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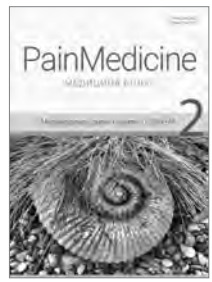

Allodynia and hyperalgesia: review

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Abstract. *The main purpose was to highlight the problem of hyperalgesia and allodynia. Main anatomic structures, which participate in nociception were mentioned in this article, with pathologic and pathophysiologic changes, that can be caused by hyperalgesia and allodynia. Main methods of diagnostics and assessment of mentioned symptoms were represented along with the modern approaches to treatment and prevention.*

Keys words: *hyperalgesia, allodynia, treatment, prevention, pathologic.*

Pain is a huge and increasing problem nowadays, which affect around one fifth of the population. This problem is more acute in ageing populations with chronic conditions, such as diabetes and osteoarthritis, which may provoke a higher occurrence and duration of pain [1]. Pain, in terms of hyperalgesia and allodynia, is a common symptom of various diseases and has been developed as an adaptation for the protection of damaged tissues, but increased sensitivity to pain can last long after the initial problem has disappeared. So, in such a case we can state, that pain is no longer a symptom, but a disease [2], which require certain approach in diagnostics and management.

When this problem was recognized for the first time, only the term "hyperalgesia" have existed, which have been defined as "a state of increased intensity of pain sensation induced by either noxious or ordinarily non-noxious stimulation of peripheral tissue" [3]. In 2008, the term of allodynia was introduced by International Association for the Study of Pain (IASP) task force, which divided the initial definition of hyperalgesia into two: one for hyperalgesia and second for allodynia.

According to the IASP, allodynia is defined as "pain in response to a nonnociceptive stimulus", with the following comment: "this term should only be used, when it is known that the test stimulus is not capable of activating nociceptors" and hyperalgesia is defined as "increased pain sensitivity', with the following comment: "Hyperalgesia may include both a decrease in threshold and an increase in suprathreshold response". Differences between allodynia and hyperalgesia according to the new definitions are described at the Figure 1.

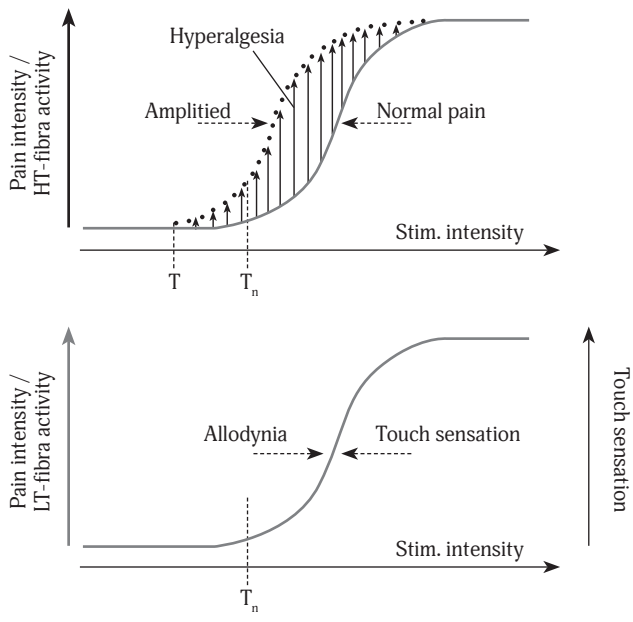

Fig. 1. Differences between allodynia and hyperalgesia [2]. T_0 – normal pain threshold, T_S – pain threshold after sensitization, $T_{0/S}$ – normal threshold to touch sensation which is equal or close to the threshold for allodynia

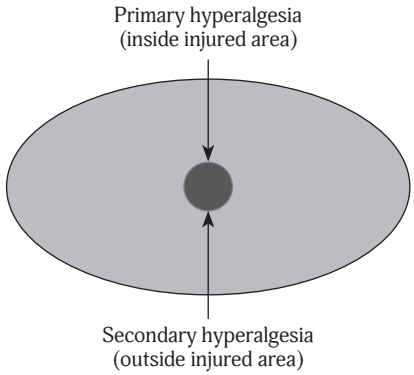

Fig. 2. Scheme of primary and secondary hyperalgesia [4]

So, according to the modern definitions all forms of the pain intensity increasing can now be accumulated under the term of hyperalgesia (red area in the top graph) and the term of allodynia should only be used in case, when the pain is provoked by low-threshold fibers.

Hyperalgesia is divided into two main groups: primary and secondary. Primary hyperalgesia occurs at the site of injury, while secondary hyperalgesia can occur in adjacent or remote areas from the site of injury. Which can be seen at the Figure 2.

Features of primary and secondary hyperalgesia differ. As it is mentioned in the Table 1, there is hyperalgesia to mechanical stimuli in the site of injury and surrounding area, but hyperalgesia to heat develops only in the site of injury, but not in the adjacent tissues [5, 6].

Table 1. Mechanical and heat hyperalgesia spread [4]

	Primary	Secondary
Mechanical hyperalgesia	Yes	Yes
Heat hyperalgesia	Yes	No

Development of the hyperalgesia syndrome is a complicated process and involves different structures at different levels of central neural system. These include sensory nerve fibers, spinal cord cells and tracts, brain nuclei and efferent nerve fibers.

To sensory nerve fibers refer:

1. Capsaicin-sensitive C-fibers [7, 8].
2. IB4-sensitive C-fibers [9].
3. Vagal afferents [10].
4. Aβ-fibers and Aδ-fibers [24]. (see

Nerve fibers have different characteristics and cause different sensations during the nociception. Main characteristics of afferent nerve fibers is represented in the Table 2.

Myelinated Aδ-fibers and C-fibers may provoke different pain sensations, which can be seen at the Figure 3, so, Aδ-fibers cause sharp punctated sensation, which is followed by a diffuse burning like sensation after the activation of slow C-fibers [24].

Tissue damage provoke the release of different substances, which can modulate pain sensation and cause local

Table 2. Afferent nerve fibers and their characteristics [24]

	Aβ-fibers	Aδ-fibers	C-fibers
Location	Skin	Skin	Skin, muscle and visceral organs
Diameter	6 to 12 μm myelinated	1 to 5 μm myelinated	0.2 to 1.5 μm unmyelinated
Conduction	35 to 75 m/s	6 to 30 m/s	0.5 to 3 m/s
Role	Light touch, proprioception	Temperature, Nociception (mechanical, thermal)	Nociception (mechanical, thermal and chemical)

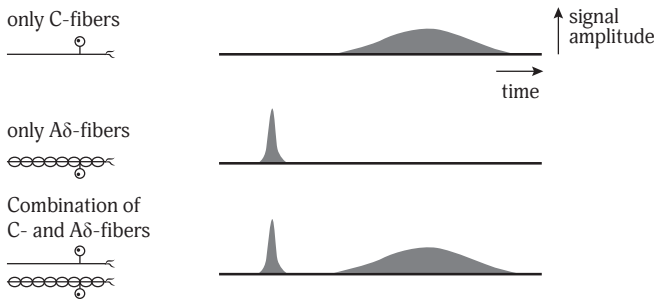

Fig. 3. Activation of different afferent nociceptive pathways

Table 3. Substances, that are released after the tissue damage

Substance	Source
Potassium	Damaged cells
Serotonin	Platelets
Bradykinin	Plasma
Histamine	Mast cells
Prostaglandins	Damaged cells
Leukotrienes	Damaged cells
Substance P	Primary nerve afferents

manifestations after the tissue damage. These substances and their source is listed in the Table 3 [25]

Spinal cord cells include the following:

1. Spinal dorsal horn neurons that express the neurokinin I receptor [11].
2. Microglia [12].
3. Astrocytes [13].

Spinal cord tracts contain the following:

4. Dorsal columns [14, 15].
5. Anterior lateral quadrant [16].
6. Lateral funiculus [15].

Stimulation of sensory nerves at C-fiber intensity causes release of different substances in the spine. These include

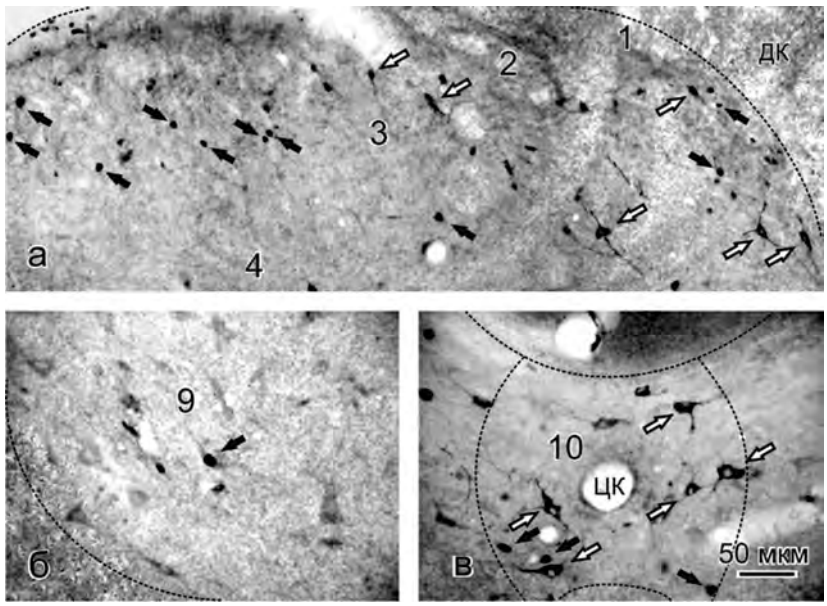

Fig. 4. Microphotograph of c-Fos expression and NADP-H-diaphorase histochemistry in transverse segments of the spinal cord in rat after the opioid-induced hyperalgesia with fentanyl. Black arrows – c-Fos immunoreactive neurons; white arrows – NADP-H-d-reactive cells

different amino acids such as aspartate, glutamate, asparagine, serine, glycine, threonine, alanine and taurine [26]; neuropeptides: substance P [27], galanin [28], calcitonin gene-related peptide [29], endomorphines [30], nociception [31] and dynorphin A [32].

Electric stimulation also causes an upregulation of c-Fos protein [33] (Figure 4) which depends on the duration of stimulation [34]. Electric stimulation of the sciatic nerve at Aδ/C intensity cause an increased expression of factors c-Jun, Jun B, Fos B, and Krox-24 in the superficial layers of the spinal dorsal horn and c-Fos and Jun D throughout the dorsal horn [35].

c-Fos is also determined in neurons of the dorsal horn after the capsaicin injection [36], and also in neurons of spinothalamic tract and postsynaptic dorsal column [37].

Nuclei in the brain include the following:

1. Rostral ventromedial medulla [17].
2. Gigantocellular reticular nuclei [18].
3. Thalamic nuclei [19].
4. Ventrobasal complex [19].
5. Anterior cingulate complex [20].
6. Ventrolateral orbital area [21].

Efferent nerve fibers include sympathetic postganglionic neurons [22].

Simplified scheme of nociception is presented at Figure 5.

Various methods are used for the assessment of hyperalgesia and allodynia (mechanical, heat, cold, electrical) in researchers, especially on animals, but only some of them can be utilized in clinical practice.

The following tests are used for the assessment of mechanical hyperalgesia and allodynia, which have the greatest utility in clinical practice:

1. Von Frey – which consists in the application of nonnoxious calibrated static hairs on skin [38].
2. Randal Sellito – consists in the application of linearly increasing mechanical force in noxious range on skin [39].

Another important problem that exist nowadays in treatment, as there are no objective diagnostic criteria, so it is difficult to perform clinical trials. But there is some data regarding the use of some medications in treatment of complex regional pain syndrome (CRPS).

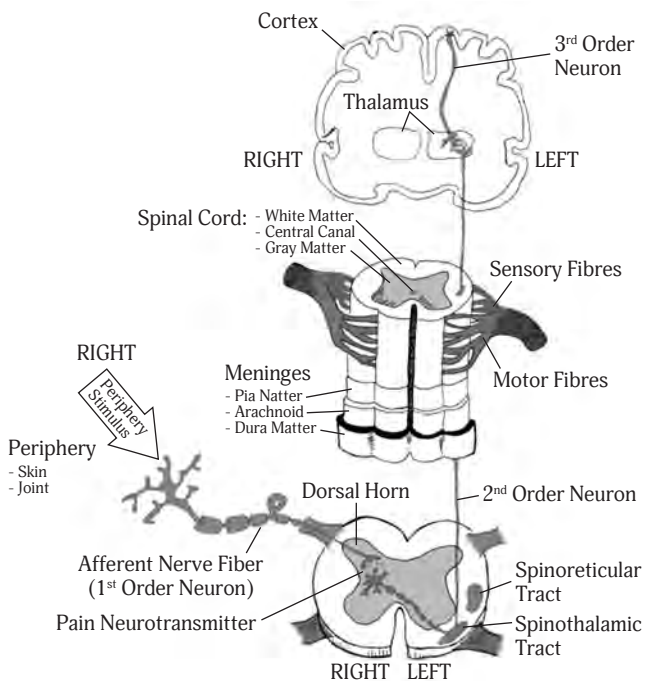

Fig. 5. Signal pathway from the periphery to cortex (only spinothalamic tract) [23]

Two small, single blind trials with 10–17 participants reported clinical improvement after the corticosteroid use within 2–3 months after injury, but no long-term follow-up was performed in these studies. But symptoms may return after the tapering of the corticosteroid dose [40, 41].

Another group of drugs, that have shown efficacy in the modifying of symptoms and morphology were calcium-regulating drugs. In one study calcitonin showed to be effective in the reduction of pain in patients with CRPS [42]. Several studies have shown a significant improvement of symptoms after the administration of clodronate and alendronate [43, 44, 45].

Opioids have shown efficacy in the treatment of postoperative inflammatory, cancer-related pain, but there is information about the opioid-induced hyperalgesia and no long-term trials were used for the treatment of neuropathic pain.

No investigation was also performed about the use of nonsteroidal anti-inflammatory drugs (NSAIDs), but mild-moderate pain can be a common reason for their indication [46].

There is some data about the efficacy of tricyclic antidepressants (TCAs) in the treatment of various neuropathic conditions. There is no data about the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of CRPS [46].

Sodium channel blocking agents were effective in reducing spontaneous and evoked pain in CRPS [47, 48]. Patch with 5% lidocaine have also shown clinically significant pain relief under the supplication site [49].

Only baclofen (gamma-aminobutyric acid agonist) have been shown to be effective in treatment of CRPS [50].

Gabapentin have preliminary evidence for an analgesic effect in patients with CRPS [51, 52], but a randomized, double-blind, placebo-controlled trial showed that gabapentin was mildly beneficial in CRPS [53]. Gabapentin is also effective in treating of neuropathic conditions, such as diabetic neuropathy and postherpetic neuralgia [54].

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Алодинія та гіпералгезія: огляд

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Резюме. *Головною метою статті було висвітлити проблему гіпералгезії та алодинії. У цій публікації було згадано основні анатомічні структури, які беруть участь у ноцицепції, з патологічними та патофізіологічними змінами, які можуть бути викликані гіпералгезією та алодинією. Представлено основні методи діагностики та оцінки зазначених симптомів, а також сучасні підходи до лікування та профілактики.*

Ключові слова: *гіпералгезія, алодинія, лікування, профілактика, патологічні.*

Аллодиния и гипералгезия: обзор

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Резюме. *Главной целью статьи было осветить проблему гипералгезии и аллодинии. В этой публикации были освещены основные анатомические структуры, участвующие в ноцицепции, с патологическими и патофизиологическими изменениями, которые могут быть вызваны гипералгезией и аллодинией. Представлены основные методы диагностики и оценки указанных симптомов, а также современные подходы к лечению и профилактике.*

Ключевые слова: *гипералгезия, аллодиния, лечение, профилактика, патологические.*