

Hopes for the Future of Pain Control

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ABSTRACT

Here we aim to present an accessible review of the pharmacological targets for pain management, and succinctly discuss the newest trends in pain therapy. A key task for current pain pharmacotherapy is the identification of receptors and channels orchestrating nociception. Notwithstanding peripheral alterations in the receptors and channels following pathophysiological events, the modulatory mechanisms in the central nervous system are also fundamental to the regulation of pain perception. Bridging preclinical and clinical studies of peripheral and central components of pain modulation, we present the different types of pain and relate these to pharmacological interventions. We firstly highlight the roles of several peripheral nociceptors, such as NGF, CGRP, sodium channels, and TRP-family channels that may become novel targets for therapies. In the central nervous system, the roles of calcium channels and gabapentinoids as well as NMDA receptors in generating excitability are covered

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including ideas on central sensitization. We then turn to central modulatory systems and discuss opioids and monoamines. We aim to explain the importance of central sensitization and the dialogue of the spinal circuits with the brain descending modulatory controls before discussing a mechanism-based effectiveness of antidepressants in pain therapy and their potential to modulate the descending controls. Emphasizing the roles of conditioned pain modulation and its animal's equivalent, diffuse noxious inhibitory controls, we discuss these unique descending modulations as a potential tool for understanding mechanisms in patients suffering from pain. Mechanism-based therapy is the key to picking the correct treatments and recent clinical studies using sensory symptoms of patients as surrogates for underlying mechanisms can be used to subgroup patients and reveal actions of drugs that may be lost when studying heterogeneous groups of patients. Key advances in the understanding of basic pain principles will impact our thinking about therapy targets. The complexity of pain syndromes will require tailored pharmacological drugs, often in combination or through drugs with more than one action, and often psychotherapy, to fully control pain.

Keywords: Analgesia; Anti-depressants; Central sensitization; Descending controls; Pain mechanisms; Pregabalin

OVERVIEW OF PAIN PROCESSING

Organisms need to process incoming sensory information and then respond to the external world. Consequently, pain alters and overlaps with other CNS functions such as those concerned with mood and responses to the outside world. All organisms need to sense their environment and so our peripheral pain receptors evolved from sensors seen in primitive creatures. Organisms need to learn about sensory stimuli and so centrally, the ability of spinal neurones to become sensitized by repeated stimuli is believed to be a part of associative learning. Thus, the ancient origins of pain and its widespread effects on CNS processes are responsible for the challenges of controlling pain and the misery it brings.

The future of pain control will involve novel agents and a better use of existing therapies, including steps towards predicting patient responses based on improving our knowledge of pain and its modulation. We are off to a solid start in terms of success in dealing with the challenges since translation from basic science to patients, and vice versa, are becoming more prevalent and connected. Parallel rodent neuronal and human psychophysical studies can inform on peripheral and central mechanisms in experimental pain and so drug development will find an easier and more predictive transition from experimental drugs to phase I studies [49, 61]. Differentiation of the modulation of on-going and evoked pains in rodent models [33] has been achieved and this separation has a bearing on responses to analgesics in neuropathic patients [18]. In this account, we highlight how anti-NGF and anti-CGRP antibodies are reaching the patient, the effect of tapentadol and the rationale for selective sodium channel blockers, which are currently being tested in patients [71].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of

human or animal subjects performed by any of the authors.

DIFFERENT TYPES OF PAIN

A key issue is defining the receptors and channels involved in pain transmission and modulation, both of which change following pathophysiological events, such as those that occur in patients with neuropathic and/or inflammatory pain. Low back pain and cancer pain can be a combination of the two, and are thus mixed pains. Indeed, there are about 40% of cancer patients with neuropathic pains and similar numbers with neuropathic elements to low back pain; the neuropathic components in pain states can be teased out by questionnaires and assessment of the sensory symptoms [13]. This is an important issue since treatments aimed at the peripheral pain mechanisms have to distinguish these two main types of pain. Pain from tissue damage (inflammatory pains) will respond to the NSAIDs and steroids, whereas neuropathic pain (resulting from a lesion or disease of sensory nerves) will respond to drugs that target the altered ion channels within the nerves. Thus, peripherally targeted treatments must reflect the type of pain mechanism.

We have managed to characterize many of the pain sensors in the body. Nociceptors have a polymodal nature so heat and cold sensors have been found as well as a large number of receptors that respond to chemical stimuli. A family of particular sodium channels, some selective to pain signaling, have been isolated [29]. The peripheral mechanisms of the broad types of pain are very different and so treatments are linked to the pain type. Examples would be the use of the NSAIDs and steroids for the aforementioned inflammatory pains, but the need for drugs acting on ion channels for neuropathic pains where the lesion or disease of a nerve leads to disordered electrical events. However, on arrival within the central nervous system, the signaling and controlling systems appear to use common mechanisms, so that

opioids, ketamine, and agents acting on the monoamine systems have broader spectrums of activity. Furthermore, the underlying mechanisms of some manifestations of pain are more likely to be central than peripheral, and here both fibromyalgia and irritable bowel syndrome are best explained by problems with brain control systems [53, 55]. The periphery provides the basic information but each patient builds up their own pain experience based on context, memory, emotions, and social/other issues. The outcome is subject to the incoming pain messages being modified and altered by the CNS, both up and down. Thus, we should never be surprised by any disconnect between the extent of peripheral damage and the pain score.

PERIPHERAL EVENTS THAT GENERATE NOCICEPTIVE PAIN

Many pains start in the periphery where pain sensors are likely to be continually activated when tissue is damaged. Chemicals are released including the prostanoids, bradykinin, CGRP, and ATP, as well as many chemokines. The problem is that, at present, only steroids and cyclooxygenase inhibitors are able to modulate these events with a ceiling on efficacy since they will only modulate some of the chemical mediators. Hopes for drugs that block the receptors for ATP are high, and here the P2X3 receptor is a key target [9]. NGF is a key target for inflammatory pains but there were problems with initial therapies and their side effects.

Anti-NGF Therapies

NGF is a key molecule for the sensitization of primary afferent nociceptors associated with tissue inflammation. It acts via neurotrophic tyrosine kinase receptor A (TrkA), as well as via p75 neurotrophin receptor (p75^{NTR}) and levels of NGF increase in inflamed tissue. The molecule has a number of direct and indirect (through Mast cells and autonomic actions) effects to enhance pain signaling. Preclinical data revealed that neutralization of endogenous NGF prevents

inflammatory hyperalgesia [35, 45, 56, 60]. NGF causes acute pain in humans but the NGF-TrkA complexes are also retrogradely transported by sensory fibers to the cell bodies, resulting in a number of genomic actions that increase the sensitivity of pain fibers. In addition to increased ion channel functions, it causes the release of substance P and CGRP at both peripheral and central levels, and therefore contributing to sensitization [60]. Hence, several studies illustrated the importance of NGF and/or CGRP sequestration strategies in the variety of pain states where tissue is damaged.

Among several agents developed to counteract the NGF-mediated sensitization, particular attention should be drawn to monoclonal antibodies like tanezumab, fulranumab, and fasinumab. Several clinical trials revealed a long-lasting (several weeks after a single injection) pronounced efficacy of tanezumab in the management of osteoarthritic, chronic low back, diabetic peripheral neuropathic, and cancer-induced bone pains [32, 39, 62].

The major obstacle linked to the use of anti-NGF antibodies that arose from clinical trials was their osteonecrotic activity, often leading to premature joint replacement. Recent trials have adjusted the dose of tanezumab used, and identified an interaction with other pharmacotherapies often used to manage inflammatory conditions. Tanezumab monotherapy does not elevate the risk of total joint replacements, however if coadministered with NSAIDs, the risk is notably manifested [59]. Also, there was a minimal incremental benefit of high doses of tanezumab high (10–20 mg) versus low (2–5 mg) doses, further restricting side effects [12, 24]. Finally, anti-NGF antibodies do not appear to have cardiovascular or gastrointestinal safety liabilities of NSAIDs, as well as undesirable effects of centrally acting analgesics such as opioids.

Anti-CGRP Agents in Headache

CGRP is a peptide found in many C-fibers and released at both their central and peripheral terminals. The latter action is a key event in the production of migraine where the peptide is likely to have both pain generating and vascular

actions in dura and scalp [27]. Antibodies to CGRP have been developed and been proven effective, and it is hoped that these agents will become alternatives to the triptans [46]. In general, monoclonal antibodies are target-specific, which limits off-target toxicities common to most small molecules. Their actions are prolonged, which leads to less frequent dosing of about once a month or less. Their long half-life may lead to these molecules being used for migraine prevention and CGRP attenuation has potential use in other inflammatory pain conditions.

PERIPHERAL EVENTS THAT GENERATE NEUROPATHIC PAIN

Ion Channels

Critical changes in ion channels, in particular sodium channels, arise after nerve injury, thought to produce abnormal peripheral transmission to the spinal cord and we have proof of concept since mutations in some of these peripheral sensors and channels cause human familial pain disorders [19]. The description of certain sodium channels, namely Nav 1.7 and 1.8, which are preferentially found in small fibers, lead to the possibility that their blockers could be novel analgesics with pain-selective actions, unlike present drugs such as lidocaine, which also blocks large fibers. Indeed, there are a number of gain-of-function of 1.7 mutations that lead to pain in the absence of injury and a loss of function mutation that renders the subjects analgesic [10, 20]. This proof of concept supports the idea that selective pain-related sodium channel blockers could become orally effective local anesthetic-like drugs [43] since their selective roles in pain would not require local administration and clinical studies with Nav1.7 blockers are on-going [71].

These drugs could have broad efficacy that includes inflammatory pains, where peripheral sensitization will also lead to altered action potential transmission. At present, we have drugs such as carbamazepine that work to

subdue abnormal sodium channel function. Potassium channels provide another interesting target since these inhibitory channels are down-regulated after nerve injury, but at present we lack drugs that act to open them [66]. Further, new analgesics could include drugs that target our sensors for heat, cold, and irritants such as the TRP family of channels. These are already pain-control targets since capsaicin is an agonist at TRPV1. A low dose desensitizes the channel whilst a high dose activates—it is the human heat pain sensor—but then causes the fine pain fibers to pull back from the area of application, producing prolonged pain relief [48]. TRPM8 is our cold sensor, responding to menthol and this channel could be a useful target in patients with cold hypersensitivity such as those receiving cancer chemotherapy [25, 51]. TRPA1 is an irritant sensor and a gain-of-function mutation leads to a pain syndrome in humans, validating the channel as a target [37].

Botulinum Toxin

Botulinum toxin has been used to control pain in migraine and in patients with peripheral neuropathy. As a paralytic agent, the drug blocks transmitter release at the neuromuscular junction, but this action can be harnessed to control pain. In headache, the local administration to sensory nerve terminals is thought to block the release of CGRP as well as the insertion of certain pain sensors into the membrane of the nociceptors [52]. In neuropathy, the authors concluded that the toxin may be transported to the central terminals of the pain fibers where it could block central transmitter release [2].

SPINAL CORD MECHANISMS OF PAIN

Whatever the cause of pain in the body, the next key stage in communication between peripheral nerves and CNS neurones is the release of transmitter into the spinal cord. Calcium channels are required for transmitter

release and so control neuronal activity of spinal neurones. Calcium channel levels and function are altered in different pain states. In particular, in both inflammatory and neuropathic pains, there are increases in their function, and in the latter the alpha-2 delta subunit is highly upregulated [15, 50]. This is the target for the drugs gabapentin and pregabalin, which appear to prevent the correct movement of the channels to the membrane [7], and so act to alter transmitter release through mechanisms brought into play by pathophysiological events. These drugs are active in certain physiopathological states (which may be generated peripherally by neuropathic mechanisms or intense stimuli), but also in disorders of central processing such as fibromyalgia, where they alter glutamate signaling in the brain [30]. Both preclinically and also in patients, the alpha-2 delta ligands appear to act preferentially on evoked hypersensitivities and not on-going pain, forming a basis for differentiation of patients who might respond to them [50].

Central Sensitization

In the spinal cord, activation of the N-methyl-D-aspartate (NMDA) receptor is produced by the repeated release of peptides and glutamate from peripheral nerves. These actions of glutamate at the NMDA receptor in persistent pain states, acting alongside other systems, produce hypersensitivity of spinal sensory neurones. Consequences of this are wind-up, long-term potentiation (LTP) and central sensitization. This leads to both an increase in the pain sensation and the receptive field size of the spinal neurones [21]. This spinal hypersensitivity is the most plausible explanation for allodynia since the deep dorsal horn neurones subject to wind-up receive both low and high threshold inputs. The NMDA receptor is a key target for controlling pain. Ketamine blocks the NMDA receptor complex at sub-anesthetic doses but with side effects, and there is a potential for drugs with better profiles through NMDA receptor sub-type selective agents. The other receptors for glutamate are unlikely to be viable targets since glutamate is the main CNS

excitatory transmitter. Tissue and nerve trauma causes abnormal impulse propagation towards the spinal cord and marked changes in calcium channels causing them to release more transmitter, thereby favoring central spinal hypersensitivity. Here, the relation between the extent of peripheral activity and central consequences diverge and shift towards central hypersensitivity. It has been difficult to directly modulate central sensitization, but certain drugs can be useful: directly as with ketamine, and indirectly as with opioids and gabapentinoids [58, 67]. Central sensitization has been observed in many patient groups, ranging from neuropathy to osteoarthritis including fibromyalgia [54]. Given that the originating events in these very different pains can be clearly peripheral or more likely central, such as in fibromyalgia, it becomes clear that altered processing and sensitization can be observed at many CNS sites.

Altered Pain Transmission in the Brain

Increased activity within spinal circuits produced by peripheral activity, whether arising from tissue or nerve damage, is the rationale for the use of regional blocks since in most cases, the spinal events are driven by peripheral inputs. Increased spinal neuronal activity will in turn trigger ascending activity to the brain. There are two parallel pathways; firstly, ascending activity to the thalamus and the cortex, the sensory components of pain, allow us to locate and describe the intensity of the pain. Equally important are the pathways to the midbrain and brainstem, where the activity contacts and disrupts the limbic brain, areas such as the amygdala, and generates the common comorbidities that follow pain such as depression, fear, sleep problems, and anxiety. The brain processes and signals, in a dynamic fashion, the sensory and affective components of pain as well as the salience and aversive aspects of pain through connections between various areas that include insula, prefrontal and cingulate cortices, as well as the somatosensory cortex [38]. The ascending pain messages from the cord that input these various brain regions

also contact descending control pathways that run from the brainstem back to the spinal cord. These monoamine and opioid projections can be inhibitory or excitatory, so that cognitive and emotional events are able to switch pain on or off.

Central Inhibitory Mechanisms

Blocking the generation of excitability is one approach, and this can be achieved by targeting the periphery or the spinal cord, but increasing inhibitions may also provide control of pain. Opioids work at spinal levels by pre- and post-synaptic mechanisms and the spinal application of morphine in animals rapidly lead to the human epidural route in patients. Systemic opioids both increase descending inhibitions and reduce descending facilitations by CNS actions. All of these mechanisms are altered as pain shifts from acute to chronic. Opioids can be useful in pain control, although this is less clear for chronic non-malignant pain where there are issues with side effects, abuse potential, and overdose risk from the opioid load and potential paradoxical hyperalgesia as the inhibited spinal neuronal systems compensate [64]. An advance has been tapentadol, which is a mu opioid with noradrenaline reuptake inhibition, a dual-action molecule, with key spinal actions [8]. The latter action targets and enhances descending inhibitions and so opioid side effects are reduced. All presently used opioids act at the mu opioid receptor but can differ in potency, pharmacokinetics, and route of administration. Recently, after many decades of attempts to produce drugs acting on the other opioid receptors, agonists at the NOP receptor have gone into patients [42].

A severe loss of spinal GABA-mediated inhibitions is reported within the spinal cord after peripheral nerve injury, which compound the gain of excitation. The widespread nature of the roles of GABA in the brain means that therapies aimed at restoring its normal inhibitions are not currently feasible. Altering the function of the chloride channel that GABA operates is being attempted [22].

Pathways from the Brain to the Spinal Cord that Alter Pain

Abnormal signaling from the spinal cord alters pain processing in the brain. Pathways from the brain can in turn alter spinal sensory processing [4]. These projections originate from the mid-brain and brainstem in predominantly monoamine systems (noradrenaline and 5HT). The actions of anti-depressant drugs in pain therefore link to these systems. These pharmacological circuits also play major roles in the generation and control of emotions such as mood, fear, and anxiety as well as in thermoregulation and the sleep cycle. Pain inputs into these areas will alter descending controls and also form a basis for pain-induced co-morbidities. Early work in this field focused on descending inhibitions, which are now known to be predominantly noradrenergic acting through the alpha-2 adrenoceptor [31]. A recruitment of descending inhibitions underlies placebo analgesia and a failure of descending inhibitions has been reported in many patient groups with diverse types of pain [68]. However, pain could equally be increased by enhanced descending facilitations through the 5HT3 receptor [57, 65]. These excitatory influences from the brain will act to favor the development and maintenance of central sensitization in the spinal cord [14]. Part of the substrates for these bidirectional controls are ON and OFF cells found in brainstem nuclei [26]. There appear to be altered descending excitatory controls in patients with severe pain from osteoarthritis [28]. In animals, there is a loss of descending noradrenaline controls after nerve injury and correspondingly, animals with nerve injury that have activated their descending inhibitory noradrenergic systems are protected against the pain and recovery from surgical pain is enhanced when the same systems operate [17].

In general, painful inputs into the limbic brain and the resultant descending controls link emotional states and the levels of pain perceived, and could be one of the ways by which higher functions such as coping and catastrophizing can modulate sensory components of pain at the level of the first relays in the spinal cord. The levels of midbrain-generated

modulation, both positive and negative, may be a key factor in individual variations in pain, the potential target for non-pharmacological therapies and contribute to some “dysfunctional” pain states such as fibromyalgia. Here, a “normal” peripheral input could be enhanced if the descending systems are abnormal and so enhance excitability of the spinal cord through central events [53, 63]. Diffuse pains may have their origins in disordered central pain modulation. Animal studies reveal that altered descending controls are important in the maintenance of persistent inflammatory and neuropathic pains [4].

Gauging Descending Inhibitions in Patients

The balance shifts towards descending facilitation in persistent pains and importantly the extent of loss of descending inhibitions in patients can be gauged. The finding that one pain could inhibit another through descending controls formed the basis for diffuse noxious inhibitory controls (DNIC) [41] and its human counterpart, conditioned pain modulation (CPM) [68], a descending inhibition that is lost in patients with brainstem lesions and spinal sections [11].

Recent studies reveal that DNIC use a descending noradrenaline and alpha-2 adrenoceptor-mediated pathway from the brain to the spinal cord [5]. Sham surgery produces no change in DNIC and no pain phenotype corresponding to reduced CPM being a risk factor for persistent pain after surgery [69]. After peripheral neuropathy, DNIC is lost, yet can be restored by drugs that enhance noradrenalin levels and also by blocking the 5HT3-mediated descending facilitations [5]. In patients, reduced CPM is seen in many pain states, including neuropathy, osteoarthritis, headache, CRPS, fibromyalgia, and others [1, 40, 70]. CPM can be quantified by one pain versus another, often heat versus cold but as with DNIC, the modality of the conditioning stimulus only has to be noxious and the wide dynamic range of the neurones in animals subject to DNIC means that the conditioned response can be noxious

or innocuous [36]. Importantly, CPM can be restored in patients with peripheral neuropathic pain by the MOR-NRI drug tapentadol and a reduced CPM is predictive of efficacy of the SNRI duloxetine, suggestive of a loss of key noradrenaline signaling in patients akin to that seen with DNIC in animals [44, 70]. Both DNIC and CPM are dynamic—CPM can be present early in a pain condition but lost later such as with CRPS and alters over the course of headaches [47].

On-Going and Evoked Pains

CPM allows for the quantification of descending inhibitions and so is a key step towards precision medicine. An overwhelming question is whether it is the spontaneous or the stimulus-evoked component of pain that is the greater problem for patients who are simply asked to rate their pain on a VAS score. Differentiating the two pain events, for example neuropathic spontaneous pain and inflammatory tonic pain from evoked, particularly mechanical hypersensitivity, is an on-going research goal both pre-clinically and clinically. Despite its terminology, spontaneous pain not only refers to the intrinsic firing of neurons active in pain-signaling pathways, but may rather—in the case of neuropathy for example—refer to deafferentation-induced spontaneous discharge in CNS neurons. The sensitization of such pain signaling neurons may then be responsible for on-going chronic pain. Stimulus-evoked hypersensitivity meanwhile refers to an enhanced neuronal, and therefore pain, response to an innocuous or noxious insult at the periphery.

The presence of spontaneous pain is a common complaint amongst chronic pain patients, for example those with a neuropathy [3]. An increased sensitivity to evoked stimuli is also present in such patients. Importantly, hyperalgesia can be pharmacologically treated in the absence of the relief of on-going pain [23] and so it is likely that the underlying mechanisms governing on-going versus evoked pain are distinct and thus should be treated clinically as separate components of the pain state. It is well accepted

that translating mechanisms in animal models can guide potential treatments in the patient domain. While detecting and mechanistically evaluating spontaneous pain pre-clinically was viewed as a complicated task, an insightful study by Frank Porreca and colleagues used conditioned place preference (CPP) to not only detect tonic pain in neuropathic rats but also to determine the efficacy of specific analgesic relief [34]. Their study provided evidence for a tonic pain state in animals that had undergone spinal nerve ligation (SNL) surgery, while the presence of a spinal cord lesion similarly coincides with the expression of spontaneous pain, with CPP this time revealing that clonidine or motor cortex stimulation was able to unmask a tonic aversive state [16]. Further studies reveal that certain brain areas such as the anterior cingulate cortex may contribute more to the longing aversive state rather than modulating evoked responses and importantly such studies impact the assessment of analgesic therapeutic potential on these different responses [33].

TARGETING PAIN MECHANISMS IN PATIENTS

Whilst awaiting new agents, our understanding of mechanisms for pain and its treatments allows for a rationale for all approaches to pain control. These could range from regional blocks to restoration of normal central modulation with drugs to cognitive behavioral approaches. Indeed, even the descending controls, embedded deep in the brain, are altered by peripheral inputs and so could be altered by peripheral and spinal interventions.

But who will respond to each particular treatment? NNTs for many pain drugs are quite high but trials have been based on etiology and so presume homogeneity, whereas the patients may have differing mechanisms and sensory profiles. Mechanism-based therapy is a laudable concept but unlikely to be helpful since how could mechanisms be identified in most patients? A brilliant variant on this would be to use the sensory phenotype of the patient as a surrogate reflection of underlying pain

mechanisms. Using the sodium channel blocker oxcarbazepine, it was revealed that those patients with “irritable nociceptors”, i.e., having evoked hypersensitivity rather than on-going pain, responded to the drug, an effect that was lost in the whole group analysis [18]. Subtypes of patients with neuropathic pain, fibromyalgia and post-surgical pain can be formally distinguished. Analysis of patients with neuropathic pain has revealed three clusters of patients: Cluster 1—those with sensory loss; Cluster 2—those with thermal hyperalgesia; Cluster 3—those with mechanical hyperalgesia. In the near future, we will know if these subtypes have differential responses to different drugs if stratified trials can be conducted, but there are already hints of differential sensitivities to treatments. Cluster 1 patients responded to oral opioids and not well to Na channel block, whereas Cluster 2 patients did respond to this drug and also to BoTox. Cluster 3 had greater efficacy of pregabalin and topical or IV lidocaine [6]. There is also the use of CPM, as discussed previously, to inform on impaired descending inhibitions and so predict responders to SNRIs and sensitivity to tapentadol. Other studies, at present limited to neuropathic pain, reveal heterogeneous responses to drugs in different subgroups of patients [13], and this needs to be extended to nociceptive pain patients and those with fibromyalgia.

There is considerable hope for the future. However, the use of both CPM and/or quantitative sensory testing are not appropriate for routine clinical practice, so if there is a relation between particular sensory profiles of patients and particular pharmacological agents, simple tests could be developed. Patients should be able to distinguish on-going from evoked pains during the taking of a history and could be asked if their pains were predominantly thermal or mechanically evoked, so delineating the clusters described above [6]. Maybe patients could be asked if one pain could inhibit their pain—bite your thumb? This could represent a simple test of CPM.

We have a lot further to go but the union of informed and thoughtful preclinical science and clinical medicine will lead us onwards.

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