Microglia and mast cells: 
new targets for the treatment of chronic pain

Abstract. The article is devoted to the problem of effective management of chronic pain. A review of the known mechanisms of development and maintenance of chronic pain and possible methods of influence is given. One of the reasons for the lack of chronic pain treatment effectiveness in some patients is the use of treatment regimens with drugs acting exclusively on the targets located in the nerve structures. Today an important role of microglia and mast cells in the development and maintenance of chronic pain conditions is well acknowledged. A new class of drugs from the group of acylethanolamides is described. One of the representatives of this group is palmitoylethanolamide. This drug may modulate the activity of microglia and mast cells, thus increasing the pain threshold and the effectiveness of therapy. The use of palmitoylethanolamide in patients with chronic pain can increase the effectiveness of therapy.

Keywords: chronic pain; microglia; palmitoylethanolamide

Introduction

The chronic pain is a healthcare problem in many countries all over the world; it causes suffering to an individual patient and the patient’s family, environment and society in general [1, 2]. According to the reference sources, the chronic pain is rather prevalent, and by various estimates, it accounts for 20 to 40 % cases in the general population [3–5]. The chronic inflammatory (nociceptive) pain is usually caused by the injury or tissue damage, while the chronic neuropathic pain is provoked by the somatosensory nervous system injuries [6–8]. It is worthy of noting that the chronic pain of a predominantly inflammatory/autoimmune genesis (for instance, attending the rheumatoid arthritis) may be associated with a neuropathic pain component [9, 10]. For instance, the leg pain may be attended by the immune cell activation and inflammatory reactions [10, 11].

The treatment of chronic pain is a complex issue. At present, the clinical practice uses the following types of painkillers: non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antidepressants, topical anesthetics, regular analgetics, and opioids. Despite the wide spectrum of medications, one can rarely achieve complete chronic pain alleviation; some patients also report side effects during therapy, resulting in a treatment regimen correction [12]. The search for and development of the effective and safe chronic pain treatment methods hold a particular relevance for the modern medical and pharmaceutical science.

As the pain impulses are being transmitted via neurons, the effect of most accessible medications at the market is targeted towards them [13]. However, in case of chronic pain, the somatosensory system neurons are not the only participants of this process. A lot of reference sources testify to an importance of inflammatory processes (neuro-inflammation) and the engaged glial cells [14, 15]. The neuroinflammation is characterized by the immune cells infiltrating the damaged tissue, healthy and glial cells being activated and anti-inflammatory mediator being produced at an increased rate; the latter playing a pivotal role in the chronic pain maintenance at the level of peripheral and central nervous system [16–18]. The chronic neuroinflammatory condition may be sustained by a long-term imbalance between the pro- and anti-inflammatory mediators [19–21].

Pain chronization mechanisms

Relying on the neuropathic pain definition, one considers that its occurrence is preceded by the nerve injury. However, the nerve injury is not always resulting in a neuropathic pain [22, 23]. One of the possible pain chronization mechanisms is an inflammation of certain peripheral or central nervous system site, observed right after their structure’s renewal at the site of initial nerve injury [24, 25]. These neuroinflammations result in a glial dysfunction accelerating and maintaining the inflammatory reactions.
Other mechanisms promoting the pain chronization include a long-term potentiation, peripheral and central sensitization, pathological neuroplasticity, ectopic neuronal activity and disinhibition. This paper will not review these mechanisms in detail.

**Microglia and mast cells**

The mast cells were first described by Paul Ehrlich, the Nobel Prize winner, in 1878, characterizing the histochemical properties and typical morphological cell phenotypes [26]. The human mast cells originate in the cerebral cells, i.e. CD34+/CD117+ pluripotent precursor cells [27]. The mast cells are circulating in the blood flow as the precursor cells, reaching their differentiation in those tissues where they will function. The mast cell role is well-documented for the allergic and inflammatory reactions, associated with Immunoglobulin E (IgE) [28, 29].

The damage of peripheral nervous system results in the slightly manifested inflammatory processes. There are such pro-inflammatory mediators described, as nitrous oxide, bradykinin and prostaglandins (PG). Under their influence, the blood vessel endothelium gets more permeable at the damaged sites, the leukocytes migrating into the damaged tissues [30].

The central nervous system (CNS) involves the blood—brain barrier (BBB) dysfunction and accentuates its permeability. It causes the leukocytes migrating from the blood flow into the surrounding tissues, where they are transformed into the microglial cells [31–34]. The activated microglia produces ever more anti-inflammatory cytokines, namely Interleukin-1 (IL-1) and tumor necrosis factor (TNF). If its turn, the IL-1 activates astrocytes, producing greater amounts of IL-1 and creating a closed circle of pathological reactions [35–37]. These changes are associated with new synaptic connections, maintaining the pain impulse transmission and enabling the extant neuronal connections being re-constructed [38–40].

**Microglia and astrocytes**

The microglial cells and astrocytes (macroglia representatives) are neuronal by nature; however, they do not have the capacity of getting alert under the nerve impulses [21, 41, 42]. By contrast, they are surrounding and interacting with neurons, they also play a pivotal role in their modulation and maintenance of inflammatory processes in the nervous tissue; they also increase the neuronal excitability, accentuation and prolongation of the pain impulsation transmitted [43, 44].

The microglial cell and astrocyte rates are greatest in their quantitative representations; they make up 70 % of all nerve cells [45]. The microglial cells initiate the neuroinflammatory processes in the CNS. It was confirmed that after 2 days after the peripheral nerve injury there occurs a pronounced proliferation of microglial cells into the bone marrow [46]. Furthermore, the microglia is implied to trigger the neuroinflammatory processes, and then they are developing ever more, sustained by astrocytes [24].

The astrocytes are most widely represented by numbers in the CNS cells; they are significantly influencing the neuronal activity. The astrocytes are star-shaped cells with long and thin processes, which take a strategic position in the CNS right between the vessels and neurons. They are affecting the neuronal activity and neurotransmitter production [43]. The astrocytes have receptors on their surface, producing a great amount of anti-inflammatory substances. A sole astrocyte may contact with 100, 000 synapses, using its numerous processes [47, 48]. This fact accounts for a huge number of astrocytes affecting the synaptic activity.

One of the mechanisms of astrocyte affecting the synaptic activity is Ca^{2+} located inside the cells. The Ca^{2+} release may be stimulated by various anti-inflammatory substances [49, 50]. The G-proteins are bound to the astrocyte surface receptors, resulting in Ca^{2+} being released from the astrocyteendoplasmic reticulum (ER) and the so-called Calcium wave being created [51]. This “wave” is able to modulate the neuronal synaptic activity, significantly increasing the impulsation rate and promoting the pain chronization [52, 53].

At present, the well-known processes of pain chronization allow us to predict that the future approaches of search for and development of new molecules to treat the chronic pain will be targeted towards the microglial cells and mast cells; this process will promote the redressing of pro- and anti-inflammatory mediator balance [19–21].

**Glial cell effect capacities**

Palmitoylethanolamide (PEA) is one of the best known and thoroughly studied substances able to affect the microglial cells and astrocytes. This molecule belongs to the class of endogenous aciletanolamides, whose great numbers are present in various tissues, namely the nervous one (Fig. 1) [54]. This molecule was first described in 1990s by the research group of Rita Levi-Montalcini, the Nobel Prize winner [55]. The PEA was found to affect the mast and glial cells, reducing their activity [56–58]. Under normal conditions, the PEA is synthesized by the human body and maintained at a certain level, depending on its functional state [54]. For instance, in case of stress, tissue damage and pain-attended conditions, the PEA rate diminishes [59].

The animal studies demonstrate the PEA’s capacity to influence the inflammation, reducing it, and, as a result, alleviating the painful sensations [60]. This effect was dose-dependent both for the chronic inflammation models and chronic neuropathic pain, and it enables not only the pain alleviation but also the peripheral nerve morphology preservation, endoneurial edema diminishing, mast cell activation and pro-inflammatory mediator production in the damaged tissues [61–64]. Relying on the experimental data, one may conclude that the PEA affecting various processes in the nervous tissue has disease-modifying capacities.

In the recent years, there are a great number of clinical trials confirming the PEA painkilling capacities under various conditions attended by the chronic pain [65, 66].

One of the watershed PEA clinical trials is the Italian group study headed by Guida [67]. The authors performed...
a double non-blind placebo-controlled randomized trial recruiting 636 patients suffering from the lower back pain with a confirmed compression of lumbosacral nerve radices. The average pain rate by the visual analogue scale (VAS) was 6.5 points. The patients were subdivided into three groups: the first one received placebo, the second one - the PEA at a daily dose of 300 mg, the third one - the PEA at a daily dose of 600 mg. The results obtained after 3 weeks of treatment were as follows: in the placebo group, the pain rate diminished from 6.5 to 4.5 points by VAS; in the PEA group of 300 mg/day, the pain rate diminished from 6.5 to 3.5 points by VAS; in the PEA group of 600 mg/day, the pain rate diminished from 7.1 to 2.1 points by VAS. The lower PEA dose (300 mg) was significantly more effective than placebo, while the higher PEA dose (600 mg) was significantly more effective than its lower dose or placebo. The adverse side effects were not observed in either patient.

Another clinical observation by Domenico Chirchiglia et al. studied the PEA prescription effect for the patients suffering from the chronic pain associated with a radical pathology of lumbar spine though having no indications for surgery [55]. There was a retrospective analysis of a series of 100 clinical cases, each of them undergoing clinical-diagnostic studies revealing a presence of vertebral and intervertebral disc pathologies, namely of degenerative character (spondyloarthrosis, spondylodiscarthrosis, disc protrusion) excluding the herniated discs, which required surgery. All patients receiving the ultramicronized PEA: during the initial 10 days in a sachet dose of 1200 mg/day, during the next 20 days in a tablet dose of 1200 mg/day, and during the next month in a tablet dose of 600 mg/day. During the initial 4 days, the patients took 500 mg of Paracetamol and 30 mg of Codeine once a day, and further on, only in case of need. There were several interesting findings obtained on the diminished pain rate (Fig. 2-4). It is worthy of note that no patient had any side effects.

Another study assessed the efficacy of 1200 mg dose of the ultramicronized PEA once a day to complement the basic therapy of patients with a diabetic or posttraumatic neuropathic pain [68]. 30 patients with a chronic neuropathic pain were examined at the onset of additional therapy, and at the 10th and 40th day of therapy. The basic therapy remained unchanged. As a result of additional therapy use, there was a significant pain rate reduction by VAS at the 10th day of treatment (from 8.20 ± 1.53 points to 6.40 ± 1.83 points (p < 0.002)). At the 40th day of therapy, the pain rate by VAS diminished to 5.80 ± 2.04 points (p < 0.001). The study revealed a significant reduction of pain rate with

![Fig. 1. The PEA molecule structure](image1)

![Fig. 2. The pain intensity dynamics of 72 patients suffering from a pronounced pain with initial VAS indices from 8 to 10 points. With treatment, the mean indices reduced from 8.7 ± 0.1 to 6.40 ± 0.15 points at the 30th day, to 4.60 ± 0.29 points at the 60th day, * - p < 0.0001](image2)

![Fig. 3. The pain intensity dynamics of 14 patients suffering from a moderate pain with initial VAS indices from 5 to 6 points. With treatment, the mean indices reduced from 5.3 ± 0.1 to 2.6 ± 0.1 points at the 30th day, to 0 points at the 60th day, * - p < 0.0001](image3)

![Fig. 4. The pain intensity dynamics of 14 patients suffering from a minor pain with initial VAS indices from 2 to 4 points. With treatment, the mean indices reduced from 3.5 ± 0.2 to 1.7 ± 0.1 points at the 30th day, to 0 points at the 60th day, * - p < 0.0001](image4)
the ultramicronized PEA; though it had a lot of limitations including a short period of observation and open study design.

The PEA medical form

The PEA is poorly dissolved in water; this is why the solubility coefficient is often a barrier in reaching the high bioavailability while ingesting the drug. The solubility coefficient depends on many various factors, one of them being the size of PEA particles. Most clinical trials use the micronized or ultramicronized PEA. The smaller size of PEA particles allows reaching a quicker absorption due to an increase of particle surface’s general area (Fig. 5) [65].

Another trial shows the PEA efficacy in osteoarthritis (OA)-attended pain reduction [69]. The OA pain is considered to belong to a mixed type, involving nociceptive and neuropathic components simultaneously. There was a double blind randomized group controlled trial of 24 patients suffering from the temporomandibular OA. The patients were divided into two groups: the first group (n = 12) received the PEA (300 mg in the morning plus 600 mg in the evening, for 7 days); the second group (n = 12) received Ibuprofen (600 mg 3 times a day during two weeks). The parameters controlled by this trial were the frequency of occurrence and intensity of spontaneous pain, as well as the degree of widest mouth opening. As a result of treatment, both parameters increased to a significant extent in the PEA group rather than in the Ibuprofen group.

The PEA effect was explored in 8 clinical trials involving patients with back pain, sciatic nerve compression and median nerve carpal syndrome; all in all, there were 1,366 patients involved. Gatti et al. held a major observation of 610 patients suffering from various chronic pain syndromes [70]. 331 patients had lumboischialgia, 54 patients had articular pains, 44 patients had post-herpetic neuralgia, 32 patients had diabetic neuropathic pain, 32 patients suffered from pain following a failed back surgery, 22 patients had oncological pain and 51 patients had compound pain syndromes. At the beginning of the trial, the mean pain index by VAS was 6.5 points. The patients were receiving the PEA in a dose of 600 mg twice a day during 3 weeks with a subsequent transfer to a once-a-day regimen during 4 weeks. The PEA was added to the basic anti-pain therapy or used as a monotherapy. With the PEA, the mean pain index by VAS decreased from 6.4 ± 1.4 points to 2.5 ± 1.3 points. The patients who received no basic therapy registered a similar PEA efficacy in the chronic pain rate reduction. Furthermore, there were no side effects or drug interactions confirmed for the PEA use.

Conclusions

Having analyzed the present reference data, one suggests that neuroglial and mast cells play a pivotal role in the development and maintenance of chronic pain and neuroinflammation. The efficacy demonstrated by the PEA in various clinical trials enables us to consider the PEA a promising molecule within the frameworks of complex therapy, considering a good tolerance and low probability of side effects associated with the medication.

Conflicts of interests. Author declares the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Мікроглія й тучні клітини: нові мішені для лікування хронічного болю

Резюме. Стаття присвячена проблемі ефективного управління хронічним болем. Наводиться огляд відомих на сьогодні механізмів розвитку й підтримки хронічного болю й можливих методів впливу на них. Однією з причин недостатньої ефективності лікування хронічного болю в деяких пацієнтів є використання схем лікування препаратами, що діють в основному на нервові структури, тоді як на сьогодні встановлена важлива роль мікроглії й тучних клітин у процесах розвитку та підтримки хронічних болю.

Ключові слова: хронічний біль; мікроглія; пальмітоїлетаноламід