every minute up to 5 min. After the application of capsaicin, sensory irritation (stinging + burning + itching) was evaluated using the following sensory irritation scale: 0 = absence of sensations, 1 = slight sensations, 2 = moderate sensations, and 3 = severe sensations. An overall reactivity score at day 0 was calculated as follows:

$$\text{Total score} = \sum_{di} = 0.17 \text{ min} - 5 \text{ min} \quad (1)$$

Treatment of sensory irritation

Each group received facial formulation (0.1 g) containing either active ingredient bPOMC or strontium chloride to right side and corresponding placebo (vehicle) to the left side, which was applied to the cleaned cheek sites, extending from the nasolabial fold to the outer cheek by circular movements twice a day for 14 days. Sensory irritation test was performed as mentioned above and the overall reactivity score was calculated on day 14 (32). The sum of scores related to each volunteer at different test times was calculated for the two zones affected by test materials and vehicle both before and after the treatment. The variation of sensations perceived before and

after treatment was calculated with the following formula:

$$\Delta P/D_0(\%) = \frac{TSD_{14} - TSD_0}{TSD_0} \quad (2)$$

$$\Delta V/D_0(\%) = \frac{TSD_{14} - TSD_0}{TSD_0} \quad (3)$$

where, TSD_0 is the total score on day 0, TSD_{14} is the total score on day 14, P is the product zone, and V is the vehicle zone. The percentage of variations compared to the placebo was calculated as follows:

$$\Delta / V(\%) = \Delta P / D_0(\%) - \Delta V / D_0(\%) \quad (4)$$

Abbreviations are as previously described.

Data analysis

Statistical analysis enables determination of the significance of differences observed for the effect of test materials vs placebo after 14 days of twice daily applications. The comparison involved the differences in the zone treated with the product and the zone treated with the placebo. Normal distribution of each quantitative variable was assessed by Kolmogorove-Smirnov test. The data was analyzed using Mann-Whitney U test for observed significance measuring between responses of the two groups. P values less than 0.05 were considered significant.

RESULTS

Overall results are listed in Tables 1, 2 and 3 and illustrated in Figs. 1 and 2. In this work, we investigated the effects of bPOMC (at 2.5%) on skin sensitivity in individuals exposed to stinging test compared to well-known anti-irritant compound strontium chloride (at 5%).

The median of scores attributed by each volunteer at different test times was calculated for the test materials and vehicle zones both before and after the treatment and are shown in Tables 1 and 2.

The median irritation sensation for bPOMC-treated zone was significantly ($P < 0.01$) less than that of the vehicle compared at 0.17, 2, and 3 min on day 0 and day 14 (Table 1).

The median irritation scores for strontium chloride was also significantly ($P < 0.01$) less than those of vehicle group, only at 0.17 min compared on day 0 and day 14 (Table 2).

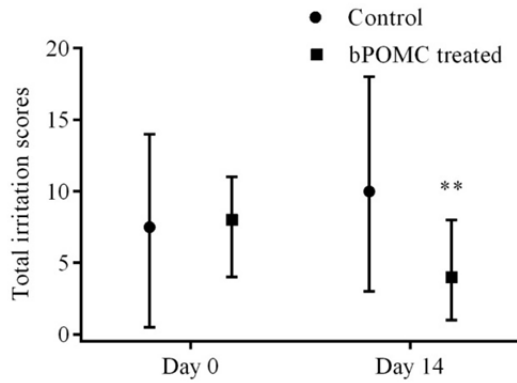


Fig. 1. Anti-irritant effects of bPOMC in methylcellulose viscoelastic gel on capsaicin-induced sensory irritation in human volunteers. (bPOMC) biomimetic pro-opiomelanocortin, Day 0 and Day 14 show the days of studies. All results are expressed as median (range). ** $P < 0.01$ compared with the vehicle-treated group.

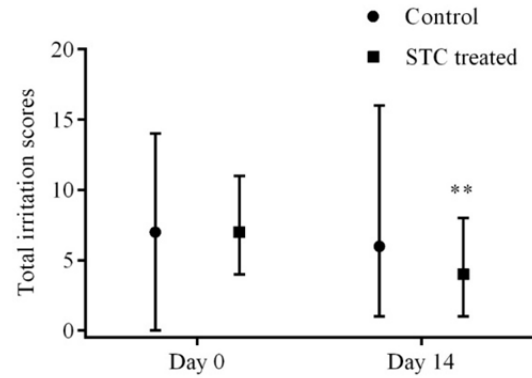


Fig. 2. Anti-irritant effects of strontium chloride in methylcellulose viscoelastic gel on capsaicin-induced sensory irritation in human volunteers. (STC) strontium chloride, Day0 and Day14 show the days of studies. All results are expressed as median (range). ** $P < 0.01$ compared with the vehicle-treated group.

Table 1. Time course of sensory irritation after the application of a solution of capsaicin before and after 14 days of treatment with bPOMC in methylcellulose viscoelastic gel or the vehicle. (bPOMC) biomimetic proopiomelanocortin, (VbPOMC) vehicle on contralateral side of bPOMC zone. Each data point represents the median (range) irritation at each time for 28 subjects. **Significant difference ($P < 0.01$) was observed between formulations and vehicle.

Group	Time (min)					
	0.17	1	2	3	4	5
bPOMC day 14	0 (0-2) **	1 (0-3)	0.5 (0-1) **	0 (0-1) **	1 (0-2)	1 (0-2)
VbPOMC day 14	2 (1-3)	1 (0-3)	2.5 (1-3)	2 (1-3)	1(0-3)	1(0-3)
bPOMC day 0	1 (0-2)	1 (0-2)	2 (1-3)	1 (0-3)	1 (0-3)	1 (0-3)
VbPOMC day 0	1 (0-2)	2 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)

Table 2. Time course of sensory irritation after the application of a solution of capsaicin before and after 14 days of treatment with strontium chloride in methylcellulose viscoelastic gel or vehicle. (STC) strontium chloride, (VSTC) vehicle on contralateral side of strontium chloride zone. Each data point represents the median (range) irritation at each time for 28 subjects. **Significant difference ($P < 0.01$) between formulations and vehicle.

Group	Time (min)					
	0.17	1	2	3	4	5
STC day 14	0 (0-2) **	1 (0-3)	1 (0-2)	1(0-2)	0.5 (0-2)	1 (0-2)
VSTC day 14	2 (1-3)	1 (0-3)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-3)
STC day 0	1 (0-2)	1 (0-2)	2 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)
VSTC day 0	1 (0-3)	1 (0-3)	2 (0-3)	2 (0-3)	1 (0-3)	1 (0-3)

Table 3. The percent reduction of total irritation score of bPOMC and strontium chloride in methylcellulose viscoelastic gel due to a solution of capsaicin. (bPOMC) biomimetic pro-opiomelanocortin, (STC) strontium chloride, (P) Significant difference between bPOMC or STC groups. All results are expressed as median (range).

bPOMC	STC	P-value
87 (-26 - 273)	40 (-325 - 117)	$P < 0.05$

Figs. 1 and 2 show the differences of total sensations perceived before and after the treatment. bPOMC thus limits irritation caused by a neurogenic substance, capsaicin, in comparison with strontium chloride and vehicle-treated groups. The bPOMC viscoelastic gel decreased the total irritation score on day 14 of the study compared to day 0 (4 for day 14 vs 8 for day 0; $P < 0.01$), and was superior to its own vehicle. The strontium chloride viscoelastic gel decreased the total irritation score on day 14 of the study compared to day 0 (4 for day 14 vs 7 for day 0; $P < 0.01$), and was superior to its own vehicle.

Clinical results showed that after a 14-day treatment, the levels of skin comfort reported in the group treated with bPOMC were significantly (87%) higher than those obtained in the vehicle group (Table 3). The differences of sensations distinguished before and after 14 days of treatment by strontium chloride was significantly better than vehicle (40%) (Table 3).

The data demonstrate that both bPOMC and strontium chloride caused inhibition of the uncomfortable sensations caused by the application of a $3 \times 10^{-4}\%$ solution of capsaicin on the wings of the nose. The results suggest that bPOMC is more effective than strontium chloride.

DISCUSSION

The field of biomimetic neurocosmetics has recently appeared as an encouraging new way to overcome cosmetic problems through an action on the cutaneous nervous system. But not much work has been done in this field and their benefits have not been conclusively demonstrated. Our research for the first time measured the efficacy of bPOMC on capsaicin-induced sensory irritation in humans. Considering the sensory irritation is a subjective symptom, there is a high degree of variation between individuals. To quantify this subjective data, we utilized a 0–3 grade scale to evaluate the sensations after 0.17 min, and then every minute up to 5 min post-application of test materials. We supposed this scale could better quantify small changes in subjective responses (33-35).

Evidences suggest that various neuropeptides and neurohormones play a significant immunoregulatory role and the complex cascade of interacting mediators is involved in the physiopathology of sensitive skin (4,33). The physiopathology of sensitive skin includes a nonspecific reaction related to cutaneous sensory innervation through unmyelinated (C) or myelinated (A δ) fibers responding to a range of chemicals and physiologic stimulants (36). Response to noxious stimuli, substance P and CGRP lead to vasodilatation and mast cell degranulation activating a process called neurogenic inflammation (9,37). Classical pathways are then triggered causing a nonspecific inflammation as a result of released eicosanoids and cytokines such as prostaglandin-E2, prostaglandin-F2, tumor necrosis factor-alpha (TNF- α), interleukin-1 α (IL-1 α), and IL-8 (38). Melanocortin MC1 and MC3 receptors, mediate the anti-inflammatory effects of melanocortin peptides. Targeting these receptors could lead to development of new anti-inflammatory therapeutic agents. Furthermore, POMC activities consist of antagonism and down-regulation of adhesion molecules and reduced inflammation by modulation of IL-10 production (13,27).

Skin is a target organ for corticotropin-releasing hormone (CRH) and POMC peptides. Thus, the skin neuroendocrine system mediated via production of CRH hormone and POMC peptides might interact with the skin immune system and organize the skin stress response system against local stress (39,40). POMC peptides exert their effects via five subtypes of heterodimeric G protein-coupled receptors with seven transmembrane domains assigned as melanocortin receptors (MC-1R through MC-5R)(16,23).

bPOMC is an innovative tri-peptide of a greater category named biomimetic peptides, linked to a lipid for optimal penetration and efficacy. Biomimetic molecules are designed to mimic natural products while increasing specificity and efficacy. Biological processes in the body are being closely monitored and active molecules are being studied in search for synthetic and better analogues. The relatively recent appearance of peptides in skin

care products can be explained by the need for more effective actives, for lower dosages, and for purer and better defined compounds. At the present time, such actives are being increasingly included into formulation to provide worldwide cosmetic products (13,41).

Our results show that bPOMC calms and soothes irritated skin and helps to maintain and restore a normal skin sensitivity threshold. bPOMC is a favorable anti-inflammatory agent without influencing melanogenesis. According to previous studies we hypothesized that biomimetic peptides exert their powerful efficacy on the reduction of capsaicin-induced inflammation, through the reduction of the consequences of substance P release and inhibit the release of IL-1-induced IL-8 production (13,42).

According to the studies conducted by Hahn, strontium salts can effectively suppress sensory irritation caused by chemical irritants (43). Papoiu *et al.* showed that the strontium chloride formulation was superior to hydrocortisone on the peak of skin itch intensity (32). So the strontium chloride was considered as positive control.

In the present study, the inhibitory effect of bPOMC was significantly 47% higher than that of strontium chloride, a well-known anti-inflammatory salt ($P < 0.05$). This finding suggests that bPOMC may reduce sensitive skin symptoms related to cutaneous neurogenic inflammation. So the addition of biomimetic peptides to formulations of topical products can significantly reduce the signs and symptoms of irritant contact dermatitis, which is a significant problem for many people using cosmetics and topical formulations (5,43). Comprehensive studies available on epidemiology of sensitive skin reveal that the hyper-reactivity of the skin is more frequently observed in women than men (33). So the most limitation in this study was to choose the volunteer panel composed of a bigger population of women.

CONCLUSION

It seems that in near future biomimetic peptides will represent a new class of inhibitors of sensory irritation and irritant

contact dermatitis. Our study indicates that the addition of bPOMC to personal care products significantly reduces the sensory irritation caused by capsaicin in a comparison with strontium chloride. These clinical data can be partially explained by the *in vitro* findings showing the anti-inflammatory effect of biomimetic peptides. In the light of the revealed anti-irritation efficacy of bPOMC, further studies investigating the antipruritic effect of biomimetic-based formulations in acute and chronic itch conditions would be timely.

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