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Review Article

Nociplastic pain: controversy of the concept

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ABSTRACT

Classically, pain can be of a nociceptive or neuropathic nature, which refers to non-neural or neural tissue lesions, respectively. Chronic pain in conditions such as migraine, fibromyalgia, and complex regional pain syndrome (CRPS), is thought to perpetuate without a noxious input. Pain in such patients can be assigned neither to the nociceptive nor neuropathic category. Therefore, a third pain descriptor, named "nociplastic pain", has been adopted by the International Association for the Study of Pain. The current controversy-focused narrative review updates little-debated aspects of the new pain concept. The most disputable feature of nociplastic pain is its autonomous persistence, *i.e.*, existence without causative tissue damage, presumably because of a malfunction of pain pathways and processing. This contradicts the fact that nociplastic pain is accompanied by persistent central sensitization that has been shown to require a continuing noxious input, *e.g.*, nerve injury. Even if sensitization occurs without a lesion, *e.g.*, in psychogenic and emotional pain, peripheral stimulus is necessary to produce pain. A logical weakness of the concept is that the word "plastic" in biology refers to adaptation rather than to maladaptation. The pathophysiologic mechanism of nociplastic pain may, in fact, be associated with background conditions that elude diagnosis because of the limitations of current diagnostic means. Misapplication of the nociplastic pain category may weaken diagnostic alertness toward occult causes of pain. Possible diagnostic errors could be avoided by understanding that nociplastic pain is a mechanism of pain rather than a diagnosis. Clinical use of this pain descriptor deserves a wider critical discussion.

Keywords: Central Nervous System Sensitization; Chronic Pain; Complex Regional Pain Syndromes; Diagnosis; Fibromyalgia; Hypersensitivity; Neuralgia; Nociception.

INTRODUCTION

Chronic pain has been estimated to affect over one third of the global population [1,2]. Most chronic pain patients have underlying diseases that cause nociceptive or neuropathic pain—the two classical categories (mechanisms) of pain. Some chronic pain conditions cannot be associated with a specific cause. This has prompted the International Association for the Study of Pain (IASP) to introduce nociplastic pain as a third mechanistic descriptor of pain. Nociplastic pain, *i.e.*, "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" [3], was adopted as the new pain descriptor by the IASP in 2017 [4], soon following publication of the conceptual proposal by Kosek et al. [5] and a couple of supporting comments [6,7]. Few objections to the concept of nociplastic pain appeared at that time [8], and this category swiftly went

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viral in the pain research community. More fundamental criticism of nociplastic pain as a mechanism emerged later [9–12] but has not received much debate. The reason may be that a couple of points have been overlooked. The current review aims to draw attention to this gap in the literature.

The material for this paper was identified by searches of PubMed, Google Scholar, and references from relevant articles. The search terms "brain", "changes", "chronic", "complex regional pain", "concept", "damage", "definition", "diagnosis", "emotional", "experimental", "fibromyalgia", "hypersensitivity", "irritable bowel", "lesion", "low back", "maladaptive", "migraine", "neck", "nerve", "neural", "neuroimaging", "nociceptive", "nociplastic", "pain", "pathophysiology", "plastic", "psychogenic", "review", "sensitization", "structural", "syndrome", "treatment", and their derivatives and combinations were used. The article search focused on uncertain pathophysiological, clinical, and terminological aspects of the nociplastic pain, with special attention to its neuropathic features. The most recent articles including reviews and discussions of the relevant topics were preferred for citation.

MAIN BODY

1. Speculativeness of the nociplastic pain pathophysiology

Generation and perception of pain is one of the protective functions of the nervous system. Contrastingly, the definition of nociplastic pain implies that this pain exists because of alteration (or malfunction) of nociceptors and does not require any noxious input. In simple terms, nociplastic pain serves no functional purpose. This is a fundamental weak point of the concept, because function is uncoupled from structure. The causative interrelation between structure and function is an established axiom of biological evolution [13].

The pathophysiology of nociplastic pain is claimed to involve nociceptive central sensitization (hypersensitivity) [4,5,11,14–16], which is considered to be an essential mechanism of all chronic pain conditions [17]. However, *symptomatic* nociceptive sensitization without continuing noxious input or pharmacological manipulation is a short-lived phenomenon [18,19], and there is no compelling substantiation of *autonomous* central sensitization [20] (which is understood to be a mechanism of nociplastic pain [11,16]). Electrophysiologically, neural sensitization means ongoing spontaneous activity (firing) of neurons [21,22], persistence of which has experimentally been shown to require supportive neuroinflammatory (*i.e.*, noxious) input *via* local nerve lesion [23]. Moreover, nociceptive axons require neuroinflammatory stimulus to become mechnosensitive, and the latter feature seems to fade along with induced neuritis [24–26]. Neural injury-induced behavioral hypersensitivity resolves in parallel with abnormal activity of sensory afferents [27]. Thus, nociplastic pain may in fact be caused by a persistence of organic pathology that eludes diagnosis but can drive central sensitization. The same conclusion can be drawn from the fact that chronic pain is usually of fluctuating nature in terms of recurrence and intensity [28], which can be explained by a periodic rekindling of latent sensitization [18,19] *via* alternating activity of some background organic condition. This reasoning questions the existence of nociplastic pain as such.

Several experimental models of acute pain transition to nociplastic pain have been introduced [29]. The follow-up periods employed by these studies seem to be too short (a maximum of eight weeks [30]) to claim induction of nociplastic pain. Diagnosis of chronic pain comes into consideration only three months after the start of unremitting pain [31], which is also applicable to nociplastic pain conditions [4]. Furthermore, these models come without any demonstration that acute pain induction has not resulted in permanent tissue damage and neural damage in particular. The injections of formalin [30], reserpine with acetic acid [32], and capsaicin with ethanol [33] apart from systemic effects may have induced long-lasting inflammation and fibrosis, which may have acted as noxious stimuli, especially upon motion. Admittedly, experimental mechanical hypersensitivity can also be induced without open peripheral injury, *e.g.*, by intrathecal injection of the brain-derived neurotrophic factor (BDNF) that stimulates microglia, which in turn activates the second-order neurons [34]. However, neurotransmitters of pain are normally only released in response to certain stimuli, such as nerve injury or inflammation. Systemic action of experimental noxious substances may produce direct selective excitation of the second and third-order sensory neurons. It is also of importance that nociplastic pain models employ post-injury (or post-treatment) animal stimulation that involves repeated warm water immersions and vibration [35]. These procedures may be too traumatic to small animals. Vibration is a well-known cause of neural injury [36]. Unnatural exposures may produce muscle spasms or postural changes, which can affect nerves at the spinal level. Many other animal models of chronic pain can also be linked to pain-induced

postural effects on spinal roots and nerves. Notably, extensive plantar injury in rats has been previously demonstrated to result in Wallerian degeneration of neural fibers of the L5 spinal nerve [37]. In healthy humans, most models of experimental pain involve direct noxious stimulation of tissue and have not been shown to last beyond three months [38]. Induction of hyperalgesia by immobilization both in humans [39] and animals [40] may also be associated with neural damage due to postural changes or direct neural compression.

Another issue of concern is that the concept of nonciplastic pain does not explain why not all pain patients invariably end up with this type of persistent pain. This question is a key test for the validity of any chronic pain theory. Aberrant changes in neurochemistry, such as glutamate/glutamine (Glx) and gamma aminobutyric acid (GABA) levels in the brain, that have been found in nociplastic pain patients have not been shown to be exclusively specific to this condition [41,42]. Similar changes in neurotransmitter levels seem to be also present in neural injury-induced neuropathic pain [43]. Naturally, genes play a regulatory role. However, while certain genes can be associated with nociplastic pain [44], specific gene-related pathophysiology remains speculative. Anatomical predisposition to a compressive proximal neural lesion may be an explanation of genetic associations in many chronic pain conditions [45,46].

2. Occult neuropathy may be the cause of nociplastic pain

Can malfunction of the nervous system occur without its structural changes? One may argue that it is possible because neural functions can be altered by neurological drugs or other compounds. However, neuroactive substances, in fact, do interfere with neural structure by affecting neural receptors and ion channels. In natural conditions, release of pain mediators requires a continuing input, which also causes reversible or permanent changes of neural structure via receptor-binding mechanisms. The necessity of neuroinflammation to induce ongoing neuronal activity and mechanosensitivity [26,47–51] (*i.e.*, sensitization) raises further doubts as to whether nociplastic pain can occur without neural lesion.

As nociplastic pain syndromes have been categorized such enigmatic conditions as fibromyalgia, complex regional pain syndrome (CRPS), chronic primary headaches, including migraine [14,52], chronic whiplash-associated disorders [53], non-specific low back pain [14], and irritable bowel syndrome [14,16]. Such views are disputable. Evidence is accumulating that neuropathy may be the cause of these and other types of chronic pain [9,54,55]. CRPS type I (that is considered to be of non-neurogenic origin, but which exhibits clinical features which are identical to those of nerve injury-based CRPS type II [56]) has been shown to be associated with histological peripheral nerve changes [57,58]. Convincing are patient series where CRPS type I was found to be related to peripheral neural damage [58–60]. Fibromyalgia, probably most frequently referred to as a nociplastic pain condition, has also been associated with neural pathology [61–64]. Widespread pain in fibromyalgia is not truly generalized but rather tends to be located in circumscribed body areas [65,66], which can be associated with distinct innervation patterns. This is in accord with segmental spread of fibromyalgia pain and trigger points [67]. Extrasegmental spread of pain [67] may be due to posture-related neural damage and neural interconnections in the central nervous system. The same explanation is applicable to non-symptomatic hypersensitivity that has been detected in some fibromyalgia pain-free areas [68]. Relevantly, Kosek et al. [4] included the presence of comorbidities (such as increased sensitivity to sound, light, and odors, sleep disturbances, fatigue, and cognitive problems) into their clinical criteria and grading system for musculoskeletal nociplastic pain. These comorbidity phenomena can also be explained by the spread of sensitization to uninvolved neural structures. Trigger points (which are observed in fibromyalgia [67], non-specific low back pain [69], and neck pain [70]) have anatomically been shown to be associated with neural entrapment at the tender sites, where nerves enter muscles [71–74] and the fascial openings contain a nerve with accompanying vessels (a "perforating triad") [75]. This implies peripheral sensitization by some lesion of afferent nerves. *Structural* brain changes that have been found by neuroimaging in fibromyalgia [76,77], CRPS type I [78], migraine [79–81], non-specific neck pain [82], non-specific low back pain [83,84], and irritable bowel syndrome [85] may be a result of peripheral neural damage and consequent reduction of afferent input (see the relevant references in [46]).

It must be noted that neuropathic pain is not necessarily accompanied by typical symptoms of neuropathy. For example, neuralgic amyotrophy can present with motor symptoms but without sensory involvement [86]. This may be due to the greater vulnerability of motor fibers as compared with sensory ones [87,88], which may also account for the cases of the co-occurring fatigue-only symptom in fibromyalgia [89].

Toda [12] has suggested regarding nociplastic pain as

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a subtype of neuropathic pain due to the similarity between treatments of these disorders. Notably, opioids have *not* been recommended for treatment of nociplastic as well as of neuropathic pain [90]. This coincidence may indicate a neuropathic nature of nociplastic pain. It is known that opioids can worsen both neuropathic [91] and nociplastic pain [92], possibly because of opioid-induced neurotoxicity [93] and neural damage [94–96]. Neuropeptides can attenuate opioid-induced hyperalgesia [97,98], which may be due to their neurotrophic effects. Therefore, opioid-induced hyperalgesia may be a consequence of neural damage rather than secondary nociplastic pain as previously suggested [99].

3. Can nociplastic pain be a mechanism of psyche-driven pain?

Emotional experience is a constituent part of the general definition of pain [3]. In this respect, psychogenic (somatoform) and pure emotional (psychological) pain are important subjects of the nociplastic pain concept. Psychogenic pain is considered physical pain caused by the psyche [100,101], while emotional pain is mental suffering without any concrete representation in the physical body [102]. However, research indicates that sensitization (neural hypersensitivity) can be caused both by psychogenic [103] and by emotional pain [104]. Emotional pain can also be linked with physical pain because emotional pain can cause immunologic and hormonal changes, which could be associated with minor traumatic brain injury [105].

On the other hand, once nociceptive pathways are sensitized, non-painful (subthreshold) stimuli may become painful. Physical pain can influence the psyche, and, thus, a vicious cycle between them may develop. Emotions can amplify somatic chronic pain [106]. Sensitization alone does not cause pain without stimulus, be it noxious or innocuous. Initial stages of some diseases, while being non-symptomatic, may affect the psyche. Psyche-driven sensitization may have a protective function, which can be in agreement with the evolutionary defensive purpose of pain (including psychogenic pain [101]) and would contradict the suggestion that central sensitization in nociplastic pain is a pathophysiological maladaptation [16,107]. Thus, while psyche-driven pain can support the nociplastic pain concept, its controversy remains.

4. Misapplication of the nociplastic pain concept may weaken diagnostic alertness

Nociplastic pain denotes the mechanism of pain, not a diagnosis [5]. Relevant concept-based studies continue to appear and include clinical research. Adherence to the category of nociplastic pain in the clinical setting may weaken vigilance toward possible occult organic causes of pain. The suggestion that a search for a causative condition can be discontinued once the diagnosis of nociplastic pain has become credible [108] is difficult to accept without discussion. For example, a neoplasm at its initial stage may be undetectable but may cause persistent pain. If the latter is defined as nociplastic, then the patient may remain in this category until the tumor becomes clinically obvious. Rigorous adherence to the suggestion to treat nociplastic pain with centrally targeted medications [4] may worsen a clinical picture by masking, and thus aggravating, possible compressive peripheral neuropathy [45]. Errors may also arise because of limited experience and diagnostic capacity. Of note, misdiagnosis in chronic pain conditions has been found to range from 40% to 80% [109], which includes frequent overlooking of neural compressive disorders [110].

Toda [12] indicated that higher "medical thresholds" in the future (which obviously alludes to advanced diagnostic standards and means) may enable us to reveal background somatosensory lesions in nociplastic pain. Hoegh et al. [10] proposed replacing the term "nociplastic pain" with the classical "pain of unknown origin" to avoid invalidating the patients who do not fall into the nociplastic pain category. The counter-argument that it is nociplastic pain category that helps to avoid invalidating patients [111] still lacks comparative clinical evidence of benefits of using the nociplastic pain concept. The term "pain of unknown origin," differently from that of "nociplastic pain," leaves the question of pain origin open and thus encourages diagnostic alertness.

5. The category of nociplastic pain is contradictory

Speculative use of the word "plastic" was often employed when observed phenomena could not be explained by the available knowledge and research methods [112]. The term "nociplastic pain," apart from the nosological challenges [11], adds another semantic confusion to the growing perplexity of interpretation of the word "plastic" [8,113]. "Nociplastic pain" is supposed to signify the pathology of nociception (initially, Kosek at al. [5] proposed alternative terms of "algopathic and "nocipathic"

pain). Meanwhile, plasticity in biology is understood as organisms' adaptivity to environmental changes [114]. Similarly, neural plasticity has been defined as the ability of the nervous system to adapt in response to experience or injury [115]. Notably, "nociceptive plasticity" (the antecedent of "nociplastic" [5]) meant neurophysiologic adaptation rather than pathology when this term was introduced by Walters [116] in 1991. The concept of *maladaptive* neural plasticity in association with chronic pain emerged around the same time [117] and was later theorized to be the mechanism of dysfunctional pain (see, *e.g.*, Costigan et al. [17]). Unfortunately, the definition of nociplastic pain comes without any reference to maladaptive plasticity [3,4,11], which does not facilitate the correct interpretation of the term "nociplastic."

The term "clear evidence" is another semantic issue of the nociplastic pain definition [3]. By common logic, the definition phrase "despite no clear evidence of actual or threatened tissue damage" indicates that any relevant evidence is absent beyond doubt. However, this phrase may also imply that some *unclear* evidence of actual tissue or somatosensory lesion (and thus of nociceptive or neuropathic pain) exists, which may leave the readers of the definition to decide for themselves what is clear and what is unclear evidence.

CONCLUSIONS

By definition, nociplastic pain is autonomous pain due to a malfunction of pain pathways and processing. The only diagnostic proof of nociplastic pain is the absence of clear evidence of structural causes of pain. A number of studies have shown that persistence of central sensitization, a mechanism of nociplastic pain, is unlikely without supportive noxious stimuli. Occult, currently undetectable, conditions associated with neural damage may explain nociplastic pain. For clinically practical purposes, understanding the term "nociplastic pain" as a mechanism of pain rather than as a diagnosis may help to avoid possible diagnostic and treatment errors. The theoretical uncertainty of the nociplastic pain concept should be further discussed, and its practical application should be reappraised.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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