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Historical perspective and modern views on pain physiology: from psychogenic pain to hyperalgesic priming

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ABSTRACT

The initial section summarizes the three conflicting concepts about pain already present at the end of the nineteenth centuries, i.e., the Specificity Theory, the Intensive-Summation Theory and the Pleasure Pain Theory and illustrates how, in the following decades, new experimental results partially support other innovative theories such as the Pattern Theory, the Central Summation Theory, the Fourth Theory of Pain and the Sensory Interaction Theory. The second half of the nineteenth century is characterized by the outburst of neurosciences that greatly affects the pain panorama: first of all the neurophysiological approach to nociception and the study of dorsal horn connectivity that leads to the formulation the Gate Control Theory, a genial intuition that is easily understood by clinicians and psychologists. At the same time the identification of nociceptors, the discovery of peripheral and central sensitization and the crucial role of inflammatory mediators such as prostaglandins and cytokines on nociceptive and neuropathic pain associated to the identification of endogenous opioids completely change the approach to pain management. More recently the pain research has been enriched by the advances in neuroimaging, neurobiology and genetics that allow new hypotheses about the mechanisms of development and maintenance of chronic pain.

Key words

Historical review • Pain theories • Neuroscience of pain

Introduction

Pain is the topic to which I mostly contributed during my scientific career, after my initial training in Moruzzi's laboratory at the time when my research was focused on the physiology of specific "states", i.e. sleep and animal hypnosis. In this review I will present, without claiming to be complete, the seminal discoveries and the consequent evolution of the concepts of pain providing the readers with sufficient details to understand the arguments and the conclusions.

The three experimental theories already formulated at the end of the nineteenth centuries – the Specificity Theory, the Intensive-Summation Theory and the Aristotelian concept that pain is an affective quality – presented three conflicting concepts about the nature of pain. The Specificity Theory, definitively formulated by Schiff (1858) and von Frey (1894), stated that pain is a specific sensation with its own sensory apparatus independent of touch. The Intensive-Summation Theory, elaborated by Goldsheider (1998) propose that every stimulus can produce pain if it is strong enough and that stimulus intensity and central summation are the critical determinants of pain.

The Affective Quality of Pain was supported by many philosophers and improved by Marshall (1895), who proposed the Pleasure-Pain Theory. In the attempt to reconcile the views of physiologists, philosophers and psychologists, Strong (1895) suggested that pain consisted of the original sensation and the psychic

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reaction provoked by the sensation while Sherrington (1900) believed that pain was composed of sensory and affective (feeling) dimensions.
The controversy between von Frey and Goldscheider continued during the twentieth century and prompted some authors to believe that pain is subserved by specific receptors which fibers project to the spinal cord where specific pain pathways in the neuraxis carry the pain information to a pain center (Head, 1920).
In the middle of the century Sinclair (1955) and Weddell (1955) proposed the peripheral Pattern Theory suggesting that all fibre endings are alike and the spatial and temporal pattern of their discharge is produced by intense stimulation of non-specific nociceptors. Livingston (1943) proposed his own Central Summation Theory in support of the intensive theory suggesting that nerve and tissue damage activate fibres projecting to spinal internuncial neuron pools creating abnormal reverberatory activity that self excite neural loops. This prolonged, abnormal activity affects spinal cord transmission cells (T) whose multiple projection convey pain information to sympathetic and somatomotor systems and to the higher structures responsible for fear and anxiety.
During the same years the concept of duality of pain proposed by Strong was reintroduced by Hardy et al. (1952) with the Fourth Theory of Pain suggesting that pain includes two components: the perception of pain and the reaction to it. The former includes the structures and the mechanisms responsible for the sensory-discriminative process, while the latter is a psychological process involving the cognitive functions of the individual and is influenced by past experience. The continuous elaboration of Goldscheider intensive summation theory led Noordenbos (1959) to propose the Sensory Interaction Theory which assumes two systems: the slow unmyelinated and small myelinated afferent fibers system, which transmits pain, and the fast myelinated system, which is responsible for the other somatosensory modalities. The former projects to the cells in the dorsal horn and the summation of their input, once transmitted to the brain, is responsible for pain. The latter inhibits the transmission of impulses from the small fibers and prevents summation. Thus, diseases selectively destroying large fibers bring about loss of inhibition and increase the probability of summation and abnormal neural firing.
During the Fifties several observations (primary and secondary hyperalgesia, referred pain, neuropathic pain, the response of peripheral unmielinated fibers to noxious stimuli, the concept of neurogenic inflammation, the existence of chemical mediators (histamine, bradykinin and substance P) that slowly increase pain sensitivity in the environment of a lesion) were systematized in the books of Livingston (1943), Noordenbos (1959) and Bonica (1953) whose book, *The Management of Pain*, was considered a bible by generations of doctors interested in pain treatment.
In 1959, Hengel (1959) summarized most of the advanced clinical approaches on psychogenic pain and developed the concepts that a) pain, especially chronic pain, is a cardinal manifestation of illness (Leriche, 1936); b) pain is both a sensation and a personal experience that observers can not recognize; c) pain is usually, but not always, unpleasant; d) what is experienced and reported during pain is a complex psychological phenomenon; e) pain does not result only from stimulation of peripheral afferents; f) in certain individuals, "pain prone patients", psychic factors play a primary role in the genesis of pain both in absence and in presence of peripheral lesions and may have an adaptive role. Although the article of Engel received a great consensus, in the clinical practice these concepts still find a great difficulty to be applied in general approach to patients.

The Gate Control Theory

The formulation of the Gate Control Theory of Pain (Melzack and Wall, 1965) was the most salient event during the sixties. In a first article Melzach and Wall (1962) reappraise the specificity and the intensive theories and criticise the former because it does not take into account that the information, once coded at the level of the peripheral receptor, can be modulated during the transmission. In addition, they say that threshold to pressure stimuli varies from low to high intensity in a continuous distribution ignoring the evidence (Zottermann, 1933; Iggo, 1959; Hensel et al., 1960) that some unmyelinated afferents respond only to high threshold thermal/mechanical stimuli and behave like nociceptors. As for the intensive theory, they believe that it is strongly supported by the evidence on central summation and input control, but ignore the peripheral specificity. Therefore, they suggest that pain can not be caused

by the neural activity occurring in nociceptive pathways traditionally considered specific for pain, but results from the activity in several interacting neural systems, each with its own specialized function. According to these considerations they proposed the gate control theory for pain (Melzack and Wall 1965) which assumes that 1) in the dorsal horn there is a mechanism modulating the transmission from peripheral afferent fibres to spinal cord T cells; 2) the activity in large fibers tends to inhibits the transmission of small fibers to T cells (gate closure) by activating the inhibitory effect of SG (substantia gelatinosa) gating mechanism; the activity in small fibres tends to excite the trasmission to T cells (gate opening) by blocking the inhibitory effect of SG gating system; the relative amount of activity in the large and small fibres systems is critical for opening the gate; 3) the SG activity and the spinal gate mechanism are influenced by the descending information from the brain; 4) SG axons inhibit presynaptically both large and small fibres projecting to T cells; 5) the large, fast conducting fibre system projects to the central control system which alerts selective cognitive processes able to influence the descending control system modulating the gating mechanisms (Fig. 1). This system is critical for identifying the sensory-discriminative aspects of the stimulus in order to program an appropriate response. Pain and pain behaviour occur when the activity of the T cells exceeds a critical level. The gate theory was expanded by Melzack and Casey (1968) who emphasized the motivational, affective, and cognitive aspects of pain experience and repeatedly re-formulated the theory to conciliate the original proposal with subsequent, incompatible findings.

The fate of the gate theory was extremely ambiguous. The "primary afferent hyperpolarization" (supposed to be produced by SG axon terminals at the level of axon terminals of A fibres synapting to T neurons) has never been confirmed and, on the contrary, both A and C fibres evoke primary afferent depolarization (Franz and Iggo, 1968; Zimmermann, 1968; Whitehorn and Burgess, 1973). Moreover, dismissal of existing data on the functional properties of specific nociceptors became the week aspects of the gate control theory. In fact, Bessu and Perl (1969) identified discrete categories of specific nociceptors and Christensen and Perl (1970) dem-

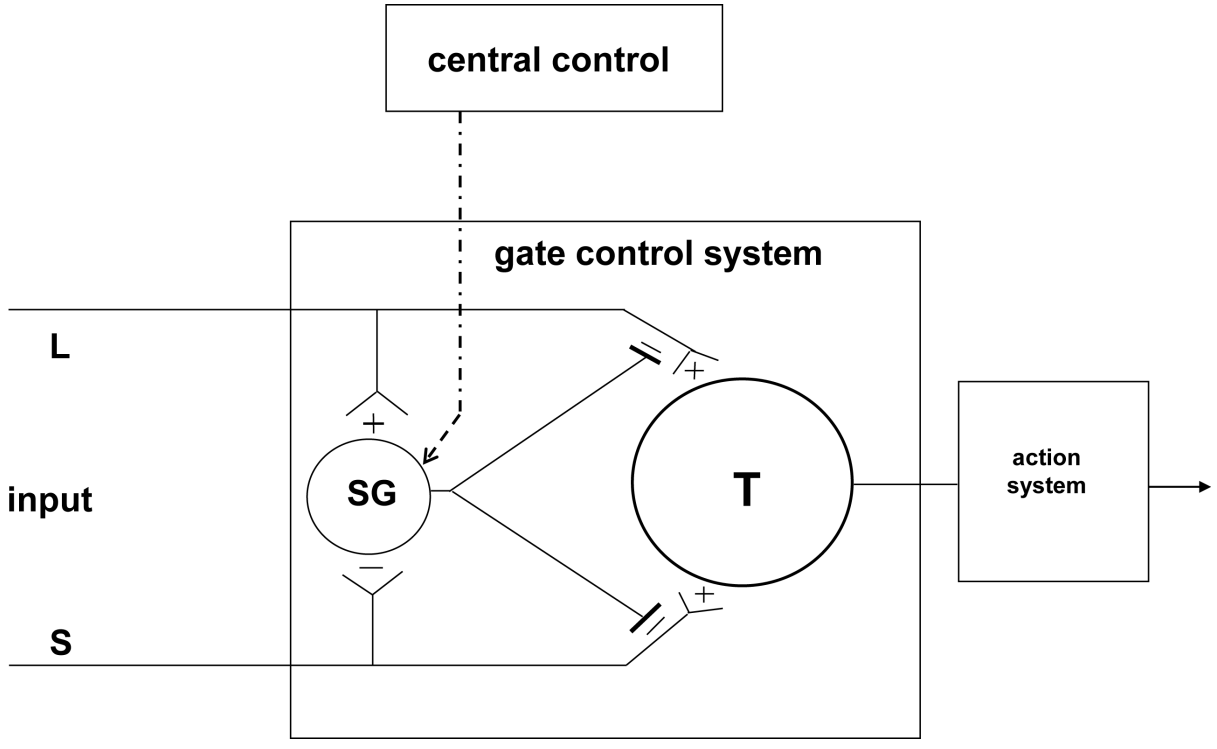

Fig. 1. - The gate control theory for pain (Melzack and Wall 1965).

onstrated nociceptor specific neurons in dorsal horn of the spinal cord. Although only the concept of convergence between different afferent inputs at spinal level proposed by the gate theory survived experimental testing, this theory has the merit to have stimulated a large amount of experiments, emphasized the dynamic/plastic components of pain sensation, drew the attention to pain modulation and to pathological aspects of pain perception.

The endogenous opioid system

Reynolds (1969) showed that electrical stimulation of the brain stem, particularly of the periaqueductal gray matter, elicits analgesia which outlasts the period of electrical stimulation. This finding stimulated a great number of experiments demonstrating that similar effects could be elicited by electrical stimulation of other areas, i.e. the dorsal raphe nucleus, and by systemic (Akil et al., 1972) or local mycroinjections of morphine (Mayer and Murfin, 1976). These effects could be reversed by the opioid antagonist, naloxone (Akil et al., 1972). At the same time, specific opiate receptors were discovered (Pert and Snider, 1973) and localized in discrete areas of the central nervous system (Pert et al., 1974); enkephalins (Hughes et al., 1975) and β-endorphins (Bloom et al., 1978) were isolated in the brain. Experiments performed both in humans and animals revealed that opioid mechanisms were involved in several conditions, such as placebo analgesia (Levine et al., 1978), acupuncture and transcutaneous electrical stimulation, painful and/or stressful manipulations (Mayer, 1979), pregnancy (Gintzler, 1980), mechanical probing of vaginal cervix (Crowley et al., 1976), and restraint (Porro and Carli, 1988). In addition, a tonic control of the nociceptive input by the opioid system and the existence of the non-opioid induced analgesia were demonstrated, like in the condition of diffuse noxious inhibitory controls (DNIC) (Le Bars et al., 1979a and b) and of human hypnosis (Goldstein and Hilgard, 1975), which differs from the naloxone sensitive animal hypnosis (Carli, 1975).

A major event characterizing the Seventies was the foundation of The International Association for the Study of Pain (IASP). In May 1973, at an interdisciplinary meeting held in Issaquah and organized by Professor John J. Bonica (University of Washington) who, after his retirement (1978), devoted all his energies to promote, worldwide, the research on acute and chronic pain and on the approaches to improve pain treatments. On that occasion, it was agreed to launch a journal, called *PAIN*, to be edited by Patrick D. Wall. Initially PAIN was a quarterly journal and the first issue appeared in January 1975. IASP has now more than 6,500 members in 123 countries, 83 national chapters and 14 Special Interest Groups (SIGs).

The publication of the McGill Pain Questionnaire (MPQ) (Melzack, 1975) was a further step in pain studies because the MPP describes the properties of different pain syndromes, contains the PRI (Pain Rating Index) which is the sum of rank values of 4 dimensions (sensory, affective, evaluative and miscellaneous) and the PPI (Present Pain Intensity), which measures the overall pain intensity and provides a standardized, simple tool for measuring the pain experience, particularly suitable in chronic diseases.

Finally, *Behavioral Methods for Chronic Pain and Illness*, a book derived from Fordice' collaborative work at University of Washington (Fordyce, 1976), referred to chronic pain as a behavioural issue, an excess of pain behaviour and relative absence of well-being, based on conditioning and learning. Fordyce shifted the focus of interest from internal influences to negative reinforcement of the social, emotional and physical context of the person's behaviour. The most important application of the psychological approach was the book *Pain and Behavioral Medicine* published by Turk et al. on 1983, which represents a mile stone in the development and utilization of cognitive-behavioral techniques (CBT). They assume that the changes in patients condition depending on ongoing life events, relationships, cognitive and affective patterns and behaviour should be critically examined, as a behavioural change can be induced by environmental manipulation whose cardinal issues are: a) cognitive restructuring; b) strategies for decreasing avoidance; c) introduction of cognitive coping strategies, including attention management, use of imagery or sensory reinterpretation; d) approaches to exercise, behavioural activation and work with family members. Due to the increasing attention to chronic

pain and to its often unsuccessful pharmacological treatment (mainly for neuropathic and cancer pain), CBT, with several subsequent revisions, rapidly became an important tool not only to reduce pain intensity but, mainly, to improve the quality of life.

The era of pain plasticity and pain memory

The initial years of the Eighties were greatly influenced by the studies of Clifford Woolf on pain plasticity and pain memory. He studied the hindlimb flexor reflex in chronic decerebrate rats and showed that the post-injury reflex hypersensitivity may last for weeks. In particular, the production of a thermal injury elicited peculiar reversible changes in the properties of single motoneurons consisting in a decrease in the cutaneous mechanical threshold, expansion in the size of receptive fields and increase in both spontaneous and pinch elicited activity not abolished by a sensory block at the site of the injury (Woolf, 1983). These dynamic changes were confirmed and extended by intracellular recordings from dorsal horn neurons and could explain both the mechanical allodynia after injury and the spread of the receptive field as a consequence of an alteration in the excitability on neurons in the nociceptive pain pathways activated by normally suthreshold peripheral input (Woolf and King, 1989). Such modifications of the spinal cord reactivity, that consolidated the Hardy' concept of secondary hyperalgesia (Hardy et al., 1952), could represent the main mechanisms occurring in the transition from acute to chronic pain condition.

The role of excitatory aminoacids (Mayer and Westbrook, 1987) and neurokinines (Womak and Jessell, 1988) in nociception was clearly defined by Woolf and Thompson (1991). The functional characteristics of aminoacids receptors (N-methyl-D-aspartate, NMDA, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA) and the specific role of nitric oxide synthase, induction of c-*fos* oncogene (Szekely et al., 1989), long term potentiation (Collingridge and Singer, 1990) and synaptic re-modelling (Linch and Baudry, 1984) were seminal findings. It was shown that both NMDA receptors activation and substance P release are involved in the slow temporal summation, a mechanisms activated exclusively by C polymodal nociceptive afferents and considered the basis for centrally mediated hyperalgesia (Dickenson and Sullivan, 1987). These and other mechanisms may be prevented by a small dose of morphine given before nociceptive stimulation, while large doses are required to suppress established hyperexcitability of spinal neurons (Woolf and Wall, 1986). Thus, in clinical pain, nociceptive stimulation should be interrupted as soon as possible, that is, before the central sensitization occurs, and an ideal pre-emptive analgesia before surgery could prevent the occurrence of chronic pain through both a peripheral and a central block of pain transmission.

New important peripheral mechanisms were also discovered. First of all, the presence of a large amount of mechanically insensitive thin fibers (silent or sleeping nociceptors) from both somatic and visceral tissues that become polymodal nociceptors following both repetitive nocicetive stimulation and inflammation and may represent and important factor for spatial summation (Handwerker et al., 1989). It was described also a new class of nociceptors (Aδ and C), which respond to mechanical innocuous stimuli only if persistent and with a delayed onset that parallels a delayed pain sensation and contribute to pain perception. They do not sensitize and do not respond to inflammatory mediators (Adriaensen et al., 1984; White et al., 1991). Moreover, Stein et al. (1989) demonstrated peripheral opioid receptors on the axon terminals of nociceptors. These receptors slowly develop at the beginning of inflammation, bind to opioids released by monocytes and granulocytes and inhibit the generation of action potentials.

As for skin hyperalgesia, it was known that primary hyperalgesia is restricted to the site of the injury, while secondary hyperalgesia is localized in the surrounding area where the tissue is not injured. According to Lewis (1942) the secondary hyperalgesia is due to diffusion of chemical substances released by peripheral fibers that excite neighboring peripheral fibers and result in peripheral sensitization, while Hardy (1952) postulated that sensitization occurs in dorsal horn neurons. A series of elegant experiments by LaMotte et al. (1991) using capsaicin, partially confirmed both hypotheses, i.e., hyperalgesia neurogenically spreads via intracutaneous nerve fibers away from the site of injury but sensitized neurons are localized in the spinal cord and play a major role in pain and hyperalgesia (Simone et al., 1991)

The explosion of the neurobiological approach

The seminal work of Sakmann and Neher (Hamil et al., 1981) enabled to study the behaviour of a single mammalian molecule in real time and to characterize many of the critical properties of ion channels serving as receptors in primary afferent neurons. Other techniques enabled the isolation of cellular mRNA, the synthesis of complementary DNA (cDNA), the tranfection approach of inducing cells to express foreign proteins allowed the study of the function of the proteins expressed in this way in relative isolation. In particular, the screening of transfected cells enabled the identification of the genes encoding receptors in sensory neurons. Once a gene was identified, it was possible to deduce the amino acid sequence of the encoded protein and to generate antibodies to localize the proteins at cellular levels. The selective inactivation of genes in knockout mice**,** genetically engineered mice in which one or more genes have been turned off through a targeted mutation (Capecchi, 1989), greatly improved the studies on the probable functions of specific genes and opened a new field, the pharmacogenomics of pain, aimed at identifying the genetic basis for the variability of drug efficacy, such as morphine (Roses, 2000).

Receptors for inflammatory substances such as bradykinin (B1 and B2), 5-HT (5-HT3) and PGE (EP2) that excite or sensitize nociceptors had been previously identified. When the first G-protein-coupled receptor (GPCR) (Nathans and Ognes, 1983) was cloned (Gilman, 1987), it became clear that many inflammatory mediators such as bradykinin, prostaglandin, histamine, and serotonin act via GPCRs. Indeed, inflammatory mediator activation of GPCR on damage-sensing primary sensory neurons results in activation of adenylate cyclase, and subsequent activation of the cAMP-dependent protein kinase PKA. This is relevant since morphine attenuates hyperalgesia via activation of another GPCR on damage-sensing primary afferent neurons resulting in inhibition of adenyl cyclase decrease in cAMP and inhibition of PKA (Levine and Reichling, 1999). Like morphine, capsaicin became a useful experimental tool for pain studies. Capsaicin, the active component of chili peppers that elicits a burning sensation when it comes in contact with mucous membranes, was first isolated in pure, crystalline form in 1876 by Thresh (1850-1932). Jansco et al. (1977) observed that capsaicin, applied to the skin, produces burning pain, owing the stimulation of peripheral nociceptors; repeated applications deplete pre-synaptic substance P, leading to blockade of neurogenic inflammation. Capsaicin and other pain eliciting substances produce desensitization of these terminals and inhibit pain, although touch and pin prick remain unaffected. In 1997, a research team led by David Julius showed that capsaicin selectively binds to a protein known as TRPV1 that resides on the membranes of pain and heat sensing neurons (Catarina et al., 1997). TRPV1 is a heat activated calcium channel, which opens between 37 and 45°C. When capsaicin binds to TRPV1, it causes the channel to open below 37°C (normal human body temperature), which is why capsaicin is linked to the sensation of heat. Neurons not containing TRPV1 are unaffected. Subsequently, the identification of a considerable number of nociceptive-specific receptors – CMR1 (cold menthol receptor 1), ASICs acid sensing ion channels) and Na+ channels, SNS/PN3 and NaN/SNS2 and inflammatory specific substances exciting/sensitizing nociceptors such as bradykinin (B1 and B2), 5-HT (5-HT3) and PGE (EP2) – suggested the immense potentials for designing new pharmachological therapies targeting nociceptor hyperexcitability.

New evidence has been accumulated that the nervous system modulates immunological and inflammatory responses and this concept has been supported by the identification of neuropeptide receptors on leucocytes and the demonstration that these peptides can regulate leucocyte functions. Mononuclear phagocytes influence host defense responses through their capacity to present antigens and to release several types of soluble mediators. These cytokines act as paracryne fashion in the local environment to stimulate immune responses and, also, in an endocrine fashion, distant

organs, including the central nervous system, that participate to the inflammatory response (Blalock, 1989; Verry et al., 2006; Di Virgilio et al., 2010). The cytokines TNF-α, IL-1β, and IL-6 have direct inflammatory and indirect effects (release of inflammatory mediators, cytokines, prostanoids, bradykinin and serotonin) and bind to the respective receptors located also in nociceptors (Furie and Randolph, 1995).

An interesting neurimmunological anti-inflammatory, fast pathway has been recently described (Tracey, 2002). Circulating cytokines activate receptors on the vagus nerve in the reticuloendotelial system including the liver and spleen. Afferents in the vagus activate sensory pathways that relay information to the hypothalamus and elicit fever and generalized hyperalgesia. Efferent activity from the hypothalamus reaches the efferent fibers of the vagus nerve and leads to acetylcholine (ACh) release in organs of the reticuloendothelial system, including the liver, heart, spleen and gastrointestinal tract. Acetylcholine interacts with α-bungarotoxin-sensitive nicotinic receptors (ACh receptor) on tissue macrophages, which inhibit the release of TNF, IL-1, HMGB1 and other cytokines. The cholinergic anti-inflammatory pathway (vagus and reticuloendotelial system) down regulate cytokines release from major producers (liver and spleen) and redirect the traffic away from periphery to spleen and linphatic nodes, reducing peripheral inflammatory activity.

Pain and chronic pain: new hypotheses

In the present millennium new experimental results have generated original hypotheses and new interpretations about the pain condition itself and the mechanisms of its generation A recent hypothesis (Craig, 2002; 2003a) suggests that pain should be regarded as a homeostatic emotion, akin to temperature, being both a specific sensation and a variable emotional state, as they are similarly processed together in the central nervous system and also non-painful thermal stimuli can elicit sensations of pleasantness or unpleasantness depending on the functional context associated with reflexive autonomic adjustments. In humans, the interoceptive information related to homeostatic and autonomic activity (pain, hunger, thirst, muscle exercise) is conveyed to the spinal cord through somatic and visceral small diameter (A delta and C) primary afferent fibers and is associated with the activity of insula which is reciprocally connected with ACC (Anterior Cingular Cortex), amygdala, hypothalamus and orbitofrontal cortex. The insula plays a crucial role in the modulation of homeostatic functions and in the generation of motivations and emotions critical for survival needs. According to Craig (2002, 2003b), insula and ACC activations provide the essential substrate for the subjective image of the "material me" (Critchley et al., 2002; Damasio, 2003; etc.), in line with the theory linking viscero-afferent feedback to emotional experience originally presented by James (1884). In particular, the same areas involved in "feeling itself" and partially responsible for the perception to be a "behavioural agent" (Craig, 2003) are activated in various pain-related conditions and by non painful information, i.e., sensual touch (Carli, 2009). The latter is conveyed by unmyelinated afferent fibres projecting to lamina 1 neurons in the spinal cord (Vallbo et al., 1999; Olausson et al., 2002; Wallin et al., 2002) and, then, by a pathway common to pain and other homeostatic information (Craig, 2003b). This suggests how a particular individual state may modulate the experience of pain and also why severe pain is not necessarily associated with a low subjective well-being (Huber et al., 2008).

Another new conceptualization proposes (Watts and Swanson, 2002; Jänig, 2006) that the coordinate activation of the three divisions of the motor system – somatic, autonomic and neuroendocrine – are integrated with the sensory representations of the body and are responsible for the generation of behaviour. The transmission of the nociceptive information can be either enhanced or reduced by environmental stimuli (Fields et al., 2006); indeed, psychological or physical stressors elicit fast and slow defence responses, that may be also activated by peripheral nociceptors, and can generate both hyper and hypoalgesia, according to the active and passive body coping strategies able to counteract the homeostatic unbalance. The former (characterized by increased vigilance, heart rate, blood pressure and limb blood flow) is organized by the hypothalamo-mesencephalic and hypothalamus-pituitary-adrenal axis systems activated by the medial prefrontal cortex and is responsible for integrative responses including non-opioid mediated analgesia and avoidance behaviour. The latter (characterized by recuperation and healing of tissues, quiescence, reduced heart rate and vasomotor activity due to parasympathetic prevalence and controlled by the orbital prefrontal cortex) is involved in the opioid mediated analgesia. Both strategies are modulated by the autonomic and endocrine activities interacting between each other (Fields et al., 2006).

Finally, recent research has emphasized the role of the glia and of ATP in pain. There is no doubt that chronic pain is characterized by enhanced sensory neurotransmission that underlies increased sensitivity to noxious stimuli and the perception of non-noxious stimuli as painful. Increasing evidence indicates that glia cells participate to central sensitization: in particular microglia (immunocompetent brain macrofages) and astrocyties, activated by peripheral inflammation and lesion, release pronociceptive mediators such as proinflammatory cytokines IL-6 and TNF-α, prostaglandis and NO (Watkins and Maier, 2002). Thus, the glia plays a critical role in the reorganization of the central nervous system sensory maps after peripheral nerve injury and in the generation of neurophatic pain (Devor and Seltzer, 1999).

It is interesting to underline the important role played by ATP on both peripheral and central sensitization. Indeed ATP, which is present in high levels during inflammation, by enhancing neuronal excitability of nociceptive fibers via the activation of specific ligand-gated ion channels, the P2X3 and P2X2/3 receptors (Burnstock, 2007; North, 2002), promotes the release of IL-1β by linphocytes, monocytes and polymorphonuclear granulocytes by binding to the P2X receptor (Perregaux and Gabel, 1994). In addition ATP activates microglia via P2X4, P2X7 and P2Y12 receptors contributing to neuroinflammation (Virgilio et al., 2010). Several lines of evidence suggest that ATP functions as a pronociceptive neurotransmitter and is able to initiate and to maintain chronic pain (Jarvis, 2010).

Some chronic pain conditions can be initiated by transient episodes of acute pain or may be preceded by episodes of fever, inflammatory diseases, physical and psychological stress. There is now evidence of interactions among intracellular protein kinases and subcellular organelles, such as mitochondria, that can produce long term changes in the excitability of peripheral nociceptors (Joseph and Levine, 2006). In experimental models, a short-lived inflammation (by very low dose of PGE2) is associated with short lived (4 days) mechanical hyperalgesia mainly mediated by activation of adenylyl-cyclase-cyclic AMP-protein kinase A (PKA) second messenger signaling cascade in nociceptive primary afferents. A second inflammatory stimulus applied in the same site after several weeks (latent state of hyperalgesic priming) elicits a drammatically enhanced hyperalgesic response which is greatly prolonged and is mediated by the Gi/o G protein activation of an additional pathway, an isoform ε protein kinase C (PKCε). Since any kind of peripheral sensitization can produce central sensitization, this observation suggests that, in some generalized chronic pain conditions, hyperalgesic priming can contribute to maintain central sensitization and ongoing pain (Reichling and Levine, 2009). Since stress may induce both a sustained condition of increased sensitivity to hyperalgesic effects of proinflammatory cytokines and an elevation of proinflammatory cytokine, hyperalgesic priming of primary afferents in stressed individuals might elicit tonic pain (Reichling and Levine, 2010). It has been suggested that, in fibromyalgic patients (FS), a local trauma generates an initial local hyperalgesic priming that, in a condition of sustained stress**,** is responsible for generalized hyperalgesia and ongoing pain. Interestingly, transient local anesthesia can relieve both hyperalgesic priming in experimental rats and ongoing pain in FS. More in general, it seams that PKCεs are involved in altering the reactivity of excitable cells, including cardiac myocites, to protect them from future repetitive stressful and ischemic events (Barnett et al., 2007).

Summary

After a brief mention of the evolution of pain theories during the last two centuries, the review discusses the main features and the impact of the Gate Control Theory, of the discovery of the endogenous opioid system and of the nociceptive induced mechanisms of plasticity. The last part emphasizes the relevance of genetic and molecular approaches in the study of the relationships between inflammation and chronic.

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