Can we conquer pain?

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Pain can be an adaptive sensation, an early warning to protect the body from tissue injury. By the introduction of hypersensitivity to normally innocuous stimuli, pain may also aid in repair after tissue damage. Pain can also be maladaptive, reflecting pathological function of the nervous system. Multiple molecular and cellular mechanisms operate alone and in combination within the peripheral and central nervous systems to produce the different forms of pain. Elucidation of these mechanisms is key to the development of treatments that specifically target underlying causes rather than just symptoms. This new approach promises to revolutionize pain diagnosis and management.

There is an extraordinary dichotomy in the pain field. Exciting progress is being made in dissecting out the molecular and cellular mechanisms that operate in sensory pathways to generate those neural signals that we ultimately interpret as pain[1,2]. However, for many patients, pain continues to produce severe distress, dominating and disrupting the quality of their lives. Much of currently available clinical treatment is only partially effective and may be accompanied by distressing side effects or have abuse potential[3]. Increasing numbers of elderly people in the population means a rising prevalence of age-related painful conditions like osteoarthritis that require successful pain treatment[4]. Improvements in the management of cancer increase life expectancy, but are accompanied by a rise in the cumulative incidence of tumor-related pain syndromes as well as of pain associated with therapy, such as chemotherapy-induced painful polyneuropathy. The unmet clinical need, the personal suffering and societal economic costs of pain are substantial. To bridge the gap between the ever-advancing understanding of the neurobiology of pain and the lack of success in clinical pain therapy, a greater and more sophisticated effort needs to be directed to the discovery of targets for new analgesics. In addition, the clinical approach to pain needs to be reevaluated: a change is required from an empirical management strategy to one where the mechanisms responsible for pain in an individual patient are identified and tackled with specific treatments[5].

Why pain?

Although we use a single word to describe any feeling that is unpleasant and hurts, this does not mean that pain is a monolithic entity. There is pain as a sensory experience and pain as perceptual metaphor of suffering or grief. We deal here only with the former. Pain the sensation can be further split into distinct categories. Pain normally serves as a warning device, an alarm system activated in response to impending damage to the organism. This nociceptive pain is activated only by noxious stimuli acting on a specialized high-threshold sensory apparatus (**Fig. 1a**). Nociception is essential for the survival of organisms in a potentially hostile environment. Nociceptive pain, once it is present, once the alarm has gone off, so dominates attention that it is more like a motivational drive than a sensation, resembling hunger, thirst or sexual desire.

The threshold for eliciting pain has to be high enough that it does not interfere with normal activities but low enough that it can be evoked before frank tissue damage occurs. This threshold is not fixed and can be shifted either up or down, which may be either adaptive or maladaptive. Shifts in pain threshold and responsiveness are an expression of neural plasticity, the neurobiological means by which changes in the nervous system can modulate the response to any stimulus. Such plasticity or modifiability of the sensory system essentially characterizes clinical pain syndromes[2,6].

Once tissue has been damaged mechanically or by infection, ischemia, tumor growth or an autoimmune process, multiple chemical mediators are released from damaged and inflammatory cells. The resulting 'inflammatory soup' is rich in cytokines, growth factors, kinins, purines, amines, prostanoids and ions, including protons[7,8]. Some inflammatory mediators directly activate nociceptors, evoking pain. Others act together to produce a sensitization of the somatosensory nervous system, which is characteristic for inflammatory pain, enabling easier activation of the pain pathway until the tissue heals (**Fig. 1b**). Maladaptive plasticity represents those changes that generate spontaneous and exaggerated pain with no discernable protective or reparative role. The pain becomes the pathology, typically via damage to or dysfunction of the peripheral or central nervous system, termed 'neuropathic pain' (**Fig. 1c**). A reduction in pain sensitivity by recruiting intrinsic inhibitory mechanisms can also occur, particularly in those conditions where an emergency reaction is a greater imperative than preventing tissue damage[9].

Pain mechanisms

Nociceptive, inflammatory and neuropathic pain result from diverse mechanisms. Some of these mechanisms are unique to one painful condition; others are present in multiple clinical syndromes, or may be expressed at different times during the natural history of a syndrome. In some patients, a single mechanism may produce their pain; in others, multiple mechanisms may contribute. The same symptom (for example, pain in response to light touch of the skin) may be generated by a number of mechanisms. Moreover, a single mechanism (for example, upregulation of a voltage-gated sodium channel) may potentially pro-

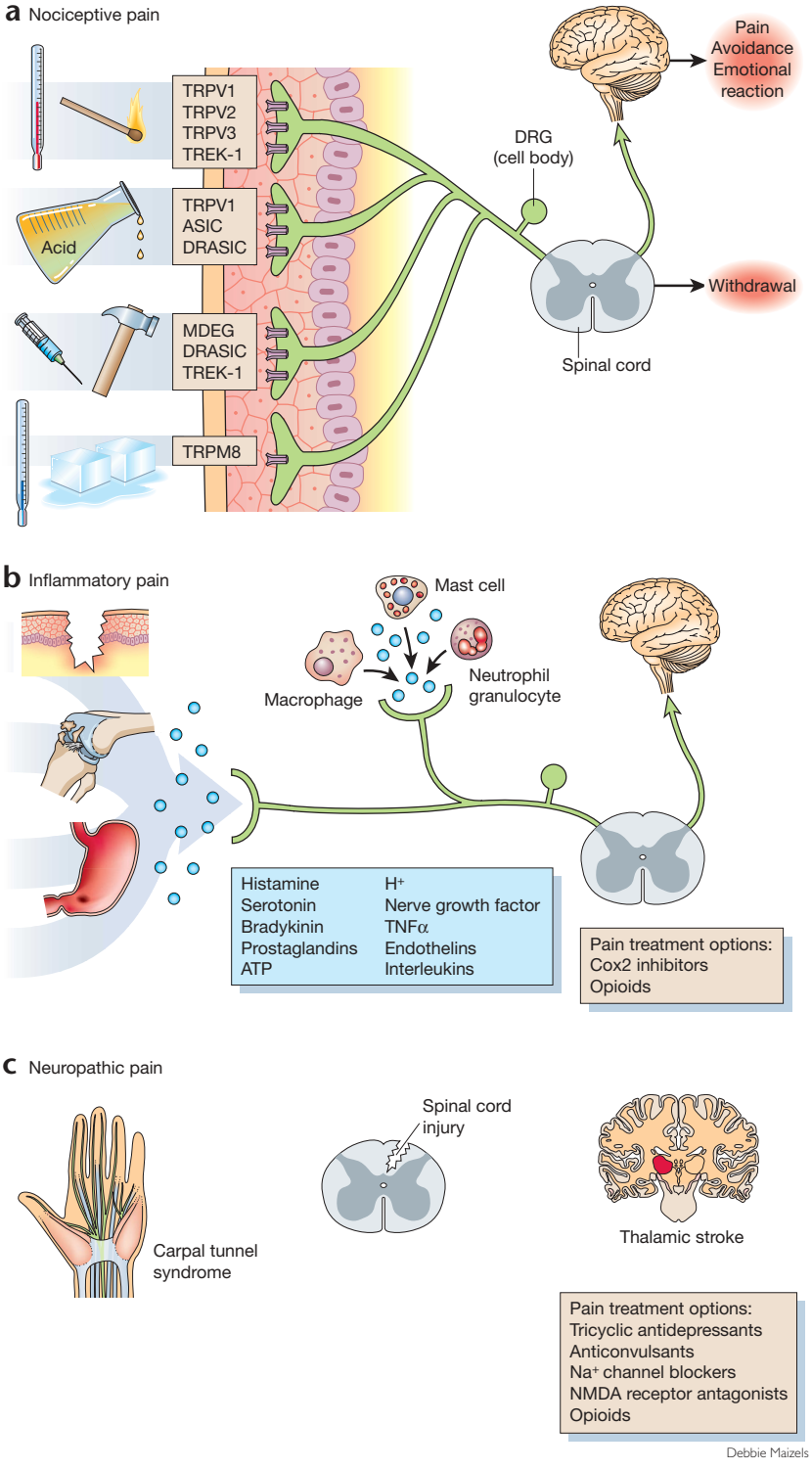

Fig. 1. Nociceptive, inflammatory and neuropathic pain. (**a**) Noxious stimuli are transduced into electrical activity at the peripheral terminals of unmyelinated C-fiber and thinly myelinated Aδ-fiber nociceptors by specific receptors or ion channels sensitive to heat, mechanical stimuli, protons and cold. This activity is conducted to the spinal cord and, after transmission in central pathways, to the cortex, where the sensation of pain is experienced. (**b**) Damaged tissue, inflammatory and tumor cells release chemical mediators creating an 'inflammatory soup' that activates or modifies the stimulus response properties of nociceptor afferents. This, in turn, sets up changes in the responsiveness of neurons in the CNS (**Fig. 2**). (**c**) Neuropathic pain arises from lesions to or dysfunction of the nervous system. Conditions affecting the peripheral nervous system, as in carpal tunnel syndrome, the spinal cord after traumatic injuries or the brain after stroke, can all cause neuropathic pain, which is characterized by a combination of neurological deficits and pain.

duce different symptoms like spontaneous burning pain, shock-like pain or paresthesias (pins and needles)[10].

Nociceptor Aδ and C somatosensory afferent terminals transduce external noxious stimuli into electrical activity. The resultant action potentials are conducted to the dorsal horn of the spinal cord, and the input is conveyed, after synaptic processing, via the spinothalamic and spinoparabrachial pathways to higher centers[11]. Activity in the spinothalamic tract relays through the thalamus to the somatosensory cortex and associated areas. The parabrachial nucleus of the brainstem has connections to the ventral medial nucleus of the hippocampus and the central nucleus of the amygdala, brain regions involved in the affective response to pain. Impulses from supraspinal centers are integrated in the midbrain periaqueductal gray, which is pivotal in modulating descending facilitation and inhibition of nociceptive input mainly via the nucleus raphe magnus[11].

Nociceptor function is substantially modified in response to tissue damage, inflammation or injury of the nervous system. Post-translational and transcriptional changes can profoundly alter the threshold, excitability and transmission properties of nociceptors, contributing to pain hypersensitivity and spontaneous pain (**Fig. 2**). Changes can be localized to the peripheral terminal (peripheral sensitization), the site of axonal injury or the central synapse, or produce general alterations in membrane properties. Some of the changes are rapid, as with a reduction in heat pain threshold following phosphorylation of the heat transducer receptors TRPV1 (VR1) and TRPV2 (VRL-1). Others require retrograde transport of signals to the cell body, activation of signal transduction cascades, changes in transcription and then orthograde transport of proteins to the peripheral or central terminals[12].

Activation of nociceptors is not, however, the only way to trigger pain. After peripheral tissue injury or damage to the nervous system, low-threshold sensory fibers, which normally

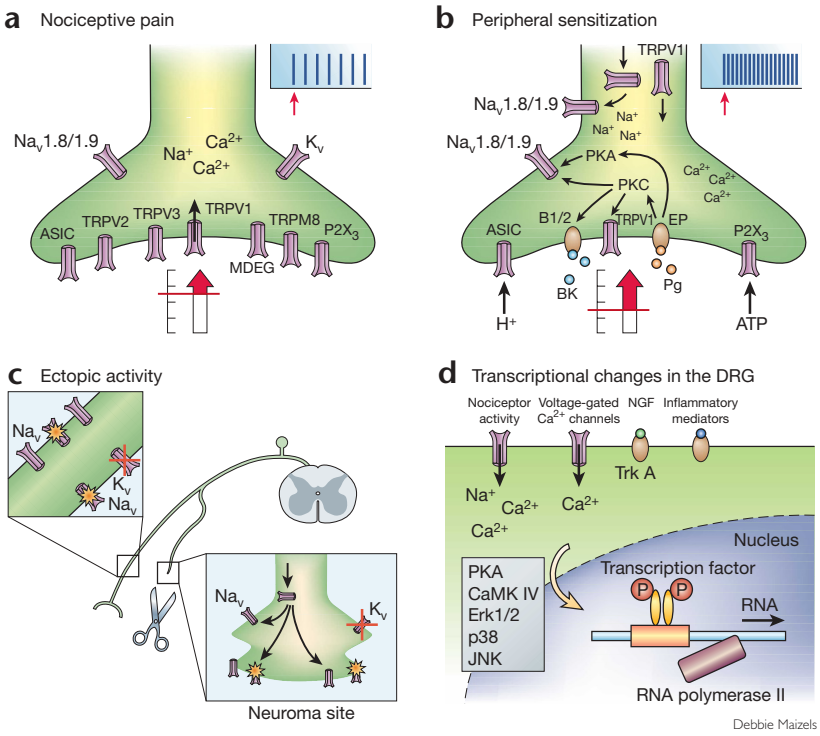

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Fig. 2. Nociceptor-mediated pain represents those pain conditions driven by activation of peripheral nociceptor sensory fibers. (**a**) Nociceptive pain is produced under physiological conditions only by noxious stimuli acting on high-threshold nociceptors. (**b**) With inflammation, components of the 'inflammatory soup', such as bradykinin or prostaglandins, bind to G-protein-coupled receptors and induce activation of protein kinases A and C in nociceptor peripheral terminals, which then phosphorylate ion channels and receptors. As a result, the threshold of activation of transducer receptors such as TRPV1 is reduced, and the excitability of the peripheral terminal membrane increases, producing a state of heightened sensitivity, termed 'peripheral sensitization'. (**c**) After injury to nociceptor neurons, increases in transcription or altered trafficking of sodium channels as well as a reduction in potassium channels increases membrane excitability sufficiently so that action potentials are generated spontaneously (ectopic activity). (**d**) Activity-dependent signal transduction cascades and signaling pathways downstream to receptors bound by cytokines and growth factors act to modify transcription in nociceptor neurons. Altered production of numerous proteins modifies the phenotype of the neurons, changing their transduction, conduction and transmission properties.

only produce innocuous sensations like light touch, can begin to produce pain, a very substantial change in the normal functional specificity of the sensory system (**Fig. 3**). Although this pain obviously no longer represents the presence of a damaging external stimulus, to the individual it feels that the pain arises in the periphery from a noxious stimulus. Such a shift in the excitability of the CNS contributes to the hypersensitivity to non-painful stimuli after surgery or during migraine attacks, as well as the diffuse muscle tenderness of myofascial syndromes, and sensory abnormalities of the gastrointestinal tract in non-cardiac chest pain and irritable bowel syndrome[13,14].

Increases in synaptic transmission in the dorsal horn (central sensitization) can begin almost immediately as a result of activity-dependent phosphorylation and trafficking of receptors or ion channels. Central sensitization can be sustained for some time by transcriptional changes, including induction of genes such as Cox2 to generate PGE_2, which alters the excitability of neurons. Structural alterations in the synaptic contacts of low-threshold afferents with pain transmission neurons, or a reduction of inhibitory mechanisms due to a loss of interneurons, represent persistent changes in the CNS that eventually result in a fixed state of sensitization (**Fig. 3**).

Immune cells may be involved in inflammatory pain, cancer pain and pain after nerve injury. They are activated both in the periphery and within the central nervous system in response to tissue damage, inflammation or mechanical nerve lesions[15]. The immune reaction may increase nociception through the release of cytokines, but granulocytes and monocytes can also promote analgesia by secreting β-endorphin and enkephalin[16].

A need for smarter drugs

Current analgesics have been discovered by empirical observation or serendipity. These include opiates—the analgesic activity of opium poppy extracts that have been recognized for millennia—and non-steroidal anti-inflammatory drugs (NSAIDs), a prototypic member of which is salicylic acid, the active ingredient in willow bark, a folk remedy for inflammation and pain. The local anesthetic activity of cocaine was reported one hundred years ago without any knowledge of sodium channels. More recently, tricyclic antidepressants and anticonvulsants, including carbamezepine and gabapentin, were found to produce analgesia empirically, not through any knowledge of their molecular targets[17]. Triptans have substantially improved the management of migraine. These 5-$HT_{1B/1D}$ agonists were initially developed to produce cranial vasoconstriction, but their inhibitory effects on trigeminal and second-order neurons may be more important[18]. One great success in modern pain pharmacology has been the introduction of Cox2-specific inhibitors, but rather than possessing improved efficacy, these drugs produce less gastric and bleeding side effects by not inhibiting Cox1 (ref. 19).

Genetic background affects nociceptive pain sensitivity in animals and may influence susceptibility to the development of persistent pain[20]. A patient's gender or genes may also interfere with the response to analgesic drugs. Different expression patterns of opioid receptors may explain why some patients are insensitive to opioids. The metabolism and biological availability of numerous drugs, including tricyclic antidepressants, codeine, tramadol and the NMDA antagonist dextromethorphan[21], depend on the allelic polymorphism of the hepatic cytochrome P450 monooxygenase system.

The mechanisms that individually or collectively produce pain now need to be seen as representing the targets for the rational development of novel analgesics. Two general approaches for the discovery of novel pain targets have evolved: either evaluation in depth after a focused search of the particular role of an individual protein in producing pain[1,2,11], or mass screening using high-throughput mRNA or proteomic screens[22]. The former has been used with great effectiveness to unravel many of those receptors

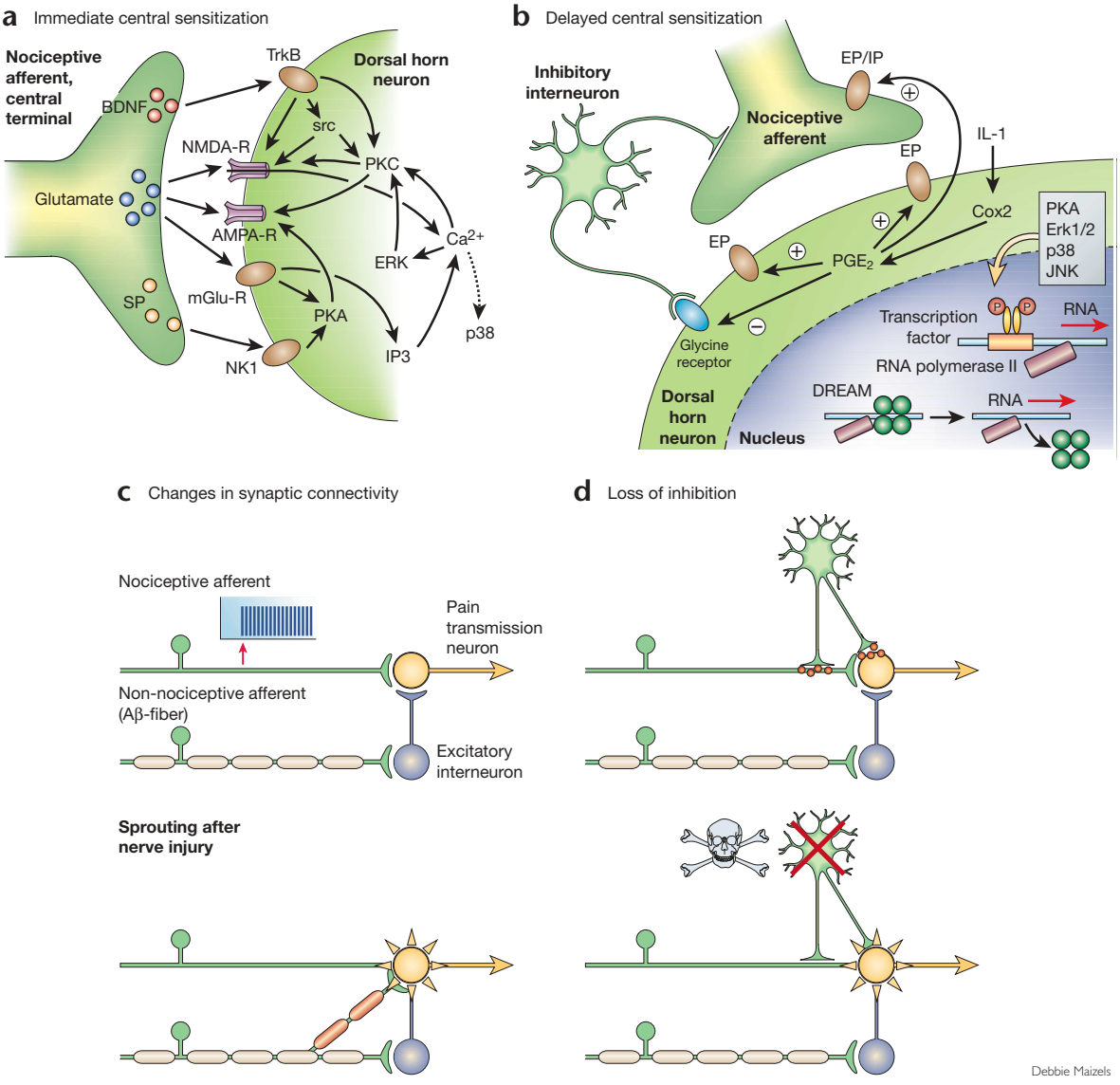


Fig. 3. Non-nociceptor-mediated pain is generated by sensory inputs that would normally produce an innocuous sensation, and reflects a change in the functioning of central neurons. (**a**) Activity-dependent central sensitization. An immediate and relatively short-lasting increase in the excitability and responsiveness of pain transmission dorsal horn neurons, which is due to phosphorylation of ion channels and receptors and follows nociceptor-driven transmitter release and activation of intracellular kinases. Eventually, the response to normally subthreshold inputs is increased. (**b**) Transcription-dependent central sensitization. Enhanced gene expression due to the activation of transcription factors, as well as the removal of repressors like DREAM, results in long-lasting changes in the function of dorsal horn neurons. Cox2 induction leads to PGE_2 production, which acts pre- and postsynaptically to facilitate excitatory and reduce inhibitory transmission. (**c**) After peripheral nerve injury, the central terminals of myelinated non-nociceptive Aβ-afferents sprout in the dorsal horn and form new connections with nociceptive neurons in laminae I and II. This re-wiring of the circuitry of the spinal cord may contribute to persistent pain hypersensitivity. (**d**) Disinhibition. Normal sensory inflow is actively controlled by inhibitory interneurons. Reduced synthesis of the inhibitory neurotransmitters GABA and glycine or loss of these inhibitory interneurons after excessive release of the excitotoxic amino acid glutamate following peripheral nerve injury increases the excitability of pain transmission neurons such that they begin to respond to normally innocuous inputs.

and ion channels responsible for transducing noxious stimuli in the periphery and for modulating sensory processing in the dorsal horn of the spinal cord (**Fig. 4**). The latter has only begun to be applied, but is revealing that many hundreds of genes change their expression in sensory neurons after damage to a peripheral nerve or exposure to inflamed tissue. These include genes never before described in the nervous system, whose function is presently unknown.

Targeting pain mechanisms

The notion that there is a class of drug, a universal analgesic, that can intrinsically reduce all pain, is obsolete and has to be abandoned. Pain is heterogeneous in terms of etiological factors, mechanisms and temporal characteristics. Consequently, treatment must be targeted not at the general symptom, the pain, or its temporal properties, acute or chronic, but rather at the underlying neurobiological mechanisms responsible (**Fig. 5**).

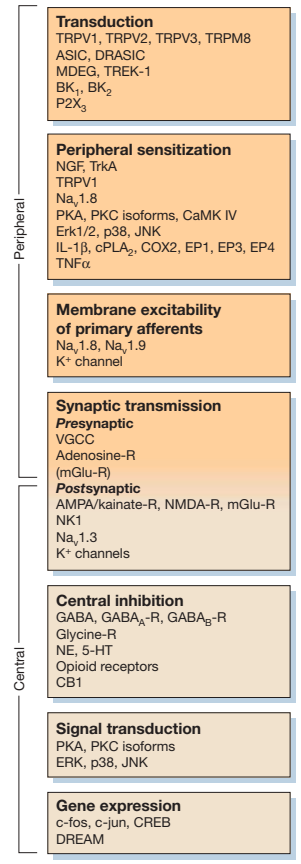
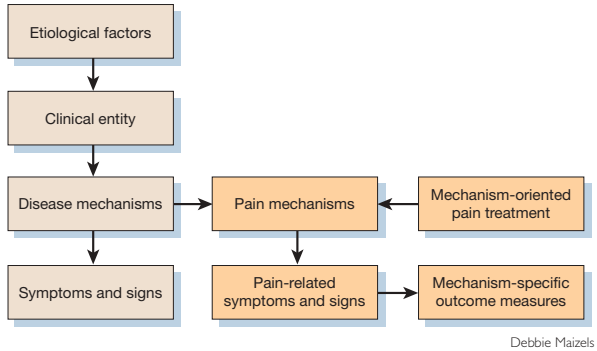


Fig. 4. Key molecular elements in the transduction, transmission and signal processing of nociceptive input in the peripheral and central nervous system represent potential targets for the development of new analgesics.

The first need, clearly, is to identify the major mechanisms that participate in producing clinical pain syndromes. The validation of animal models, showing that they are actually surrogates for mechanisms present in human patients, is a key issue. Although it is possible to produce a stereotyped pain-like behavior in animals, this does not mean that the mechanisms involved in these models are identical to those found in patients, where the complexity, onset and persistence of pain tend to be very different. Some conventional outcome measures in animal nerve injury models, like heat pain hypersensitivity, are not features of clinical neuropathic pain. Moreover, spontaneous pain, a major clinical problem, cannot be directly measured in animals[23]. Although functional imaging reveals the regions in the human brain activated during pain and may provide an objective way of assessing pain and its response to treatment[24], it does not disclose mechanisms.

Fig. 5. Rational treatment of pain requires identification of pain mechanisms as targets of drug therapy. Conventionally therapeutic interventions are aimed at disease mechanisms (disease modifying) or providing symptomatic pain relief, based on empirical knowledge and evidence from drug trials. However, pain is driven not by disease but by pain mechanisms. A standardized assessment of pain-related symptoms and signs is required to determine the pain mechanisms present in an individual patient, and management of pain needs to be targeted at these mechanisms. Outcome measures should reflect changes in pain mechanisms instead of the overall intensity of pain.



The second need is to develop therapeutic tools to specifically interrupt the particular pain mechanisms. This will require identifying the key molecular targets involved in the manifestation of the mechanism and finding specific activators or inhibitors, whatever appropriate, by high-throughput pharmaceutical screens with proof-of-concept trials in patients. One problem is what clinical outcome measures should be applied to evaluate effects on pain mechanisms. Current clinical analgesic trials select patients on the basis of disease and use crude global outcome measures; no effort is made to identify mechanisms. Symptoms, signs and special investigations should be used to define mechanisms participating in the generation of a painful condition. The number needed to treat (NNT), a measure of how many patients have to be treated to see a 50% response, varies from 1.7 to over 10 for the analgesics currently available for neuropathic pain[3]. This reflects the lack of efficacy of empirically administered analgesics, some of which are aimed at targets that may not be expressed in a given patient. Cox2 inhibitors will only work, for example, if Cox2 has been induced.

Although this decade has been dedicated the "Decade of Pain Control and Research" by the US Congress, too little attention continues to be directed at pain research, and success at controlling pain remains limited. However, conquering pain, using the understanding of its nature, mechanisms and molecular components to drive the pharmaceutical screening and development of new analgesic drugs, is at last a realistic prospect, albeit a daunting challenge.

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