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Editorial

Pain and Neurobiology

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Neurobiology is an expansive field of studies encompassing the nervous system's anatomical and physiological aspects [1]. This complex framework's deep study and understanding have facilitated a more intricate comprehension of the interconnections among various nervous system components implicated in pain perception, transmission, modulation, and adaptation.

The IASP several years ago defined pain as "…an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [2]. This definition was a brilliant and elegant description of the concept already present in "L'Homme" of Monsieur René Descartes, published after his death [3]. It was not illuminating the intricate dynamics of one of the most challenging universally encountered human experiences. Since then, various aspects have modified and better shaped the definition of pain. In 2010, the complexity of the dynamic process called "pain" was magisterially described with the details known at that time, and it was clear that the neurophysiological phenomenon represented by the first IASP definition was a tiny part of what had been discovered meanwhile [4]. Further physiological studies, summarized by Kuner et al. [5], have shown the complexity of the phenomenon called "pain." Still, we do not know everything, considering that in the same year of this last publication, the Nobel Prize for Physiology and Medicine was awarded to 2 neurobiologists because they discovered new receptors involved in pain perception [6].

It is evident that the studies on neurobiology and pain have opened new frontiers in this intriguing field of studies within medicine, e.g., we know that there are at least three types of pain [7]:

1. **Nociceptive pain** results from detecting harmful stimuli by specialized sensory receptors called nociceptors in the peripheral nervous system.
2. **Neuropathic pain** results from nerve injury or malfunction in the neurological system, prompting research into the neurobiological processes underlying the altered signaling pathways of damaged nerves.
3. **Nociplastic pain** is defined by alterations in the processing of pain signals without any observable tissue damage inside a sensitized nervous system.

The first is the neurobiological explanation of "pain" in the initial IASP definition. The alteration of normal physiological processes in any of the body's tissues generates an alarming input in the central nervous system (CNS), potentially resulting in pain.

However, in cases where the nervous tissue is abnormal, a peculiar pain may arise, which is called neuropathic pain [8]. Macroscopic or microscopic lesions may derive from trauma or surgical interventions. Also, chemotherapeutic agents and radiotherapy can induce neuropathic pain due to their neurotoxic effects [9, 10]. Many diseases, including diabetes mellitus, Guillain-Barré syndrome (GB syndrome), genetic channelopathies, muscular atrophy of the spine, and viral illnesses like herpes zoster, affect the neurological system and may generate discomfort and pain as secondary symptoms [11].

Nociplastic pain has been recently described by neurobiological scientists as a third form of pain [12]. Though its pathophysiology is not yet well-studied, it is associated with some chronic diseases such as irritable bowel disease, fibromyalgia, and complex regional pain syndromes type I [13]. The classical pharmacological therapies for nociceptive and neuropathic pain are not always valuable for nociplastic pain. Indeed, physicians must know more about this new entity when affording chronic pain patients.

Pain perception is inherently subjective, challenging to quantify, and, consequently, it poses difficulties in diagnosis [14]. Reliable diagnostic criteria for chronic pain include several items, such as:

- comprehensive medical history about pertinent lesions or diseases;
- evaluation of the pain distribution's neuroanatomical structures;
- diagnostic tests;
- specialized questionnaires to evaluate the subjective experience of pain.

This aspect of pain patient management has received enormous support from neurobiological studies. It is constantly under the attention of researchers, both from the neurobiological and, more widely, from a biological point of view [15, 16]. Physicians have specific challenges when coping with patients affected by neurological chronic degenerative diseases [17].

The transmission of sensory neurons can be altered by inherent modulatory mechanisms and from the glutamate transmission within the sensory pathways [18]. Many monoaminergic transmitters play a critical role in preventing pain, including dynorphins, naturally generated opioids like met-and leu-enkephalins, serotonin, and cannabinoids like anandamide. These compounds can regulate sensory transmission, which plays a role in the intricate mechanisms that control how we perceive pain [19].

The field of pain science, which studies brain activity patterns and the associated regions involved in the emotional side of pain, especially its unpleasantness, is marked by a substantial amount of dispute and evolving understanding. Several prominent neuroimaging studies have identified specific brain regions, including the dorsal posterior insula, the ventrolateral thalamus, and the secondary somatosensory cortex [20]. Furthermore, several brain areas, including the medial thalamus, dorsal anterior cingulate cortex, and anterior insula, have been associated with emotional impact and mood. Imaging techniques allow observing neural activity across several geographical and temporal domains [21]. Optimally, a comprehensive technique entails utilizing various imaging tools to tackle the inquiries raised earlier.

Chronic pain has a significant adverse effect on the overall quality of life, and the use of medication to manage it can lead to increased costs for both social and medical care [22]. Chronic pain is far more common in women, with a prevalence nearly six times greater than in men [23]. Gender disparity is observed in various medical disorders, including tension headache, migraine, fibromyalgia, rheumatoid arthritis, musculoskeletal pain, chronic regional pain syndrome (CRPS), procedural and postoperative pain, as well as temporomandibular discomfort. Significantly, among chronic pain syndromes with identical diagnoses, women demonstrate considerably higher levels of pain compared to men [24]. This increased sensitivity to pain in women may explain the observed trend of women seeking healthcare services more frequently for both painful and non-painful conditions.

Studies on brainstem pain regulation have provided insights into the mechanisms contributing to adequate or inadequate pain relief. Treatments frequently involve a combination of various approaches to address the numerous characteristics showing the intricacy of relationship between neurobiology and pain within the nervous system. Physicians may prescribe analgesics or adjuvant medications that alter the function of neurotransmitters or target specific nervous pathways. In general, opioids, anti-inflammatory agents, or anticonvulsants are employed based on the intensity and nature of pain [25]. Physical therapy has always been helpful in pain management, including some specific painful pathologies [26]. Other studies also show the intricacy of interactions between neurobiology and pain, demonstrating how chronic pain patients may benefit from the beauty of the arts [27, 28]. Additionally, cognitive-behavioral therapy, which instructs individuals on how to better cope with pain by altering their beliefs and actions is beneficial [29]. This reinforces the strict connections between pain and neurobiology.

By addressing both the physical and mental aspects of pain, alternative therapies such as massage, acupuncture, and mindfulness meditation can be utilized in conjunction with opioid receptors conventional treatments [30]. Physicians guide this process, and the optimal combination of these alternatives is contingent on the patient's unique pain situation. The primary mechanism of action is through central processes, especially when central sensitization is present. That is especially true for some pathologies, like low-back pain, where the influence of multidimensional and multimodal therapy is crucial [31].

In conclusion, the intricacy of pain perception arises from the subtle interaction between neurobiology and subjectivity. The subjective nature of pain experiences, influenced by genetic, psychological, and cultural factors, complicates our comprehension of pain as an objective phenomenon. Recognizing this intricacy is crucial for formulating all-encompassing and tailored strategies for pain management that extend beyond merely addressing the physiological aspects of pain to embrace the diverse array of human experiences and perceptions. Hence, Pain Physicians

and Neurobiologists form an inseparable team that should consistently collaborate for the optimal well-being of patients grappling with severe pathologies like chronic pain. Moreover, that is why this dedicated "special issue" is proposed.

Author Contributions

The author did all the research work of this study.

Competing Interests

The author has declared that no competing interests exist.

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