Topical analgesic creams and nociception in diabetic neuropathy: towards a rationale fundament

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Topical analgesic creams and nociception in diabetic neuropathy: towards a rationale fundament

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Abstract

In diabetes mellitus low grade inflammation is one of the key pathogenetic factors, leading to many of its complications and neuropathic pain. Such inflammatory processes are also documented in skin tissue, where peripheral sensitization originates. We will discuss new findings pointing out that there are multiple important targets in the skin to be influenced by topical analgesics alone or in combination with anti-inflammatory agents. By specifically targeting the skin, analgesia seems possible, effective and safe and thus topical analgesic creams may become an important new treatment modality for the treatment of neuropathic pain. We will present a case and discuss a new rational fundament for the treatment of diabetic neuropathic pain via local mechanisms in the skin, using an analgesic cream consisting of baclofen and the anti-inflammatory agent palmitoylethanolamide.

Introduction

Since the end of last century topical analgesics are increasingly explored and discussed as serious options for treating different classes of pain [1-5]. Such formulations are reported to have a number of advantages over classical painkillers such as absence of troublesome side-effects, low propensity for drug-drug interactions, and low risks for accumulation in poor metabolizers.

Analgesic and anti-inflammatory agents used in compounded topical creams can be selected based on having a multitude of effects at different targets in the skin, thus influencing various biological functions related to nociception and immunity [6]. Keratinocytes for instance are in close functional contact with sensory afferent nerves. In response to noxious stimuli, keratinocytes release various growth factors and pro-inflammatory cytokines [7-9]. These molecules trigger the expression of nociceptive relevant receptors, such as the adrenoceptor, on nerve fibers and other cells in the injured tissue [10,11]. Autonomic nerve endings in the skin release norepinephrine, whereas sensory nerve fibers release neuropeptides [12]. This again leads to a further production of pro-inflammatory cytokines, such as interleukin-6, creating a pain-inflammation sensitization cascade [13]. The cross-talk between nerve endings, keratinocytes and other cells of the skin make the skin a valuable target for compounded multi-target analgesic creams.

In our clinic for neuropathic pain we see exclusively patients suffering from neuropathic pain, who usually are non-responders to classical oral neuropathic pain medication, such as amitriptyline, duloxetine, pregabalin, gabapentin and carbamazepine. Most patients cannot tolerate these classes of medication due to severe side effects, or the prescribed medication does not result in adequate analgesia. Since 2010 we have started to develop a variety of compounded creams leading in general to good responses in refractory patients, without serious side effects.

Case report

In November 2015, a 71-year-old woman with diabetes mellitus type II since 2005, came to our Institute for Neuropathic Pain with complaints of neuropathic pain in both legs up to her knees. In 2009 neuropathic pain started in both her feet, and at the first visit was characterized as pins and needles, burning and painful cold with numbness in the same area. She scored her pain as 8 on the 11-point numerical rating scale (NRS). Pain worsened during the day. Her glucose level was under control with gliclazide 80 mg twice daily, metformin 500 gm trice daily and a short acting insulin 36 unit per day. Oral amitriptyline and pregabaline resulted in too much side effects, and patient felt quite drowsy. Physical examination revealed the following: lowered knee tendon reflexes, absent Achilles tendon reflexes, disturbed warmth/cold sensation up to 15 cm below her knees, absence of vibratory sensation in malleoli and metatarsalia of both feet, hypesthesia for touch and pinprick and no allodynia. We tested clonidine 0.2% cream and baclofen 5% cream in a cream base including palmitoylethanolamide 1%. After 20 minutes the patient experienced 50% pain reduction of her pain at the area were baclofen 5% was applied. Clonidine 0.2% was less effective. Following this positive response-test we prescribed baclofen 5% cream with the instruction to apply the cream up to 4 times daily, depending on the duration of the analgesic effect. One month later she reported that all pain sensations were disappeared due to the application of baclofen 5%-palmitoylethanolamide 1% cream two times daily. The only remaining sensation was numbness. The patient is using this cream already for 7 months in a row, without experiencing any side effects.

Low grade peripheral inflammation in diabetes

Low grade inflammation is one of the key pathogenetic factors

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in diabetes, and recently an identified therapeutic target for diabetes mellitus [14,15]. Such chronic low grade inflammation is recognized also to play a role in other axonal neuropathies (e.g. thin fiber neuropathy, sarcoidosis-associated neuropathy) and post-infectious neuropathies [16,17]. Low grade inflammation has even been identified in Charcot-Marie-Tooth neuropathies as a disease amplifier, and is thus seen as a new target also for this specific disease [18].

The cell surface enzyme neutral endopeptidase, which degrades substance P, was used as a peripheral marker for inflammation in diabetic skin. This marker was found to be significantly more frequent in skin of diabetes patients compared to normal skin [19]. The authors pointed out that elevated levels of this marker in the skin may contribute to enhanced neuro-inflammatory signaling [19]. Low grade inflammatory processes may subsequently lead to peripheral nerve damage, enhance transmitter release within the spinal cord and induce central sensitization [20]. This sequence of events, leading from peripheral derangements to central wind-up and sensitization, might also plays a role in the chronification of acute pain as seen in post-surgical pain syndromes.

Skin matters in diabetic neuropathic pain

In the epidermis we find an intimate interplay between many non-neuronal cells, such as keratinocytes, with various dermal immunocompetent cells, such as dendritic cells, gamma-delta T cells and mast cells, as well as with the nerve endings in the skin [21,22]. Sensory nerves extend into the epidermis and make close contact with keratinocytes via membrane-membrane apposition [23]. Non-neuronal cells of the skin can release many neuroactive substances, which can contribute to the initial transduction process in the nerve endings [24,25]. Non-neuronal cells, such as the mast cells and keratinocytes, cross-talk with these nerve endings. Nociceptors terminate in the skin as free nerve endings and can directly contact injured tissue, which all serve as a sensory receptors of the injury [26]. In skin tissue we also find a great variety of receptors and inflammatory markers which play a role in nociception such as the adrenoceptors, voltage-gated sodium channels, temperature-sensitive transient receptor potential ion channels, substance P and inflammatory markers such as caspase-1 and interleukin receptors. Clearly this is all in support for topical treatment: 'Skin matters in pain treatment!' [27].

Palmitoylethanolamide as a mast cell modulator

Skin keratinocytes express neurotrophic growth factor (NGF) after loss of contact with the axon, as in painful diabetic neuropathy, and subsequently nerve fibers in skin exposed to excess of NGF are triggering hyperalgesia [28]. Professor Rita Levi-Montalcini, who was awarded the Nobel prize for her work in the field of NGF, pointed out that certain immune-competent cells in the skin producing NGF, such as the mast cells, can be targets for local modulation with autacoids. She proved her hypothesis by administering the autacoid palmitoylethanonolamide in various animal models and could demonstrate this compound could indeed reduce the mast cell production of NGF. These experiments led to the use of palmitoylethanolamide in mast cell related disorders as well as in neuropathic pain [29-31]. Palmitoylethanolamide is currently available as a food supplement (400 mg capsules) as well as a topical cream (1%) [32].

Topical analgesia

Given the above lines of argumentation, we feel topical treatment of neuropathic pain may bring relief of pain, through influencing multiple targets in the skin, related to nociception and inflammation. These topical agents can be used either as monotherapy or as part of multi-model therapy. We compounded different analgesic and anti-inflammatory agents in a cream base and currently explore the value of such analgesics and palmitoylethanolamide in these creams. Doing so we have developed a variety of compounded creams in one specific base. This base is optimally suited to contain both lipophilic as well as hydrophilic agents, enabling mixing various analgesic components in order to create a multi-target topical cream. We have successfully combined amitriptyline, ketamine, clonidine, baclofen with the autacoid and anti-inflammatory agent palmitoylethanolamide and reached therapeutic synergies [5,33-36].

Conclusion

The skin needs to be recognized as an important therapeutic inroad in treating neuropathic pain via the many pathogenetic mechanisms we identified and discussed. Both anti-inflammatory as well as analgesic agents can serve in topical formulations to target and influence the various components of the skin in diabetic neuropathic pain. Topical creams might contribute significantly to the treatment of neuropathic pain in diabetes mellitus.

Conflict of interest statements

The authors report no conflict of interest.

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