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Pain diagnosis and treatment according to the pain generating factors

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ABSTRACT. Chronic pain impacts on many aspects of patient life affecting autonomy, sleep, social activities and also employment.
Adequate pain control is often challenging in patients with chronic pain, despite the availability of many medications and interventional techniques. Limitations to successful pain treatment are the poor understanding of contributing mechanisms and the lack of a mechanism based approach in clinical practice.
The purpose of this article is to identify the factors contributing to pain generation in order to guide a personalized treatment. We analyze tissue specificity for chemical and physical stresses potentially causing pain, the changes that occur in the peripheral and central pain pathways during disease, the stimuli that, acting on a pathological pain pathway, can trigger pain. The pain generating factors should be recognized in each patient and addressed with pharmacological, rehabilitation and invasive interventions.

Key words: *chronic pain, pain generators, mechanism based pain treatment, targeted pain treatment.*

RIASUNTO. Il dolore cronico interferisce con molti aspetti della vita del paziente limitando l'autonomia, il sonno, le attività sociali ed anche l'attività lavorativa. Spesso risulta difficile ottenere un adeguato controllo del dolore nonostante la disponibilità di numerose terapie farmacologiche e tecniche invasive. I limiti ad un soddisfacente trattamento del dolore sono rappresentati dalla scarsa conoscenza dei meccanismi che contribuiscono alla sua genesi e dalla mancanza di un approccio mirato sui meccanismi patogenetici nella pratica clinica.
L'obiettivo di questo articolo è di valutare i fattori che contribuiscono alla genesi del dolore (pain generating factors) al fine di guidare un trattamento personalizzato. Vengono analizzati la specificità dei tessuti per eventi chimici e meccanici che possono causare dolore, le modificazioni funzionali che avvengono nelle vie nocicettive a livello periferico e nel sistema nervoso centrale in corso di patologia, gli stimoli che, agendo su una via nocicettiva anomala, possono scatenare il dolore.
I fattori che causano il dolore devono essere riconosciuti in ogni paziente e trattati in modo specifico con terapie farmacologiche, riabilitative ed invasive in modo multimodale.

Parole chiave: dolore cronico, cause che contribuiscono al dolore, trattamento del dolore basato sui meccanismi, trattamento del dolore mirato alle cause.

Introduction

Chronic pain represents a social burden with an impact on many aspects of patient life affecting autonomy, sleep, social activities and also employment. Pain is a major cause of sick leave and job loss (1).

Adequate pain control remains still challenging in patients with chronic pain, despite the availability of many pain killer drugs and interventional techniques.

Which are the assumptions we focus on during the diagnostic process that lead to the therapeutic decision today?

1) Pain diagnosis is mainly based on the differentiation between nociceptive and neuropathic pain but, while there are pharmacological algorithms for neuropathic pain, nociceptive pain treatment is often based only on intensity.

If we consider the last reviews on neuropathic pain treatment (2), we can observe that the number needed to treat (NNT: number of patients treated to have 1 patient with at least 50% pain reduction) varies from 3.4 for tricyclic antidepressants to 7.7 for pregabalin among the first line systemic drugs for neuropathic pain (3,4), with poor adherence to the prescribed treatment (5).

For nociceptive pain, treatment guidelines are more confusing, pharmacological options include mainly NSAIDs (nonsteroidal anti-inflammatory drugs), acetaminophen and opioids (6), and the majority of interventional procedures are poorly supported (7). Nociceptive pain is defined somatic if originating from skin, muscles, joints or bones, and visceral when internal organs are involved; specific treatment options are mainly based on disease diagnosis instead of pain mechanisms.

2) Some Authors suggested, in order to improve the outcome of pain treatment, to evaluate pathogenetic mechanisms underlying a pain syndrome to choose drugs and interventions with a specific target (8). This approach is much more promising, giving an opportunity to deepen the diagnosis beyond the simple classification of nociceptive or neuropathic pain. Still, there seems to be a long way to the insight of individual molecular pain mechanisms to relate to a targeted treatment (9).

3) The term chronic pain is often associated with the hypothesis of irreversible functional and structural changes in peripheral and, more frequently, in central ner-

vous system, sufficient to generate pain without any peripheral afferent stimulus. This is certainly true in any painful condition secondary to a lesion inside the central nervous system (from plexus avulsion to post-stroke pain), and it can be supposed in primary pain syndromes such as fibromyalgia, irritable bowel and interstitial cystitis in which underlying mechanisms are still poorly understood and many hypotheses have been proposed (10,11).

However, in clinical practice, we observe patients suffering for many years reporting their pain to disappear for weeks or forever when the cause is diagnosed and can be removed. This is true not only for nociceptive pain but also for neuropathic pain, such as the case of nerve lesions due to entrapment in scar tissue resolved after sensory nerves relocation, described by Watson and colleagues (12).

Even the dramatic structural changes observed in many cerebral areas involved in pain perception in patients with chronic low back pain on pharmacological therapy (pain modulation) have been demonstrated to reverse when patients were effectively treated with interventions (analgesia) (13).

We propose an analysis of all the variables present in a pain syndrome that should be diagnosed and addressed in clinical practice.

The "pain generating factors"

The variables to be evaluated or "pain generating factors" are: the tissue(s) involved, the pathogenetic mechanism(s), the stimulus(i). We consider in this review mainly the biomechanical model of pain but, in clinical practice, the psycho-social aspects of pain have to be evaluated and addressed, too.

If we consider the pathway of pain signal from its origin to conscious perception (Figure 1), the majority of pain syndromes originates in peripheral tissues; from a survey of Torrance and co., only 17% of chronic pain patients have neuropathic pain (14), the remaining 83% of patients suffer from nociceptive pain.

At the nociceptor terminal, in physiological conditions, physical (mechanical, thermal) and chemical stimuli are transduced by channel-receptors to generate a receptor potential (membrane depolarization) that, if wide enough, will be encoded by voltage-gated ion channels (mainly Na^+ channels) in a series of action potentials characterized by rate, duration and rhythm (16).

The "message" travels along a pathway with at least two synapses (spinal cord and thalamus) to reach the cerebral areas responsible for conscious perception and affective interpretation (Figure 1). The "message" can be modulated by the dorsal root ganglion (17) and at each transmission site.

In acute and short lasting pain what matters is only the stimulus and the involved tissue; if the skin of your hand is too close to fire, you move it away (involuntary reflex) and after a while burning pain vanishes; if you have muscle pain while running, you stop to interrupt pain. In chronic pain conditions, functional changes occur at nociceptor level, and at all the pain pathway steps, that modify pain sensation. The most frequent cause of pain sensitization in peripheral tissues is inflammation, a physiological response to tissue damage, with different characteristics and biochemical mediators. When a lesion in the pain pathway is present, other pathological mechanisms occur that modify pain onset and transmission.

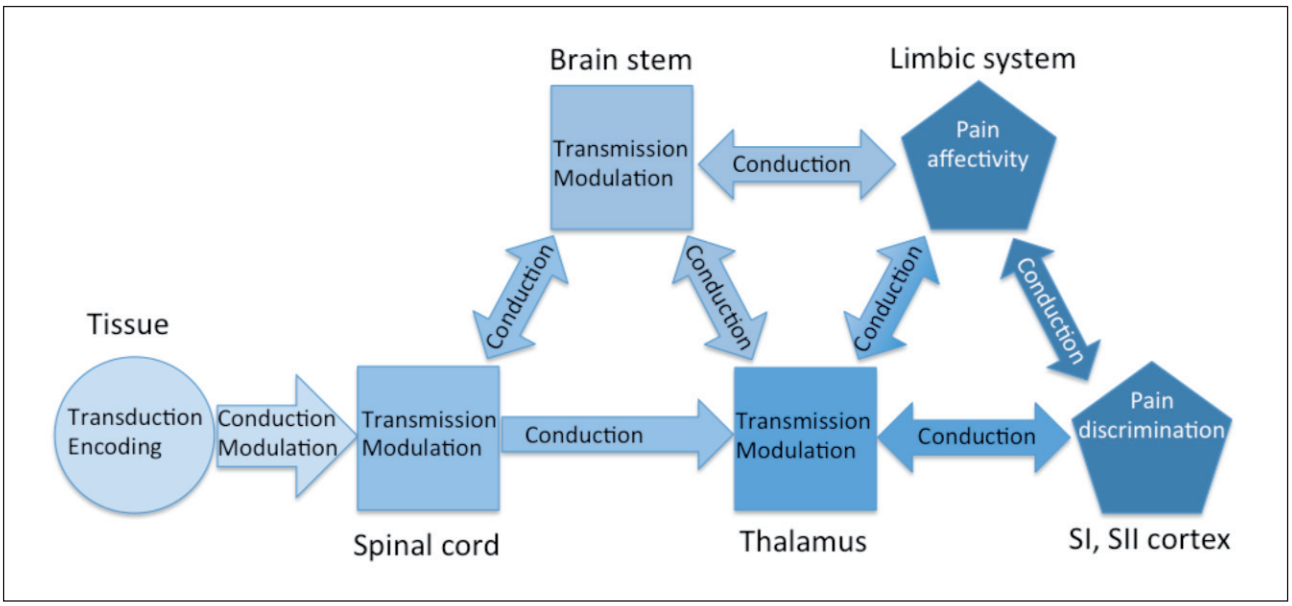

Figure 1. ***Physiologically the pain signal originates at the nociceptor terminal for the transduction of a stimulus, physical or chemical, intense enough to be encoded in an action potential with a certain frequency and amplitude. During its conduction along the first neuron it can be modulated by dorsal root ganglion activity. At each transmission step in the spinal cord, in the brain stem, in the thalamus, it can be modulated at synaptic level from local and descending inhibitory control. The term limbic system includes the cortical areas involved with the affective component of pain (Anterior Cingulate Cortex, Prefrontal Cortex) (15)***

To understand the different variables underlying a pain syndrome, more factors should be considered that influence pain perception. We can consider "pain generating factors":

- the involved tissues;
- the pathological changes that modify pain sensation (mechanisms);
- the stimuli originating pain.

Tissues

Nociceptors are characterized by the expression, at their peripheral terminals, of channel-receptors sensitive to different stimuli and able to evoke a change in the transmembrane potential (transduction), defined receptor potential. If the stimulus is intense enough, the receptor potential can give origin to a series of action potentials characterized by rate, duration and rhythm (encoding). Nociceptors terminals express different receptors (18) according to the tissue they innervate.

Skin. Skin innervation has the role of evaluating external environment with homeostatic purposes, and of detecting physical or chemical potential dangers. Skin nociceptors present different TRP (transient receptor potential) receptors sensitive to temperature variations in both directions, chemicals, mainly pungent, like capsaicin, pH decrease or protons; ASIC (acid sensing ion channels) receptors sensitive to protons, pH variations and mechanical stimuli; K+ TREK (Twik-related K+) and TRAAK (Twik-related acid-arachidonic activated K+) channels activated by membrane deformation and temperature changes, antagonizing or facilitating potential generation according to amplitude of variations. Skin nociceptors express also a series of receptors for the substances involved in inflammation such as bradykinin, prostaglandin-2, serotonin, nerve growth factor (NGF), interleukin; the activation of these receptors sensitizes the terminal, lowering the threshold for stimuli to generate action potentials (allodynia) (16,18).

Muscle. Muscle nociception senses pH changes for the expression of ASIC and TPRV1 receptors sensible also to temperature increase, the presence of ATP (adenosin triphosphate) released in case of muscle cells lesion by P2X3 (purinergic ligand-gated) receptors, osmotic variations and protein degradation products by TRPV4 and TRPA1 receptors. Mechanoreceptors are present in muscles and tendons. Muscle nociceptive terminals express receptors for inflammation mediators and growth factors able to sensitize nociceptors to other stimuli (19).

Joint. Joint nociception is mainly activated by excessive mechanical stimuli applied to the elastic structures, capsule and ligaments. Joint mechanoreceptors fire at progressively higher rates according to the tension applied. In case of inflammation or trauma, the synovial fluid increases with an increase of intra-articular pressure, mediators of inflammation sensitize mechanoreceptors and activate silent nociceptors; pain can be caused by movement in the normal range or even at rest. Besides prostaglandins, leukotrienes, lipoxins and thromboxanes, sensory neuropeptides SP (substance P), CGRP (calcitonin gene related peptide), VIP (vasoactive intestinal peptide) and N/OFQ (nociceptin/orphanin FQ) are involved in the generation and promotion of joint pain (20).

In case of cartilage degeneration, nociceptors are sensitized by cartilage degradation products, and subchondral bone nociceptive terminals are exposed to higher pressures during load (21).

Bone. In the bone tissue, periosteum is richly innervated while nociceptors are poorly represented in mineralized bone or bone marrow. Aδ fibers are more represented than in other tissues (60%) and TrKA (Tropomyosin kinase A) receptors sensitive to NGF are expressed in about 80% of fibers. Periosteal nociceptors are sensitive to mechanical stimulation and can be sensitized by mediators of inflammation and metabolites of bone remodeling like ATP and protons due to osteoclast activity. Bone marrow is sensitive to hypoxia, like in painful ischemic episodes in patients with sickle cell anemia (22).

Viscera. Viscera include different organs with functional differences, therefore nociception presents peculiar characteristics according to the organs. Generally nociceptors respond to mechanical stimuli, like distension, and ischemia, are poorly sensitive to chemicals and to heat; viscera are not sensitive to cut and cauteriziation. Inflammatory mediators can activate silent nociceptors and sensitize mechanical nociceptors (23).

Nervous tissue. The nervous tissue is peculiar because, a part from the activity of nervi nervorum innervating the connective structures of the nerves, sensible to mechanical stimuli and sensitized by inflammatory mediators like nociceptors of any other tissue (24,25), any lesion involving the myelin sheath or directly the fibers, can generate ectopic action potentials or modify the incoming action potentials (pulses multiplication and neurons cross talk) (26) giving origin to a message without the specificity for stimulus or intensity (code). The change of activity at the ectopic site is mainly related to ion channel expression and permeability variations (27).

Tissue specific therapy

Peripheral nociception is more complex at tissue level than presented above, but this knowledge is useful to understand that, even if the use of anti-inflammatory drugs or central acting analgesics (acetaminophen, opioids) is correct and often effective for different kinds of "nociceptive" or "neuropathic" pain, we can prescribe more specific drugs according to the tissue involved. Understanding the peculiarity of tissue innervation is particularly important in pain syndromes poorly responsive to opioids, like incident pain originating from bone (e.g.: fractures, metastasis) or pleural lesions (e.g.: mesothe-

lioma). These structures have a predominant Aδ fiber innervation (22,28); it has been demonstrated that morphine administration is effective mainly on secondary pain mediated by unmyelinated C fibers (29) but higher doses (about thirty times more) are necessary to reduce nociceptive reflexes mediated by Aδ fibers (30). These data explain the need for high doses of rapid onset opioids for incident breakthrough cancer pain.

In *muscle* pain, when excessive contraction is present, we can use a muscle relaxant in order to decrease mechanical stimulation, but also to reduce muscle metabolism and to increase muscle perfusion, thus modifying pH and reducing metabolites like ATP (31).

In *bone* pain, when osteoclast activity is involved (not only in bone metastasis, but also in some cases of osteoporosis with micro fractures, or bone remodeling in degenerative or chronic inflammatory diseases, such as complex regional pain syndrome - CRPS - type I), bisphosphonates (32) or antibodies that interfere with RANKL-RANK (Receptor Activator of Nuclear Factor κB Ligand) binding, osteoprotegerin or denosumab, represents effective analgesic options (33) for their action on osteoclast activity and the consequent metabolic changes. The presence of a high percentage of bone nociceptors expressing TrkA receptors for NGF has induced the research to target this molecule with antibodies in models of bone pain due to fractures, but also osteoarthritis, with promising results (34,35).

In case of *joint* pain mainly due to degenerative disease, intra-articular injection of hyaluronic acid provides pain relief through different mechanisms including condroprotection, proteoglycan and glycosaminoglycan synthesis, mechanical absorption and lubrication of the joint capsule, preventing degeneration through decreased friction, protection of subchondral bone as well as anti-inflammatory effect (36).

Visceral pain can have many different causes, from reflux esophagitis to cardiac ischemic pain, at chest level; chronic / recurrent abdominal pain or discomfort associated with altered bowel habits such as irritable bowel syndrome, or urinary colic from upper urinary tract calculi, at abdominal level. Pharmacological treatment differs very much according to the organ and the mechanisms involved; it varies from nitrates and calcium channel blockers in angina, to proton pump inhibitors in gastroesophageal reflux disease (GERD), bulking agents, antidiarrheals, antispasmodics for irritable bowel syndrome (IBS) (37).

Mechanisms

Peripheral sensitization. Nociceptors are characterized by high threshold to mechanical stimuli responding only to potentially noxious ones; even if some neurons respond to thermal stimuli below the noxious level, they increase their discharge frequency with more intense temperature variations; the majority of nociceptors respond also to chemicals and are therefore polymodal (38). In addition to polymodal nociceptors, most tissues present silent or mechano-insensitive nociceptors that begin to respond to mechanical and thermal stimuli only when sensitized by inflammation (39).

An injury to a tissue induces protective and reparative responses; plasma extravasation and cell rupture bring different substances involved in inflammation to the site of injury. The activation of nociceptors evokes the propagation of impulses not only toward the dorsal horn but also antidromically to arborizations innervating other nearby areas (axon reflex), causing the release of peptides (e.g.: SP, CGRP, somatostatin) and other bioactive substances from the terminal (e.g.: cytokines) into the interstitial space. CGRP and SP cause vasodilation and increase vascular permeability with edema and further extravasation of blood cells and inflammatory mediators (neurogenic inflammation) (40).

Nociceptors present receptors for molecules involved in the inflammatory process (e.g.: prostaglandins, cytokines) and other mediators, such as growth factors (Figure 2). These receptors are coupled with ion channels or, more frequently, activate a second messenger modifying ion channels permeability. Sensitization due to inflammatory mediators begins in a few minutes reducing the threshold to mechanical (prevalent in deep tissues) and thermal stimuli (prevalent in the skin). If the inflammatory process persists, an up-regulation of ion channels and receptors is induced that contributes to the maintenance of pain (39). Sensitization is responsible for spontaneous pain (when body temperature is sufficient to evoke pain) or, more frequently, for pain induced by sub-threshold stimuli (allodynia) or increased pain due to noxious stimuli (hyperalgesia).

Ectopic discharge. At the site of nerve injury, the modified expression of Na^+ and K^+ channels alters membrane properties favoring spontaneous discharges at high frequency and without the coding typical of action potentials generated at nociceptor terminal (41). Altered membrane excitability at the site of lesion can also change the discharge rate of action potentials generated at the periphery (pulses multiplication), modifying the message code and causing allodynia (42). The ectopic discharge can originate at the site of lesion, in the sprouting terminals (neuroma) or in the dorsal root ganglion (43,44). Uninjured axons, mainly C fibers, in the vicinity of the damaged ones can discharge spontaneously (41).

Following a nerve transection, regenerative unmyelinated sprouts grow from each axon forming a neuroma; the neuroma sprouts present spontaneous activity, abnormal excitability and discharge characteristics. Regenerating sprouts develop increased mechanical, thermal and chemical hypersensitivity to bradykinin, histamine, serotonin, capsaicin and other substances able to excite nerve endings. Cytokines such as interleukin-1 and TNFα are able to evoke mechanical hyperalgesia in animal models of nerve lesion (46).

Studies of tissues from patients with trigeminal neuralgia suggest ephaptic neurotransmission (or cross talk) between adjacent denuded axons as the mechanism underlying brief lancinating pain paroxysms caused by touch or movement in the territory of the affected branch (47).

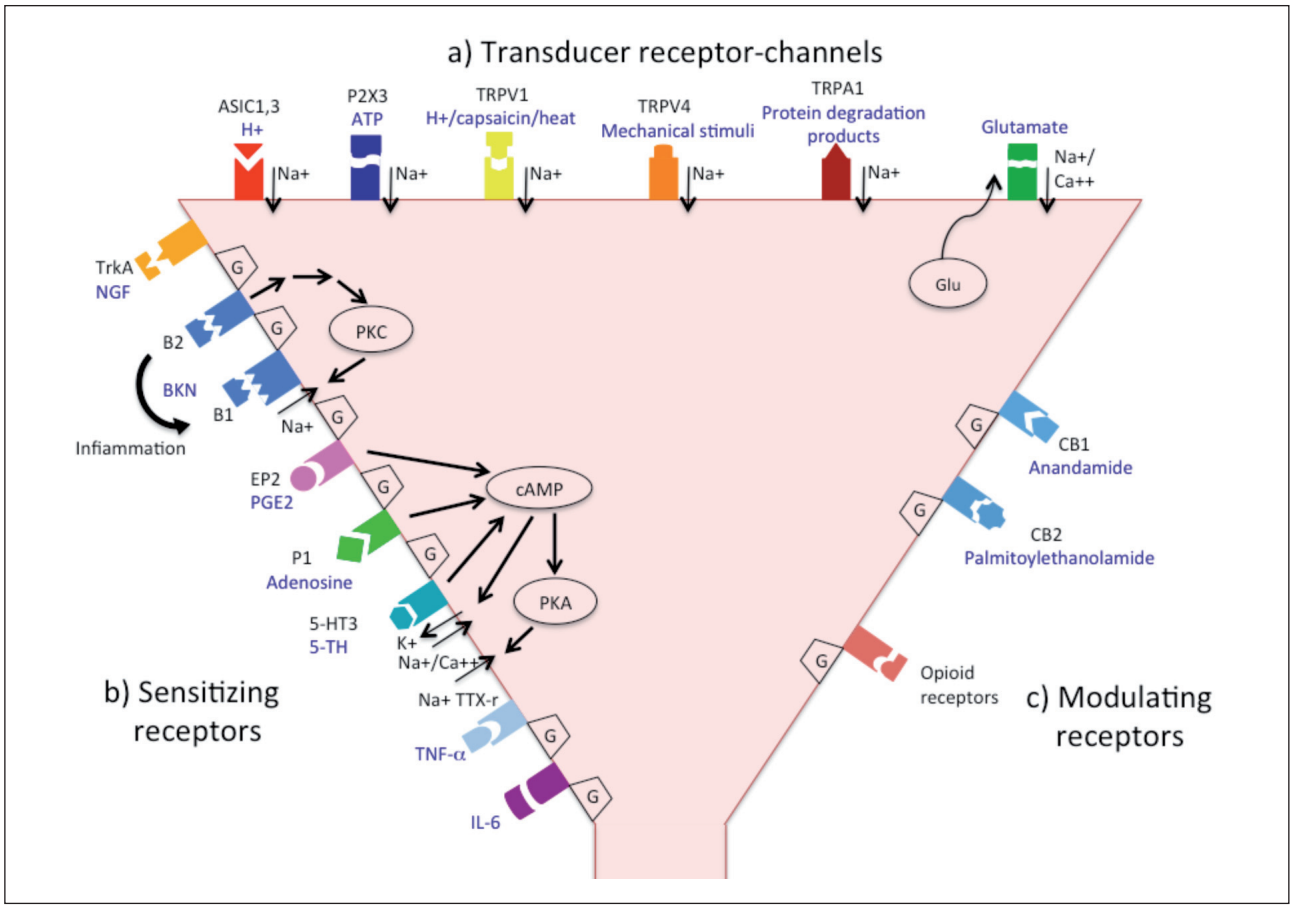

Figure 2. ***The nociceptive terminal expresses different transducer channel-receptors (a), according to the tissue and fiber type, able to transduce chemical or physical stimuli in receptor potentials. On the terminal membrane are also present receptors (b) for molecules involved in the inflammatory process (e.g.: prostaglandins, cytokines) and other mediators, like growth factors, which are coupled with ion channels or, more frequently, activate a second messenger modifying ion channels permeability and thus, sensitizing the nociceptor. There are also receptors (C) for endogenous opioids and cannabinoids with inhibitory function. NGF = nerve growth factor, BKN = bradykinin, PGE2 = prostaglandin-2, 5-TH = serotonin, TNFα = tumor necrosis factor α, IL-6 = interleukin 6, G = protein G, PKC = protein kinase C, PKA = protein kinase A. (Modified from Mense and Gerwin) (19)***

Injured axons are sensitive to inflammatory mediators, such as bradykinin, cytokines and nitric oxide (NO) produced by white cells and Schwann cells at the site of lesion (39). It has been demonstrated that also sympathetic mediators can activate or sensitize injured axons at the site of lesion, at their terminals or at the dorsal root ganglion (DRG) (43).

Peripheral nerve injury induces up-regulation of the Ca^{++} channel $\alpha_2\delta$-1 subunits in dorsal root ganglia (DRG) and in the presynaptic element in dorsal spinal cord, contributing to central sensitization in neuropathic pain (48).

Dorsal horn sensitization. At spinal dorsal horn level, the nociceptive message from different tissues is transmitted with characteristic modalities: while a message from the skin is well localized and pain is perceived only in the area where the stimulus is applied, a message from viscera is poorly localized and often pain is referred to superficial areas distant from the origin, due to the overlap of fibers from different tissues on the same second order neurons. C fibers from the skin project mainly to superficial laminae while the fibers from viscera, joints and muscles project also to deeper laminae. Aδ fibers project to nociceptive specific (NS) neurons in lamina I and to wide dynamic range (WDR) neurons in lamina V. WDR neurons receive non nociceptive afferents from Aβ fibers. Both NS and WDR neurons encode the intensity of a noxious stimulus but WDR neurons respond in a graded fashion from innocuous to noxious while NS begin to discharge only at the noxious intensity (39).

While a brief painful stimulus is transmitted to the second order neuron through the release of glutamate at synaptic level, a long lasting nociceptive input causes also the release of substance P generating second order neuron sensitization due to activation of NMDA (N-methyl-D-aspartate) receptors, able to generate allodynia and hyperalgesia in an area outside the peripheral lesion (secondary allodynia and hyperalgesia) (49).

A lesion of a peripheral nerve generates a series of functional changes at dorsal root ganglion level, at presynaptic level (e.g.: increased synthesis of neurotransmitters and expression of Ca^{++} channels) (50,51) and at postsynaptic level (e.g.: Aβ fibers loose their inhibitory role and

become excitatory, there is a loss of GABAergic - Gamma-aminobutyric acid - and glicinergic inhibition, microglia releases excitatory neurotransmitters, like BDNF - Brain-derived neurotrophic factor) (41). These functional changes are the basis of signs such as allodynia and hypelagesia in the peripheral territory innervated by the involved nerve; secondary allodynia and hypelagesia are usually not present (except in causalgia were they can be found outside the territory of innervation) as well as referred pain.

Supraspinal sensitization and altered inhibitory control. Functional changes occur also at all synaptic levels of the pain pathways in the central nervous system, causing an unbalance between inhibitory and excitatory control. Mechanisms underlying central sensitization at brainstem level (52), mainly reticular formation and periaqueductal gray, thalamic level (53), anterior cingulate and prefrontal cortex are similar for both neuropathic and nociceptive chronic pain (41). A particular situation is represented by deafferentation pain where a spontaneous high frequency activity has been demonstrated in second and/or third order neurons in the pain pathways (54); in this condition, descending inhibitory control acting mainly on the first spinal synapsis looses its efficacy.

Mechanism based treatment

When peripheral sensitization due to inflammation is present, the drugs of choice are anti-inflammatory drugs or COX-2 inhibitors, limiting PG metabolism, but also steroids acting on immune-mediated inflammation, on cytokines expression and phospholipase inhibition preventing the formation of arachidonic acid (55). Anti-inflammatory drugs and, even more, corticosteroids are effective also in neuropathic pain when inflammatory mediators contribute to altered membrane sensitivity at the site of injury (56). Steroids seem to exert a membrane stabilizing effect (57).

Inflammation can be also addressed by biologics directed to TNF and interleukins used in reumatologic diseases (58).

Altered excitability of neurons at the site of injury can be treated with Na^+ channel blockers such as carbamazepine, oxcarbazepine, lamotrigine (59), lacosamide, topiramate but also triciclic antidepressants (60). Local anaesthetics can be injected systemically (61), at the DRG (62), at the site of injury or applied topically where the spared fibres express an increased number of Na^+ channels (63). When overexpression of TRPV1 receptors on spared fibres is supposed, capsaicine can be applied (64).

Drugs acting on specific subunits of Ca^{++} channels involved in pain transmission and upregulated in case of peripheral nerve lesion (e.g.: gabapentin, pregabalin and ziconotide) have been demonstrated effective in neuropathic pain (65,66). The intrathecal administration of ziconotide is recommended also for nociceptive pain resistant to systemic therapy (66) and gabapentinoids have been proven effective in models of nociceptive pain (65).

NMDA antagonists, such as ketamine, dextromethorphan and memantine, can reverse spinal sensitization due to NMDA receptors activation (58) even if their clinical use is limited by side effects (2).

Inhibitory control of synaptic transmission in the dorsal horn can be potentiated by opioids, acting at pre- and post-synaptic level but also at different supra-spinal sites enhancing descending inhibition, non-selective antidepressants, increasing the availability of inhibitory mediators (norepinephrine and 5-hydroxytryptamine), α2-agonist clonidine, GABA agonists, such as baclofen and benzodiazepines (41).

At supra-spinal level, inhibitory mediators in the pain pathway are mainly endogenous opioids, GABA, dopamine, noradrenaline and serotonin. Monoamine reuptake inhibitors are not only effective for neuropathic pain but also on anxiety and depression, often present in chronic pain syndromes (67). Antipsychotics, acting with different modalities but mainly as D2 receptors antagonists, have been used for different types of chronic pain resistant to other treatments (68).

Stimuli

Nociceptors are physiologically activated by stimuli intense enough to be potentially harmful. When peripheral sensitization is present, low intensity mechanical and thermal stimuli, such as light touch, or stimuli normally not perceived, such as body weight on a joint or body temperature (69), may evoke pain (allodynia). While a patient is conscious of a mechanical stimulus, such as the load on an inflamed joint, and tries to avoid it, it is more difficult to identify a thermal stimulus; when vasodilation is evident and temperature is increased in the affected area, often patients find benefit from the application of cold. Patients with erythromelalgia, a genetic neuropathy affecting the Nav1.7 channels and characterized by burning pain, warmth and redness of the extremities, typically dip the feet or hands in ice or cold water to alleviate pain (70).

Visceral pain is usually considered spontaneous but we have to consider that physiological pressure changes (mechanical stimuli) can be perceived as painful in a condition of peripheral sensitization (23) (such as bladder filling in a patient with cystitis or bowel movement in a patient with inflammatory bowel disease) or of central sensitization (such as bowel movement in a patient with esophagitis) (71).

In case of peripheral nerve lesion, pain may be ongoing, spontaneous, or originate from an innocuous stimulus applied on the nerve endings or at the site of lesion. Nerve endings can be hyperexcitable for phenotypic changes (e.g.: Na^+ channel expression, TRPV1 and other transducers expression) secondary to partial nerve lesion; a stimulus normally transduced and encoded as non painful in the periphery can be interpreted as a noxious one for the ectopic multiplication of impulses at the site of nerve lesion where the myelin sheath is altered (42); a mechanical stimulus originated in Aβ fibers can pass to an Aδ fiber in a site of myelin loss for ephaptic transmission (or cross talk), as it is supposed in trigeminal neuralgia (47).

At the site of partial lesion, nerve fibers acquire transduction properties and become sensitive to mechanical (72), thermal (TRPV1 expression) and chemical stimuli (73); they reflect mainly the receptive properties of their endings (74). Nerve sprouts in neuromas present similar characteristics (46). Mechanical sensitivity accounts for "Tinel sign", when a light stimulus, such as tapping the area of nerve injury, evokes paresthesias or dysesthesias (72).

In clinical practice, nerve entrapment syndromes are examples of mechanical sensitivity of nerve fibers partially injured by chronic compression; in carpal tunnel syndrome, for example, tendon movement during wrist flexion and extension elicits paresthesias and dysesthesias in the hand.

Stimuli targeted treatment

Usually patients with musculoskeletal pain try to find strategies to avoid painful stimuli but behavioral changes are not always functional in the long term and, when associated to psychological and social reinforcements, can contribute to the persistence of chronic pain and disability (75).

The control of stimuli that evoke pain in pathological conditions can be obtained with rehabilitation and physical interventions aimed at limiting the load or movement of affected structures (e.g.: muscle reinforcement, use of orthosis or bust). Education and ergonomic measures in the work place can improve and prevent pain (76).

Stimuli that evoke visceral pain are more difficult to treat because they are often related with physiological functions.

Clinical example

If we consider a patient with carpal tunnel syndrome, the information the patient gives us about the symptoms (pain and paresthesias), the site (palm of the hand and fingers), the time of the day (at night when the wrist is motionless or during the day at wrist flexion-extension movements) can suggest the diagnosis. Clinical evaluation can confirm the presence of sensory deficits in the territory of the median nerve in the hand (in the initial stages of the entrapment syndrome sensory deficits can be absent) and, in late stages, loss of grip strength and muscle atrophy at the base of the thumb (77); Tinel sing is a symptom of mechanical hyperexcitability of the nerve fibers such as pain and paresthesias evoked by repetitive flexion-extension of the wrist. At this point we can speculate a median nerve entrapment at the carpal tunnel due to swelling of soft tissues, aggravated by mechanical stimuli. The diagnosis can be confirmed by electrophysiological testing and ultrasonography can demonstrate enlargement of the median nerve at the distal wrist crease (78).

Even if carpal tunnel syndrome is a case of neuropathic pain, gabapentinoids have been proven equal to placebo in relieving symptoms (79) and literature on the use of Na^+ channel blockers or antidepressants is poor. Sensitivity of nerve fibers is increased by inflammatory mediators (cytokines), therefore the injection of corticosteroids can improve the symptoms (80) acting also on edema that contributes to compression. The symptoms of carpal tunnel syndromes can be alleviated by splinting, that limits the range of movement and, therefore, mechanical stimulation (77). The purpose of surgery is to free the nerve from compression. Removing or reducing the stimuli, in this case, is more effective than acting on pathogenetic mechanisms such as Na^+ and Ca^{++} channel overexpression and hypeactivity. Drugs and interventional treatments are in this case selected according to the pain generating factors.

Conclusions

Pain therapies prescribed according to underlying disease or pain type (nociceptive versus neuropathic) often fail to reach satisfactory analgesia (2). The distinction between nociceptive and neuropathic pain does not consider the presence of overlapping mechanisms, such as peripheral sensitization due to inflammatory mediators or growth factors and central sensitization at different levels of the pain pathways; an example is the effect of corticosteroids for both joint inflammatory diseases and some conditions of radicular pain.

Only clinical and instrumental evaluations that take into account the pain generating factors allow in every patient the prescription of targeted treatments. The three different factors can influence each other and frequently a therapy addressed to one of them is sufficient to improve pain. Hypersensitivity of nociceptive tissue terminals or of ectopic sites does not necessarily cause pain but requires the presence of stimuli.

Every effort should be made to understand in each patient the pain generating factors and their mutual relationships responsible for pain. This could explain why some medications properly prescribed by pain type are not effective.

Unfortunately, in some pain syndromes we cannot demonstrate a defined site of pain origin (positive result of an anesthetic block) and we can formulate only hypotheses. This is, for example, the case of pain due to deafferentation where it is difficult to establish the neural dysfunction that causes pain and why awakening or alerting are stimuli sufficient to cause pain.

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