Physiopathology of pain in rheumatology

M. Cazzola[1], F. Atzeni[2], L. Boccassini[2], G. Cassisi[3], P. Sarzi-Puttini[2]

[1]Rehabilitation Unit, Busto Arsizio Ospedale di Circolo, Presidio Ospedaliero di Saronno (VA);
[2]Rheumatology Unit, L. Sacco University Hospital, Milan;
[3]Rheumatology Branch, Specialist Outpatients Department, Belluno, Italy

SUMMARY

Pain is the main manifestation of many rheumatic diseases (be they overtly inflammatory such as rheumatoid arthritis or dysfunctional such as fibromyalgia) but, at least initially, the mechanisms involved in the genesis, amplification and chronicisation of the persistent pain characterising the various conditions can be very different. The main peripheral mechanism underlying acute nociceptive pain is a change in the activity of the nociceptors located in the affected anatomical structures (joints, tendons and ligaments), which makes them more sensitive to normally painful stimuli (hyperalgesia) or normally non-painful stimuli (allodynia). This physiopathological mechanism of peripheral sensitisation plays a primary role in rheumatic diseases characterised by acute inflammation, such as the arthritides due to microcrystals. In the case of chronic rheumatic diseases that do not regress spontaneously, functional and structural central nervous system changes cause a generalised reduction in the pain threshold that is not limited to the anatomical structures involved, thus leading to the appearance of hyperalgesia and allodynia in many, if not all body districts. This is the physiopathological basis of chronic, widespread musculoskeletal pain.

Key words: *Allodynia, Chronic rheumatic diseases, Hyperalgesia, Peripheral mechanisms.*

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INTRODUCTION

Musculoskeletal pain is the main reausculoskeletal pain is the main reason inducing patients to consult a rheumatologist but, despite this, it was a long time before researchers made a serious attempt to interpret the physiopathological mechanisms underlying the symptoms. Until a few years ago, the pain associated with many rheumatic diseases was considered to be peripheral in origin and induced by the well-known mechanisms of acute or chronic inflammation, or morphostructural alterations in the involved joints (1-5). This interpretation is still supported by many rheumatologists despite the repeated clinical evidence of a discrepancy between the intensity and characteristics of the pain reported by patients and the extent of the anatomical alterations detectable at the sites of the perceived pain, as in the case of the radiological grading of osteoarthritis (OA) (6). Over the last 20 years, the greatest advances in interpreting musculoskeletal pain have been made in the ambit of the widespread extra-articular forms of rheumatism, particularly the protypical form of fibromyalgia (FM) (7-12). Studies of fibromyalgic patients have made it possible to recognise multiple neurophysiological modifications in the perception, transmission and, above all, processing of nociceptive afferents at the level of the central nervous system CNS (13-17). These modifications seem to be caused by what has come to be called "sensitisation": i.e. a permanent state of neuronal hyperexcitability involving all of the peripheral and central structures of the nociceptive system (18-23). It has only recently been postulated by some researchers that sensitisation of the nociceptive system plays a major role in determining the intensity and chronicisation of the pain accompanying other rheumatic diseases such as OA and rheumatoid arthritis (24-26).

SENSITISATION OF THE NOCICEPTIVE SYSTEM

The abnormal receptor sensitivity underlying the pain characterising many rheumatic diseases causes perceived pain even in the

Corresponding author:
Marco Cazzola
Rehabilitation Unit
Busto Arsizio Ospedale di Circolo
Presidio Ospedaliero di Saronno (VA), Italy
E-mail: mcazzola@aobusto.it

case of the stimulation of low-threshold receptors whose impulses are transmitted by Aβ fibres and, under physiological conditions, generate innocuous sensations. This spontaneous clinical pain is not only due to early post-translational alterations in peripheral nerve endings and the primary sensory neurons located in the spinal dorsal root ganglia (DRGs), but also to late transcriptional changes in the primary sensory neurons and the wide dynamic range (WDR) neurons located in the dorsal horn of the spinal cord (DHSC) (27, 28).

The result of these processes modifies two distinct aspects of sensory neuron function:

- basal sensitivity: i.e. the capacity of low-intensity peripheral stimuli to induce a painful sensation (peripheral sensitisation);
- stimulus-induced hypersensitivity: i.e. the capacity of peripheral stimuli of particular intensity and duration to induce persistent modifications in the sensitivity of the nociceptive system (central sensitisation).

The variations in basal receptor sensitivity are largely due to early post-translational alterations (27), whereas transcriptional changes modify the phenotype of the sensory neurons and make the entire nociceptive system persistently hypersensitive.

The three processes underlying a wide range of chronic inflammatory, neuropathic or dysfunctional painful conditions are increased neuronal excitability, structural reorganisation and reduced inhibition, which may occur sequentially or simultaneously.

Peripheral sensitisation

The sensitivity of the peripheral endings of nociceptors can be modified by repeated mechanical or thermal stimuli or, in the case of inflammation, by variations in the chemical milieu (29).

It is widely agreed that peripheral receptor sensitisation is the mechanism underlying the allodynia and hyperalgesia characterising acute inflammatory conditions such as the arthritides due to microcrystals, but its role in other rheumatic diseases such as FM is more controversial. There have long been reports of morphological, biochemical and functional alterations involving the peripheral tissues of patients with FM, but their significance and specificity have never been clarified. The most recent published data indicate that the skin biopsies of fibromyalgic patients show an increased expression of the 2D subunits of *N*-methyl-D-aspartate (NMDARs) receptors, interleukin 1 (IL-1), IL-6 and tumour necrosis factor alpha (TNFα), and greater mast cell infiltration (30-32), and the combination of these findings suggest nociceptor sensitisation. Furthermore, in comparison with other muscle areas, tender points (TPs) have higher concentrations of protons, substance P (SP), TNFα, IL-1β, serotonin (5-HT) and norepinephrine (NE), all of which are capable of modifying receptor sensitivity (33, 34).

Central sensitisation

Peripheral sensitisation affects the Aδ and C fibres that normally transmit nociceptive stimuli. However, persistent nociceptor stimulation also sensitise the Aβ fibres that are not involved in physiological nociception, and induces them to express neuropeptides such as SP and the calcitonin gene-related peptide (CGRP), as well as neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (35). These neurotrophins are transported along the fibres to the DRGs, where they stimulate the expression of SP, CGRP and BDNF, which are secreted into the DHSC, where many of the actions of BDNF are mediated by the neurotrophic receptors TrkA and TrkB. As NGF regulates the expression of SP, CGRP and BDNF, it probably plays a key role in neuronal sensitisation (36).

Central sensitisation can be defined as a state of neuronal hyperexcitability in response to peripheral stimuli that permanently modifies sensory processes, particularly nociception.

The sensitised neurons are low-threshold WDR neurons, and their repeated afferent stimulation by C fibres can lead to a series of temporal synaptic summations that gradually increase their amplitude and discharge frequency (wind-up). Clinically,

this gives rise to a sensation of progressively increasing pain when constantly intense stimuli are administered more frequently than once every three seconds.

Glutamate is the most frequent excitatory amino acid in the CNS, and its action is mediated by many receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), kainite receptors (KARs), and NMDARs (37). The role of central sensitisation in the pathogenesis of musculoskeletal pain has been widely studied in patients with FM, whose cerebrospinal fluid (CSF) contains increased levels of SP (38, 39), glutamate (40) and NGF (41), and reduced levels of glial cell-derived neurotrophic factor (GDNF) (42), a substance with antinociceptive activity at the level of the DHSC that is probably mediated by the inhibition of SP release and the expression of sodium channel subunits. Glutamate, SP and NGF induce the wind-up of WDR neurons, whereas GDNF inhibits it.

THE ROLE OF THE DESCENDING MODULATORY PATHWAYS

Spinal cord WDR neurons are not only sensitised by nociceptive stimuli coming from the periphery, but also by the disinhibition or stimulation of regulatory tone. As this is normally provided by the pathways descending from the supraspinal centres, which the endogenous opioids, 5-HT and NE as neurotransmitters (43), it is possible that the algogenic threshold is modified as a result of facilitating activity originating from them (for, example under conditions of stress or hypervigilance), or because of a reduction in inhibitory activity.

It is thought that the descending control system of nociceptive afferents underlies various phenomena related to the experience of pain depending on its inhibitory or facilitating action, including the placebo effect, stress-induced analgesia, anticipatory hyperalgesia, and the clinical response to cognitive-behavioural therapies.

Functional nuclear magnetic resonance (fNMR) studies have shown that a nociceptive pressor stimulus causes greater activation of the anterior cingulated cortex (ACC), periaqueductal grey matter (PAG), and dorso-lateral prefrontal cortex (DLPFC) in patients with OA than in controls (44). As the facilitating descending fibres of the nociceptive pathways originate from the ACC, it is thought that pain in OA patients is partially mediated by excessive facilitating activity. Furthermore, the fact that the pressor stimulation threshold is not increased by the experimental application of a nociceptive stimulus suggests a functional deficit in the diffuse noxious inhibitory control (DNIC) system (45).

INTERACTIONS BETWEEN THE IMMUNE AND NERVOUS SYSTEMS

Although pain is a sensation processed by the CNS, the immune system, astrocytes and microglia may contribute to the process of sensitisation and the consequent development of chronic pain. An emerging concept is that immune cells, glial cells and sensitive neurons form an integrated network in which activation of the immune system is capable of modifying the excitability of the nociceptive pathways.

Activated resident immune cells, such as mast cells, macrophages and dendritic cells, intervene in the early phases of peripheral sensitisation by releasing chemokines, complement factors (C3a and C5a) and vasoactive amines; subsequently, the monocytes and T lymphocytes that accumulate at the sites of tissue damage release pro-inflammatory cytokines, such as IL-1β and TNF-α that contribute to receptor sensitisation.

Astrocytes and activated glial cells may play a role in the centrally sensitising nociceptive pathways and amplify pain by releasing glutamate and D-serine, which activate NMDARs at neuronal level, or by inducing the collateral sprouting of the nerve endings of the Aβ fibres in laminae III and IV of the DHSC in order to form new synapses with the secondary neurons

of laminae I and II (46). Consequently, under conditions of chronic pain, the changes in the pain matrix are both functional and structural.

THE ROLE OF THE AUTONOMOUS NERVOUS SYSTEM

The role of the autonomous nervous system (ANS) in the genesis and chronicisation of pain has been widely documented in a series of clinical conditions known as "reflex sympathetic dystrophy" until the mid-1940s, but more recently called "complex regional pain syndrome" (47, 48).
Many painful neuropathic conditions arise after partial lesions of the peripheral nervous system. In experimental animal models involving partial nerve trunk lesions, the primary sensory neurons underlying the lesioned fibre and those underlying fibres unaffected by the lesion both acquire a *de novo* capacity to express genes, thus changing their phenotype. In combination with other soluble and diffusible factors such as IL-1β and TNF-α, tissue growth factors such as NGF not only sensitise the receptors, but also generate ectopic activity (49). One example is the induction or up-regulation of catecholamine receptors at the level of undamaged nociceptors; under these conditions, the nociceptors are activated by NE and the consequent neuropathic pain has been defined as "*pain sustained by the sympathetic system*" (50). An inversion in the phenotypical shift is associated with a reduction in pain intensity, and so it is hoped that identifying the various diffusible factors that modulate gene expression at the level of the DRGs will allow the development of directed therapies that are more efficacious than those currently available (51-53).

THE ROLE OF PERIPHERAL TISSUES

However, while recognising the nervous system as the principal factor determining pain duration and intensity, we should not forget the role of the peripheral tissues from which the nociceptive inputs initially originate because the maintenance of central sensitisation in any case requires the contribution of albeit moderately intense peripheral tonic impulses (54). Lidocaine infiltrations of TPs at the level of the trapezius muscle in FM patients raises the nociceptive threshold not only in the infiltrated area (primary hyperalgesia), but also in distant sites such as the forearm (secondary hyperalgesia) (55). Kosek has demonstrated that the neurophysiological modifications indicating central sensitisation during the course of OA (alterations in the DNIC system, secondary hyperalgesia, and the presence of more extensive receptive fields) normalise after the prosthetic replacement of the joint involved (25). The therapeutic approach to many diseases of the musculoskeletal apparatus should therefore also take into account the role of peripheral tissues in the genesis and maintenance of pain.

THE ROLE OF THE STRESS REACTION SYSTEM

The clinical observation that, like that of other central sensitisation syndromes such as chronic headache, irritable bowel syndrome and temporo-mandibular disorders, the onset of FM often coincides with physically or mentally stressing events has led some authors to include it in the spectrum of stress-related diseases (56-62). Furthermore, there is evidence that many of the neuroendocrine pathways involved in the reaction to stress show more or less marked functional alterations in fibromyalgic patients (63, 64). It also seems that persistently high cortisol levels, such as those encountered in situations of chronic stress, cause quantitative alterations in the expression of adrenergic and dopaminergic receptors, and qualitative alterations in the subunit composition of GABA and aspartic acid receptors (NMDARs), and that such alterations underlie the hyper-reactivity of the CNS to external stimuli.

Furthermore, it has been recently demonstrated in experimental animal models that stressful situations are capable of significantly modifying the transduction sensitivity of muscle nociceptors, thus inducing peripheral sensitisation (65).
It is therefore likely that, by causing changes in the stress response system and, consequently, neuroendocrine dysfunctions and quantitative and qualitative alterations in the receptor systems involved in nociception, external traumatic factors predispose at least a subgroup of patients to the adult development of many chronic painful syndromes.

THE ROLE OF GENETICS

It is known that sensitivity to pain varies widely in different breeds of rodents, and similar variability also exists among humans (66, 67). Population studies have demonstrated that 50% of chronic pain is inheritable, and it has been estimated that the role of inheritance is 29% in the absence of pain and 44% in the case of severe pain. Even after correcting the data for confounding factors such as age, body mass index, gender, income, occupation, physical activity levels and family habits, inheritance has a weight of 30% in determining severe chronic pain (68).
It has long been known that genetic mutations in a specific subunit of sodium channels known as NAV 1.7 cause rare genetic diseases characterised by opposite disturbances: very intense pain in the case of familial erythromelalgia and paroxysmal extreme pain disorder, or complete insensitivity to pain (69-70). Mutations in the gene encoding sodium channels can also explain the presence of chronic pain (particularly neuropathic pain) in much more frequent clinical conditions such as peripheral neuropathies (71).
Various studies have demonstrated the importance of genetic factors in causing FM, the rheumatic disease that is prototypical of chronic musculoskeletal pain (72), particularly polymorphisms of the genes encoding the enzymes and/or receptors involved in the metabolism and transport of monoamines, the mediators that play a critical role in sensory processes and stress responses (Tab. I). It has more recently been shown that these polymorphisms are not specific to FM but also play a role in causing many other chronic painful conditions. In a large series of patients with hip OA, van Meurs *et al*. found that the presence of the 158Met variant of catechol-O-methyltransferase (COMT) triples the risk of developing pain regardless of its radiological grading (73).

Table I - Genetic markers of fibromyalgia.

System	Genetic markers
Serotoninergic	Polymorphism of the serotonin 5-HT2A receptor (phenotype T/T) Polymorphism of the promoter region of the serotonin transporter (5-HTTLPR)
Dopaminergic	Polymorphism of the dopamine D4 receptor
Catecholaminergic	Polymorphism of the catechol-O-methyl transferase (COMT) emzyme

THE ROLE OF THE EMOTIONAL-COGNITIVE FILTER

Depression is a common denominator of chronic painful conditions (74-77), but the relationship between pain and depression seems to be bi-directional: chronic depression can induce central sensitisation and lower the nociceptive threshold, and chronic pain can be associated with changes in character that can reach the point of depression. Furthermore, of the three symptomatological clusters of depression (affective, cognitive and somatic), the somatic cluster includes physical symptoms that overlap those of many chronic, dysfunctional and painful syndromes (headache, low back pain, and aspecific visceral pains). This parallelism leads to pathogenetic situations in which there is both depression and pain not only at neurotransmitter level, but also at the level of the hormonal, immunological and neurotrophic systems. In particular, the changes in neurotropin levels encoun-

tered in chronic pain conditions also lead to neurodegenerative phenomena, such as the neuronal apoptosis and reduced hippocampal volume observed in patients affected by depression (78). In addition to the previously mentioned facilitation of collateral Aβ fibre sprouting and neosynaptogenesis, the secretion of IL-1β and TNFα by activated microglia activates the indoleamine 2,3 dioxygenase enzyme that converts tryptophan into kynurenine, thus interfering with the synthesis of 5-HT and giving rise to depressive symptoms (79). Finally, the processing of nociceptive stimuli at the level of the medial prefrontal cortex is increased in depressed subjects, which seems to explain the discrepancy between detectable morphostructural damage and the pain perceived by depressed subjects who are also affected by one of the many highly prevalent diseases of the musculoskeletal apparatus such as low back pain or OA.

THE ROLE OF COGNITIVE-BEHAVIOURAL VARIABLES

Despite our increasing knowledge of the mechanisms governing various sensory processes, including nociception, many aspects of the pain characterising most rheumatic diseases have not yet been fully clarified. The experience of pain is a result of the intersection of multiple biological, environmental, social, cultural, racial, cognitive and behavioural variables that underline the uniqueness of individual patients not only in terms of the clinical manifestations of their symptoms, but also in terms of their responses to treatment. The significance attributed to pain in the context of personal experience contributes to determining the behavioural strategy adopted by patients in order to cope with their condition: subjects with a high sense of self-efficacy (which can be defined as an awareness of being capable of confronting a changed external situation) tend to use active coping behaviours until they have successfully reached their goal, whereas those with a low sense of self-efficacy soon discontinue coping strategies because they expect them to fail. This *maladaptive* style of confronting one's situation is known as "*abnomal illness behaviour*" and defined as "*mislearning how to perceive, evaluate and act in relation to one's state of health*" (80, 81). Maladaptive coping affects the intensity of subjective pain and the global impact of a disease (82, 83), which is why the discordance between the degree of disability reported by patients and that measured by means of specific questionnaires is greater in patients with FM than in those affected by other rheumatic diseases such as RA (84, 85). *Hypervigilance* (paying greater attention to both intero- and exteroceptive stimuli) can also be considered a maladaptive model that leads to a perceptive style of amplifying sensations, including nociception (86).

Another model that can help us to understand the cause of the chronicisation of musculoskeletal pain is that called "fear-avoidance" by Lethem in 1983 (87). The central concept underlying this model is the fear of pain, which leads to the two extreme responses of confrontation and flight. Confrontation (i.e. the activation of active coping mechanisms) will eventually lead to strategies aimed at reducing painful symptoms, whereas flight will tend to exacerbate the fear until, in extreme cases, it leads to the onset of an outright phobia (88).

CONCLUSIONS

The physiopathological mechanisms underlying musculoskeletal pain have been sufficiently clarified in some clinical conditions characterised by acute inflammation, such as the inflammatory *poussès* of the arthritides due to microcrystals. It is more difficult to understand the causes of the chronic musculoskeletal pain that does not seem to be caused simply by persistent activation of peripheral nociceptors, but by changes in the sensitivity of the nociceptive system as a whole (peripheral and central) in genetically predisposed subjects, a pathogenetic interpretation that has been widely studied in algodysfunctional

syndromes, particularly FM, over the last twenty years.

Much more recent is the recognition that the neurophysiological mechanisms underlying central sensitisation syndromes may also play a role in causing the painful symptoms characterising rheumatic diseases, which were previously considered to be peripheral in origin. Neurophysiological alterations compatible with the sensitisation of both the peripheral and central nociceptive pathways have been demonstrated not only in RA, but also in highly prevalent conditions such as OA and aspecific low back pain.

Finally, the induction of peripheral receptor sensitisation in situations of psychological stress supports the hypothesis that, regardless of the underlying rheumatic disease, the chronicisation of pain is due to the interaction of neurohysiological (neuroplasticity), psychological (anxiety/depression) and social factors (familial and working support, income, etc.) (89, 90).

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