Neuropharmacology of Pain

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15.1 Introduction

Pain, in its acute nociceptive form, is essentially a physiological phenomenon aimed at signaling to individuals exposure, or possible exposure, to forms of high-intensity energy that can damage them, in particular mechanical energy (the impact with a moving body), thermal energy (too hot, too cold), and chemical energy (acidic or basic pH). Pathological pain is identified, with the exception of acute inflammatory pain, with chronic pain, a pain that persists or recurs over time, but which is essentially characterized by a fundamental aspect: the alteration of one or more rules of physiological nociception. Although there are hundreds of pathologies that are dominated by pain, the pathogenetic mechanisms of pain, in their essential aspects, are in extremely limited numbers and identify as many types of pathological pain. In terms of pathogenetic mechanisms, we recognize inflammatory pain, neuropathic pain, mixed pain (that is, with pathogenic mechanisms that can be traced back to both inflammatory and neuropathic pain), dysfunctional pain (for example, fibromyalgia), and mechanical-structural pain (e.g., non-inflamed arthritis). Pelvic pain does not escape this pathogenetic framework.

The recognition of the specific pathogenetic mechanisms along with the identification of the violated nociceptive rules is essential to establish a correct pharmacological approach.

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15.2 Physiology of Pain in a Pharmacological Perspective

The process of painful stimuli is organized into five essential phases: transduction, conduction, modulation, transmission, and perception [1–3].

Transduction is the process that converts forms of high-intensity energy, which are potentially dangerous, into an electrical signal, the generator potential, which in turn favors the onset of the action potential. This phenomenon occurs in the peripheral terminals of the primary, somatic and visceral afferent nociceptive fibers, which have their bodies in the dorsal ganglia. The primary nociceptive neurons of the dorsal ganglia, better known as nociceptors, are high-threshold neurons, specialized in responding to stimuli of high intensity. They possess a peripheral fiber, which innervates the tissues, and a centripetal fiber which penetrates into the spinal cord and enters into synaptic contact with one or more spinothalamic neurons. Their peripheral terminals express in the plasma membrane highly specialized transducer proteins, many of which are ion channels that open in response to specific high-energy stimuli. The influx of calcium and sodium determines the depolarization of the terminal.

Conduction is the phase in which the action potentials travel along the axons to reach the spinal cord. Several isoforms of voltage-gated sodium channels are known, with Nav 1.7, 1.8 and Nav1.9 which are the most abundantly expressed in nociceptors. Nociceptors can have unmyelinated fiber (C fiber) or small myelinated fiber (Aδ fiber). C fibers, which have a slower conduction, are probably those most involved in chronic pain. When action potentials reach nociceptor terminals in the dorsal horns of the spinal cord, N-type voltage-gated calcium channels open and calcium inside the terminal promote the fusion of synaptic vesicles and neurotransmitter release. *Transmission* corresponds to synaptic communication between first- and second-order neurons. The synapse between the nociceptor, or first-order neuron, and the spinothalamic neuron, or second-order neuron, is mainly glutamatergic. In acute nociceptive pain, glutamate binds mainly to AMPA receptors, which are ligand-gated ion channels, highly permeable to sodium ions. They depolarize second-order neurons, triggering the train of action potentials that will reach the thalamus. Spinal synapse activity is finely controlled by several mechanisms that are part of pain *modulation* processes. In fact, not all the impulses coming from the periphery reach the thalamus because the synaptic transmission in the spinal cord is regulated by the action of local interneurons and by projections that descend from the brain stem. The main neurotransmitters inhibiting dorsal horns are opioids, noradrenaline, serotonin, anandamide, and GABA. The opioid system is the main endogenous analgesic system. Opioids produce analgesia by multiple actions in the brain, in the brain stem, in the spinal cord, and, in some cases, also in the peripheral terminals of nociceptors, in the course of inflammation. Endogenous opioids bind to G protein-coupled receptors, which are traditionally divided into three classes: μ, δ, and κ receptors. More recently, a fourth receptor has been added which with its ligand constitutes the nociceptin system. All opioid receptors are coupled to inhibitory G proteins and receptor activation inhibits adenylate cyclase and intracellular

generation of cAMP. However, the coupling of opioid receptors to ion channels for potassium and calcium is believed to be the most important mechanism by which both endogenous and exogenous opioids produce analgesia [4]. In particular, in the dorsal horns of the spinal cord the great majority of opioid receptors is of the μ type, with a presynaptic localization, about 70%, on the spinal terminals of the C and Aδ fibers coming from the periphery. The remaining 30% is located postsynaptically, on the dendrites of spinothalamic second-order neurons. At presynaptic level, the μ receptors are predominantly localized on the C fibers, with a priority role in the control of "slow" pain and especially of chronic pain, of which the C fibers are mainly responsible. Physiologically, endogenous opioids are released in the dorsal horns mainly from interneurons, in turn stimulated by the descending pathways coming from the brain stem, with particular reference to the periaqueductal gray (PAG). Mu receptors have also been identified at this level where their activation unlocks the descending pathway, confirming the supra-spinal contribution of opioids in analgesia. At the spinal level, the presynaptic μ receptors inhibit the opening of N-type calcium channels, preventing the entry of calcium and the vesicular release of neurotransmitters. On the postsynaptic neuron the μ receptors cause the opening of potassium channels, with the outflow of these ions and consequent hyperpolarization and reduced excitability of the second-order neuron. Figuratively, opioids render the first-order neuron "mute" and the second-order neuron "deaf," achieving a profound inhibition of the spinal synapse that underlies their powerful analgesic activity. The *perception* of pain is realized when nociceptive stimuli reach the sensory cortex and is the result of complex phenomena of integration with areas of vegetative and emotional life that make pain "a subjective and multidimensional experience, with an important impact on the physiological state and psychology of the individual" (IASP).

15.3 Pathological Pain

15.3.1 Inflammatory Pain

As mentioned above, pathological pain is characterized by the alteration of some mechanisms of physiological nociception. Modification of the neural structures occurs in acute and, above all, chronic inflammatory pain in which nociceptors at the level of peripheral terminals lower their activation threshold and increase their excitability. This phenomenon is known as peripheral sensitization and is mainly the result of the phosphorylation of numerous molecules peripherally involved in the processing of painful stimuli, including the TRPV1 and the Nav 1.8 voltage-dependent sodium channel [5]. Following phosphorylation, TRPV1 is activated at 37 ° C, instead of at 43 ° C, and Nav 1.8 decreases the duration of its refractory period, opening more frequently and allowing the conduction of high-frequency action potentials. The phosphorylation of these substrates is the consequence of the activation of different kinases by sensitizing agents that operate through their own

membrane receptors, with particular reference to prostaglandins and cytokines, released by inflammatory cells that infiltrate the inflamed tissue. Thus, the pain evoked by generally non-algogenic stimuli (allodynia) or even the spontaneous pain that accompany inflammation is the expression of a reduction or abolition of the nociceptor stimulation threshold, caused by the presence of sensitizing agents. Thus, blocking the synthesis of these agents becomes an essential pharmacological strategy for the treatment of inflammatory pain.

15.3.2 Neuropathic Pain

Neuropathic pain is the result of the lesion or pathology of peripheral, spinothalamic or thalamocortical nociceptive neurons. The peripheral fiber of the dorsal neuron is more frequently affected, with consequent structural and functional modifications affecting both the lesion site and the proximal fiber that reaches the spinal cord from the ganglion. At the point of the lesion, where the fiber can be interrupted, there is a functional reorganization of the proximal stump of the fiber, with the appearance of Nav 1.3 sodium channels and with the progressive reduction of the potassium channels. NaV 1.3 are present during the embryonic life and are particularly excitable, whereas potassium channels are responsible for hyperpolarization and therefore for electrical stabilization of the neuron. The global result of these two modifications is that the DRG becomes much more excitable. It is interesting to note that the expression of some relevant potassium isoforms is under the negative control of BDNF and that some tumors, such as those of the prostate, pancreas, and lung, are able to produce BDNF. Thus, the pathogenetic mechanisms of neuropathic pain are enriched and complicated by the active biochemical contribution of the tumor. Painful stimuli no longer originate from nociceptive terminals, but from the ectopic site that formed at the point of injury. The ectopic site, due to its electrophysiological characteristics, discharges at very high frequency, sometimes spontaneously, sometimes because stimulated by external stimuli [6]. Functional modifications also affect the fiber that reaches the spinal cord. At the presynaptic level, on the fiber terminal, an increase, up to 10 times, in the number of N-type calcium channels occurs. This involves a massive calcium entry and a huge glutamate release, also supported by the high discharge rate of the peripheral fiber. Therefore, in neuropathic pain, blocking the activity of voltage-dependent sodium channels and blocking N-type calcium channels are first-line pharmacological strategies.

15.3.3 Spinal Transmission and Central Sensitization

Whatever the cause in pathological pain there is a massive release of glutamate in the spinal synapse with a greater postsynaptic depolarization. This persistent depolarization removes the Mg^{2+} voltage-dependent blockade of NMDA receptors, the other class of glutamate receptors expressed in second-order neurons, which are

extremely permeable to calcium ions. Activation of the NMDA receptor is an essential step in central sensitization, a phenomenon that always accompanies chronic pain, in which the spinothalamic neuron lowers its activation threshold and transmits nociceptive stimuli more easily. In fact, calcium, acting as a second messenger and activating kinases, participates in phenomena of pathological remodeling of the synapse and spinothalamic neuron [7, 8]. In chronic pain spinal synapse represents a primary pharmacological target to reduce nociceptive transmission and limit the phenomena of synaptic plasticity that worsen the painful state.

15.4 Pharmacological Strategies for the Treatment of Pain

The pharmacological strategies for treating pain should be based on the pathogenetic mechanisms that generated it. Thus, we may recognize four different drug classes with the following actions: counteracting peripheral sensitization, inhibiting the propagation of action potentials, inhibiting spinal transmission and central sensitization, and enhancing the action of descending pathways.

15.4.1 Drugs Acting on Peripheral Sensitization

These are drugs that inhibit the synthesis of prostanoids and cytokines, which are mainly responsible for peripheral sensitization. NSAIDs, COXIBs, and corticosteroids belong to this group. NSAIDs and COXIB inhibit COX-1 and COX-2 with different selectivity and potency. They are appropriate in all forms of inflammatory pain. Corticosteroids have different mechanisms of action, but their anti-inflammatory activity depends mainly on the inhibition of the transcription factor NFκB. NFκB regulates gene transcription and therefore the expression of several pro-inflammatory cytokines, including IL-1, IL-6, TNFα, INF-γ, some enzymes, including COX-2 and inducible NOS, and proteins variously involved in inflammation. Corticosteroids are often used for their anti-edema properties in neuropathic pain, thus reducing the compression on nerve fibers.

15.4.2 Drugs Acting on Nerve Fibers

These are drugs that act directly on the damaged nerve fiber, counteracting the propagation of action potentials and the abnormal release of neurotransmitters at the level of the spinal synapse. They act on voltage-dependent sodium channels and on N-type voltage-dependent calcium channels. They are appropriate for neuropathic pain and mixed pain. Voltage-dependent sodium channel blockers arise as anticonvulsants, anti-arrhythmics, or as local anesthetics such as carbamazepine, oxcarbazepine, lamotrigine, and lidocaine. The drugs that act on the N-type calcium channels are pregabalin and gabapentin. Despite the name, their

mechanism of action does not involve the gabaergic system, but even defining them as blockers is certainly inaccurate. As previously described, in the lesion of the first-order neuron there is a modification which also affects the proximal fiber entering the spinal cord, with an increase up to 10 times in the expression of the N-type calcium channels. This phenomenon is believed to be due to an accumulation of the channel in the cell membrane due to defects in its cellular "trafficking," i.e., the channel is introduced into the membrane but is no longer removed. In this traffic block, specific for calcium channels, the α2δ accessory subunit could play a role: in fact it is the α2δ subunit that makes contact with the extracellular matrix and acts as an anchor that prevents channel internalization. The gabapentinoids, also known as ligands of the α2δ subunit, by binding to these subunits would favor the un-anchoring and internalization of the channel. So these drugs do not block N-type channels but promote a reduction in their number by restoring their cellular traffic, thus reducing the release of glutamate in the synapse [9]. This mechanism of action underlies the fact that these are not fast-acting drugs, they must be administered for sufficiently long periods of time and are not appropriate for inflammatory pain. Ziconotide, a synthetic analogue of ω-conotoxin, a peptide produced by a marine snail, is a direct blocker of the opening of the N-type calcium channels. It is a first-line drug for intrathecal administration, both for nociceptive and neuropathic pain.

15.4.3 Drugs Acting on the Spinal Synapse

This group of drugs interferes with spinal synaptic transmission and through this action counteracts the establishment and effects of sensitization.

15.4.3.1 Paracetamol

Paracetamol is generally classified among NSAIDs, with which it shares the antipyretic and analgesic actions, but not the anti-inflammatory action. Its belonging to this pharmacological class depends on its ability to "in vitro" inhibit COX-1 and COX-2. However its power of inhibition is very small compared to other members of the class. Furthermore the action of paracetamol is inhibited in situations of high concentration of peroxides, as typically happens in inflamed tissues. This would explain the absence of anti-inflammatory effects of paracetamol and would suggest that also its analgesic effects may rely on molecular and cellular mechanisms distinct from those of NSAIDs. Paracetamol easily crosses the blood–brain barrier and is metabolized in the CNS in a compound known as AM 404. The chemical structure of AM404 is very similar to that of anandamide, one of the most important endogenous cannabinoids, and this is basis of its mechanism of pharmacological action. AM404 is a weak agonist of the cannabinoid receptors CB1 and CB2, but above all it is an inhibitor of the transporter responsible for the reuptake of anandamide, causing its synaptic accumulation and prolonging its pharmacological effects. Therefore paracetamol, through its metabolite AM404, would enhance the

endocannabinoid tone in numerous areas of the nervous system, including the dorsal ganglia and the dorsal horns of the spinal cord, where the metabolite performs part of its analgesic activity [10].

15.4.3.2 Opioids

Opioids constitute the reference pharmacological class in the treatment of cancer pain and pain related to surgery. However, in the last 20 years, because of their high analgesic activity, opioid use has been extended to chronic pain [4]. The opioid drugs used in analgesia are frequently full μ receptors agonists. These include morphine, oxycodone, hydromorphone, fentanyl, and methadone. These opioids are generally referred as strong opioids. All these drugs, although having comparable efficacy, where the efficacy coincides in this case with the maximum possible analgesic response, have different potencies. This means that to produce the same analgesic effect they must be used at dosages sometimes very different from each other. The different potency of opioid drugs can be a problem when it is necessary to switch from one drug to another, to so-called opioid rotation, a relatively frequent occurrence in the treatment of cancer pain. For this reason the concept of "equianalgesia" was introduced, which underlies the fact that to obtain the same analgesia, passing from one opioid to another, different dosages must be used according to a conversion system, dictated more by clinical practice than by rigorous pharmacodynamic and pharmacokinetic arguments, that consider morphine as the reference opioid for calculations. In both cancer and non-cancer pain, partial agonists are frequently used and are generally referred as weak opioids. In fact these drugs activate μ receptors, but they produce a reduced maximal effect than full agonists. The reduced efficacy of weak opioids is often referred as "ceiling effect." Interestingly, buprenorphine, a weak opioid, has a higher potency than morphine. So, at the higher doses, buprenorphine will show "a ceiling effect" compared to morphine, but at lower doses the analgesic effects of buprenorphine are higher than morphine. Other partial agonists are tramadol and tapentadol, which compensate for their modest activation of the μ receptors with a second mechanism of action: the inhibition of the reuptake of serotonin and noradrenaline, or of the noradrenaline alone, respectively. Codeine, which has always been considered the most typical of weak opioids, is simply a prodrug that must be converted to morphine through the action of CYP450 2D6. From this brief discussion it is clear that the old distinction between weak and strong opioids is greatly simplifying and of little clinical use, especially in chronic non-cancer pain.

15.4.3.3 Cannabinoids

The endogenous cannabinoid system is particularly widespread and presides over various functions including the control of nociception. For this reason its components, receptors, ligands, and enzymes, are strategically located in essential nodes for the control of pain, such as the dorsal ganglia, the dorsal horns of the spinal cord, the PAG, the thalamus, and the cingulate cortex. In the spinal synapse the endocannabinoid system could physiologically function "on demand," basing its activity on

retrograde transmitters, acting as a brake on nociceptive transmission. The role of phytocannabinoids and synthetic cannabinoids in the treatment of pain is the subject of numerous studies, especially with a view to their use in combination with opioids. Their possible use in some types of neuropathic pain is promising and widely debated, but no clear clinical evidence have still emerged [11, 12].

15.5 Drugs Potentiating the Activity of Descending Pathways

The pathways descending from the brainstem mainly release serotonin and noradrenaline, which, directly or through the activation of interneurons, inhibit the spinal synapse. In particular, norepinephrine can be released from fibers descending from the *locus coeruleus*, the most important noradrenergic nucleus of the CNS. Norepinephrine binds to α2-adrenergic receptors located on the presynaptic membrane of the spinal synapse, which inhibit calcium channels and therefore glutamate release. The pharmacological manipulation of the descending pathways can be obtained according to three different strategies: increasing the discharge of the descending pathways, prolonging the action of serotonin and noradrenaline in the spinal synapse, and mimicking their action. Regarding the first aspect, there are several drugs that possess the property, often ancillary, of activating the descending pathways, or removing a tonic inhibition exerted on them by inhibitory interneurons. For instance, both opioids and gabapentinoids by acting in the brainstem can inhibit inhibitory interneurons whose activity prevents the discharge of descending pathways: an inhibition of an inhibition. A direct activation can be obtained with paracetamol, especially if given as i.v. bolus, and cannabinoids; both activate central TRPV1 expressed by PAG neurons, causing their depolarization. The second strategy is the best known: the use of serotonin and norepinephrine reuptake inhibitors, namely tricyclic antidepressants such as amitriptyline or SNRIs such as duloxetine and venlafaxine. It should be stressed that the effects of these drugs is independent of their action on the mood and that the onset of their analgesic activity is not delayed as their antidepressant activity in the psychiatric setting. The third strategy mainly concerns agonist drugs directly stimulating α2-adrenergic receptors expressed in the spinal cord: clonidine and dexmedetomidine.

15.6 Conclusions

The knowledge of the pathogenetic mechanisms underlying pain is an essential prerequisite for the appropriate use of analgesic drugs. On the other hand, the definition of the pharmacological classes on the basis of their targeted pathogenetic mechanisms is a need to maximize therapeutic results, minimizing adverse effects.

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