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Short Communication

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Posttranslational Sodium ion Channel Modifications and the use of Topical Phenytoin in Painful Diabetic Neuropathy (PDN)

Jan M. Keppel Hesselink[1, 2]

[1]*Department of health, University of Witten/Herdecke, Germany*

[2]*Institute for Neuropathic Pain, Bosch en Duin, the Netherlands*

***Corresponding author:**
Jan M. Keppel Hesselink, Department of health, University of Witten/Herdecke, Germany;Institute for Neuropathic Pain, Bosch en Duin, the Netherlands. Email: jan@neuropathie.nu

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Abstract

Phenytoin is a broad acting sodium channel blocker we deem fit for topical formulations to treat localized peripheral neuropathic pain. We tested this cream in a number of patients suffering from neuropathic pain syndromes and found it to be especially of use in small fiber neuropathic pain and in painful diabetic neuropathy. The fact that patients report an onset of action within 30 minutes, and the absence of detectable plasma levels of phenytoin, support an intra-epidermal mechanism of action. In this paper, we launch a hypothesis why phenytoin might be of particular use in peripheral neuropathic pain syndromes such as painful diabetic neuropathy.

Keywords: Diabetes Mellitus, pathogenesis, pain, treatment, mechanism, methylglyoxal

Abbreviations

Painful Diabetic Neuropathy - PDN
Dorsal Root Ganglion - DRG
Diabetes Mellitus - DM
Small Fiber Neuropathy - SFN
Transient receptor potential cation channel, subfamily A -TRPA
Sodium channel - Nav

Introduction

At our institute for neuropathic pain treatment we started developing topical formulations containing (co-) analgesics in 2010. We discovered that in order to create an effective analgesic cream, relative high concentrations of (co-) analgesics are needed, for instance 10% of ketamine or amitriptyline [1]. In order to try improving the number of patients responding, we created a phenytoin 10% cream. Phenytoin is a broad acting sodium channel blocker and we argued that such drug would possibly have superior properties due to its pharmacological profile and the fact that it is a small lipophilic compound which easily penetrates the epidermal layers. Meanwhile we treated many patients by prescribing 10%,15% and even 20% phenytoin creams, and found no detectable phenytoin levels in the plasma, indicating a dermal mechanism of action, as we described elsewhere [2]. In this paper, we present the rationale why phenytoin in a topical formulation might have efficacy in small fiber neuropathic pain and especially in painful diabetic neuropathy (PDN).

Painful diabetic neuropathy

Around half of older type 2 diabetic patients having signs and symptoms of a distal neuropathy [3]. The most common painful neuropathy is characterized as a chronic sensorimotor distal symmetrical polyneuropathy. PDN is characterized by the classical symptoms of localized peripheral neuropathic pain, such as burning, shooting and electric shocks. Even when treated by recommended drugs, the suffering remains serious. Ourpharmaco-therapeutic options are just a few, all characterized by frequent and disabling side effects: gabapentin, pregabalin, duloxetin, or if pain is still inadequately managed, adding an opioid to these analgesics [4]. Recently the latter step was discouraged, due to an increase in adverse event risks leading to death. Moreover, it is also discouraged to prescribe one of the gabapentanoids in in patients with peripheral edema. This situation clearly supports the development of new therapeutic inroads.

As said, at our institute for neuropathic pain we initiated the development of topical formulations containing relative high concentrations of co-analgesics, selected on the base of the likelihood of a plausible peripheral mechanism of action for these drugs. There, where we did not follow this principle, for instance compounding a central acting analgesic such as gabapentine in a cream, we stumbled upon therapeutic failures, leading us to discourage this approach [5]. After prescribing a number of various co-analgesics in topical formulations, such as ketamine, baclofen, amitriptyline and clonidine, we selected the unselective, broad-acting sodium channel blocker phenytoin for exploring in more detail in the treatment of various peripheral neuropathic pain syndromes. Step by step our experiences lead us to belief that especially disorders where small fiber neuropathy is playing a role in the pathogenesis of pain, we find

most responders to topical treatment with phenytoin formulations [6-8]. Here we will discuss a hypothesis supporting our assumption.

Small fiber neuropathy and posttranslational channelopathies in PDN

It has been speculated since decades, that if metabolism of the distal ends of the long axons leading impulses from the nociceptors to the dorsal root ganglion (DRG) is compromised, either by lack of nutrients or oxygen, or by toxic metabolites, the small fibers start to malfunction and will degenerate, leading to burning pain and associate symptoms [9]. Toxic metabolites are quite well known to accumulate in the intracellular milieu of nerves in DM [10]. It is therefore plausible that such neurotoxic metabolites compromise the function of small fibers. And small fiber pathology seems to stand at the beginning of the pathogenetic cascade in PDN, as patients diagnosed with DM for at least 10 years, even without clear signs or symptoms of peripheral neuropathy, in general are found to have SFN [11].

The reduction of Intraepidermal nerve-fibre density has therefore been identified as a biomarker of the course of neuropathy in patients with PDN [12]. Even in patients with glucose intolerance, without the diagnosis of diabetes, C-fiber neuropathy has been documented, pointing to the detrimental effects ofhyperglycemia on neuronal physiology [13].

It has long been speculated that certain metabolites related to glucose were responsible for many aspects of its pathology. Already as early as in 1981 it was pointed out that DM led to a three-fold increase in peripheral nerve glycosylation, measured in tissue homogenates from diabetic rats and dogs [14]. The relevance of glycosylation of nerve elements have been supported by certain experiments, for instance by intra-plantar injections of the glycosylation inhibitor neuraminidase indiabetic mice, which completely reversed mechanical and thermal hyperalgesia [15].

Methylglyoxal and sodium ion channels dysfunction

Recently is has been found that tissue levels of the glycolytic toxic metabolite methylglyoxal play a key pathogenetic role, as methylglyoxal leads to posttranslational modifications of key sodium ionchannels on the nociceptors, the Nav1.8, and Nav1.7, as we will discuss in more detail hereunder.

Methylglyoxal concentrations in plasma are related to the degree of hyperglycemia in diabetic patients, and the increased levels are due to both an enhanced production via the glycolysis andan impaired enzymatic degradation by glyoxalase [16]. The latter enzyme concentrations in peripheral nerve tissue is quite low, correlating with high endoneural concentrations of this detrimental glucose metabolite [17].

Methylglyoxal was found to compromise the functions of the nerves and increases its release of calcitonin gene-related peptide, while inducing nociceptor hyperexcitability, thermal and mechanical hyperalgesia [18]. Plasma methylglyoxal in patients who have diabetic pain were found to be significantly higher in diabetic patients who do not experience pain [19]. Both posttranslational modifications as well as gain-of-function variants of sodium channels are documented frequently in cases of idiopathic painful SFN. Nav1.7. mutations have been shown to lead to overexcitation of the DRG, resulting in increasing pain [20-21]. Axonal degeneration and reduced axonal regenerative capacity have also been contributed to the Nav1.7 mutations in PDN [22]. Comparable findings exist for Nav1.8 mutations, and such mutations have been described in patients suffering from SFN. The above described channelopathies led to the idea that these Nav1.8 and 1.7 mutations may offer a plausible explanation for pain in SFNs and are suggestive for new targeted treatment [23].

Lysine and arginine seem to be the primary targets for binding tomethylglyoxal. For the TRPA ionchannels, calcium imaging studies have indicated that high intracellular concentrations of methylglyoxal induce fast channel activation, resulting ina rise of intracellular calciumcncentrations [24]. Furthermore, various protein-arginine-methylglyoxal posttranslational modifications are known, making this mechanism also plausible for the modification of sodium channels. In fact, such post translational modifications have been described, making the channel more available for sodium influx [22-23]. Furthermore, there are indications that the increased methylglyoxal concentrations influence ionchannel trafficking,also resulting in an increased sodium influx leading to nociceptive hyperexcitability [25].

Six of the nine sodium channels have been identified related to neuropathic pain, and are expressed in the nociceptors in the skin, probably the Nav1.7 and Nav1.8 being the most important ones [26]. Sodium channels are found on afferent fibers and nociceptors, as well as in epidermal structures such as the keratinocytes and the immune-competent cells [27]. Those cells seem to cross-talking with each other and with the nociceptors. The use of a non-selective sodium channel blocker in compounded analgesic topical formulations to inhibit over activity of these ion channels in the epidermal tissue compartment therefore seems a plausible choice [27]. Phenytoin is a non-selective blocker, and thus blocks a number of subtypes of sodium channels, most probably due to the fact that its binding-site is situated at the inner cytoplasmic membrane: the inner vestibule of the pore (figure 1a and b). This is a conservative site for all sodium ion channels. Moreover, the sites of the glycolysation of the channels arealso situated at the intracytoplasmatic loops.

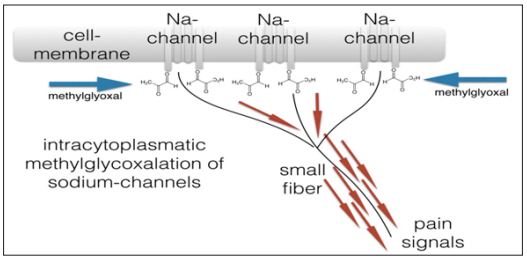

Figure 1a: Methylglucoxalation of intracytoplasmatic loops of the sodium channel leads to enhanced pain signals

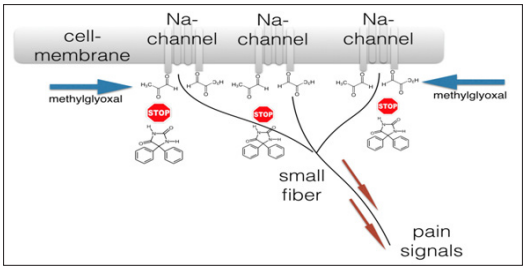

Figure 1b: phenytoin inhibits the sodium channel activation by the methylglucoxalation leading to fewer pain signals

Conclusion

If the small nerve fibers and epidermally situated nociceptors are in a hyperexitatory state due to posttranslational modifications of the sodium channels and changed channel trafficking, a broad acting topical applied sodium channel blocker, able to penetrate the epidermis seems a plausible therapeutic option. Phenytoin is a small lipophilic molecule able to do so, and if formulated in a cream, patients report back to us that analgesic effects are noticeable within 30 minutes after application.Due to such quick response time, and as phenytoin plasma levels are below the threshold for detection, its mechanism of action in peripheral neuropathic pain states seems to be located in the skin.

Conflict of interest

The author is a patent holder of two patents related to the topical formulations of phenytoin in the treatment of neuropathic pain.

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