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Capturing novel non-opioid pain targets

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Abstract

The relatively high efficacy of opioids for the management of acute and terminal pain, together with their addictive properties, tolerance and dependence, has been a major driver of the opioid crisis, through availability, over-prescription and diversion. Eliminating opioids without an effective replacement is, however, no solution, substituting one major problem with another. To deal successfully with the opioid crisis we need to discover novel analgesics without involvement of the mu opioid receptor but with high analgesic potency and low adverse effects, particularly no abuse liability. The question is how to achieve this? There are several necessary elements; first we need to understand the nature of and mechanisms responsible for pain, and second, we need to adopt novel and unbiased approaches to the identification and validation of pain targets.

Keywords

pain; analgesia; drug target; opioids; abuse; stem cells

What is analgesia?

Analgesia is the reduction, elimination or prevention of pain. For decades the medical profession thought of pain simply and exclusively as a symptom and considered it only in terms of its severity; mild, moderate and severe, and then used this as the basis for selecting analgesics; successively, non-steroidal analgesics, weak opioids and strong opioids. This approach, as captured by the original World Health Organization's "Analgesic Ladder"(1), is however, fundamentally wrong, and has contributed significantly to the overuse of opioids(2). Pain is not a unitary phenomenon(3, 4) and therefore there is no, and cannot be a, single class of universally effective analgesic - one that the blockbuster model of pharmaceutical development sought for many years. Instead it is crucial to appreciate that there are four major pain subtypes, each requiring distinct therapeutic strategies, with further subgroups within each subtype.

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Disclosures

Dr Woolf is a founder of Nocion Therapeutics and sits on the SAB of Biogen and Nocion Therapeutics. He has six issued patents in pain related areas and several additional ones pending.

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Nociceptive pain is that pain arising from the activation in the periphery of nociceptors, those primary afferent sensory neurons specialized to be activated only by intense mechanical or thermal stimuli or by exogenous and endogenous chemical irritants, and hence which detect the presence of noxious, tissue- damaging stimuli(5–7). Under physiological circumstances this is, therefore, a major adaptive protective mechanism, and its absence, as in congenital insensitivity to pain due to the failure of the development or function of nociceptors(8, 9), results in cumulative damage from every day interaction with the environment without the ability to detect the ever-present danger of tissue injury.

Continued presence of noxious stimuli can produce pathological nociceptive pain, as in a damaged joint in patients with osteoarthritis, where cartilage disruption can result in excessive forces being generated in response to normal range of joint movement activating nociceptors(10), but this is a relatively rare cause of chronic pain.

How to deal with nociceptive pain; one strategy is to identify those molecular targets responsible for the transduction of noxious stimuli into inward currents in nociceptor terminals - such as TRPV1 or TRPA1(5, 11), another is to prevent the generation or transmission of action potentials in nociceptors by voltage- gated sodium channels blockers, locally by non-selective blockers that enter into neurons through large pore channels(12) or systemically by Nav1.7 or 1.8 selective blockers(12, 13); a third is to block transmission of nociceptor input to the second order neurons in the spinal cord or brain stem by preventing transmitter release by N-type calcium channel blockers(14, 15) or action, by neurotransmitter receptor antagonists(16, 17), and finally by directly blocking activity in those central nociceptive pathways/circuits that lead to activation of the cortical regions that generate the subjective experience of pain or by activating circuits that suppress transmission within the nociceptive circuits, as with opioids(18).

It is very important to appreciate that switching off nociceptive pain runs the risk of the loss of its protective function. Systemic treatment that eliminates pain in response to noxious stimuli would result in a loss of appreciation of the difference, for example, between a warm and a damaging hot stimulus or between a firm pressure stimulus and one that is tissue damaging. Such systemic treatment has an important role though, in the management of acute trauma and in the elimination of pain during and immediately after surgery and possible end of life care, but it is not suitable for the management of persistent pain.

Inflammatory pain is that pain that occurs in the presence of tissue injury and active inflammation. It is characterized by the presence of spontaneous pain - pain arising in the absence of an obvious external stimulus, such as with a streptococcal throat infection or burn injury, and most prominently by pain hypersensitivity, where stimuli that would normally not produce pain do so - the phenomenon of allodynia, producing tenderness to touch of a surgical wound or the pain that arises in response to warm innocuous stimuli with sunburn.

Inflammatory pain is the consequence of the activation and alteration of nociceptor function both by immune signals and those arising from damaged cells(19). Some of these signals drive activation of nociceptors directly, most though, produce changes in sensitivity that reduce the threshold of the nociceptor, such that it can now be activated by innocuous

stimuli; a change known as peripheral sensitization, which largely results from post-translational changes in ion channels in the nociceptor peripheral terminal and contributes to pain within the active site of inflammation(11, 20, 21). Reduction in immune response and immune mediator release, reduce peripheral sensitization, and this is a major contributor to the analgesic actions of NSAIDS/COX-2 inhibitors that reduce PGE2 production, which via EP2 receptors activate kinases that phosphorylate ion channels in nociceptors(22, 23).

A major additional feature of inflammatory pain is the pain hypersensitivity surrounding an injured/inflamed zone; the phenomenon of secondary hyperalgesia(24, 25). This is the consequence of use-dependent changes within the central nervous system secondary to a barrage of nociceptor input producing amplification of nociceptive circuits through increased excitation and reduced inhibition; constituting the phenomenon of central sensitization(26, 27). Although opioids do reduce this central amplification(28), this neural plasticity is most effectively reduced by N-methyl D-aspartic acid (NMDA) receptor antagonists like ketamine - however such antagonists also produce psychotomimetic effects, limiting their utility(29, 30).

Inflammatory pain may be accompanied by transcriptional changes in nociceptors and in the CNS, which contribute to the degree of the hypersensitivity and its duration(30). Typically, inflammatory pain is present only while the inflammation persists, but the central amplification component can be sufficiently large that the degree of pain may not correlate simply with the extent, nature or timing of the immune reaction and this may vary from individual to individual due to differences in genetic background. While treatment of inflammation with anti-inflammatory agents is important, it may not be sufficient, neural targeting may be required in addition to produce effective analgesia.

Inflammatory pain in the setting of tissue injury is adaptive, aiding healing by preventing use of the injured body part until the damage is repaired. If, for example, postoperative pain were eliminated, surgical wound healing could be impaired if patients were excessively active soon after surgery. Furthermore, if a tissue is permanently damaged, as in chronic osteoarthritis, elimination of pain by encouraging excessive use of the damaged joint may accelerate its destruction. The aim then needs to be to reduce inflammatory pain and its associated hypersensitivity but not to eliminate its warning/protective elements, a delicate and difficult balance.

Recent metaanalyses reveal that neither opioids nor NSAIDS show much if any sustained effective relief of pain in patients with chronic non cancer pain conditions(31, 32) and in consequence, their use for persistent inflammatory pain should therefore be limited -we urgently need alternatives that work well in patients with ongoing inflammatory pain as in rheumatoid arthritis.

Neuropathic pain is that pain that follows an injury to or disease of the somatosensory nervous system, most frequently the peripheral, but also the central nervous system(33, 34). The neural injury necessarily produces negative symptoms, loss of sensation or sensitivity, and positive symptoms; spontaneous pain or paresthesia, allodynia (typically tactile and cold) and hyperalgesia/hyperpathia - exaggerated responses to noxious stimuli(35, 36).

Unlike inflammatory pain neuropathic pain usually long outlasts the initiating trigger, be it nerve trauma, diabetic or chemotherapy induced neuropathy, spinal cord injury or a stroke. Mechanistically, the pain arises both from changes in injured neurons (such as development of ectopic action potentials arising from hyperexcitable membranes) and in structural and functional alterations in CNS circuits due to a permanent facilitation of some excitatory and loss of inhibitory synaptic connections, often accompanied by changes in microglia and astrocytes(36–39).

Peripheral axonal injury results in profound gene expression changes in injured primary sensory neurons(40) including upregulation of some analgesic target proteins like the alpha2 delta subunit of calcium channels on which gabapentinoids act to reduce calcium channel trafficking to the membrane to reduce synaptic drive(41, 42), as well as an action on NMDA receptors(43, 44). The extent, nature and duration of the changes in the nervous system underlying neuropathic pain represent a disease state of the nervous system(34, 45). Pain is here, not a symptom of pathology, but a consequence of pathological alterations in the nervous system triggered by its injury. Treatment can be directed at reducing the activity of pain-driving circuits by reducing excitation or increasing inhibition (as with gabapentinoids and dual amine uptake inhibitors respectively(46–50)) but ideally, the strategy should be to prevent the evolution of those changes that lead to persistent pain; a disease-modifying approach - no such treatment is though available at the present time(51). Since not all individuals with neural injury develop neuropathic pain a further critical missing piece of information is, who is at risk and what drives susceptibility(52, 53).

Dysfunctional pain captures those pains that occur in the absence of a noxious stimulus, inflammation or damage to the nervous system. These are often widely distributed - constituting the group of chronic widespread pains, of which fibromyalgia, irritable bowel syndrome and temporomandibular joint disorder are major, often co-morbid, examples(54–56). This pain is generally not the consequence of some peripheral pathology but rather of an abnormally functioning nervous system, where amplification of normal or mild pathological sensory inflow leads to pain. While originally considered psychosomatic, it is now recognized that this is a true disease state of the nociceptive nervous system(57–59). The major challenges for dysfunctional pains are; what is the cause of the pain amplification and how to prevent/treat the condition - it is likely that effective treatment will only follow elucidation of the cause. Recently, the International Association for the Study of Pain (IASP) have introduced the term **Nociplastic Pain** to capture those pain conditions driven by maladaptive plasticity within the CNS.

All pains are accompanied by changes in mood, attention and motivation which exacerbate the sensory disturbance(60, 61). The extent to which the sensory and affective components of pain are mechanistically linked remains though, to be fully determined. If the sensory component of a patient's pain condition is reduced by some analgesic strategy, will the affective elements remain, having become independent of the sensory ones? The extent to which engagement of negative affective processes may become autonomous needs to be further explored, especially as some current drugs used to treat pain feed into the same circuits that mediate negative affect, suggesting that specifically targeting such circuits may need to be part of an overall strategy to reduce both the perception of pain and its mood-

altering states. Furthermore, we need to recognize that pain is part of our global nervous system function and can be affected in unsuspected ways. Disruption of sleep, for example, increases pain sensitivity and reduces the efficacy of analgesics(62).

What analgesic targets do we currently have?

There are at present only a rather limited number of targets on which drugs act to produce clinically meaningful analgesia (Table 1). In most cases the molecular target of these analgesics was only elucidated well after the discovery of the analgesic action of the compound, as for morphine or salicylate/NSAIDS, and many cases the analgesic action was found secondary to some other clinical indication (anti-inflammatory, anti-epileptic, anti-depressant or anesthetic).

Only three pain targets were identified first, and then became the basis for finding drugs with an analgesic action, of which two are approved only for migraine. Essentially this indicates that the target selection strategy for the development of analgesics, has not so far been very successful, relying more on serendipity and empirical observation than on rational design. We need to learn from this and try change our analgesic drug discovery process to one that is more effective. A further problem is that even for these validated targets and their associated clinically used analgesic compounds, there are patient responders and non-responders and we do not have any way at present of reliably identifying/predicting who will respond or not. The number need to treat (NNT) is a metric that indicates how many patients need to be treated to get one patient with a greater than 50% reduction in their pain; typically, that number ranges from ~3.5 at best to 15 for currently-used analgesics(63–66) a reflection of how poor efficacy is for most patients.

Ideally, we need to match the treatment with conditions where particular targets are prominent and detectable drivers of the pain the patient experiences(45). Part of our diagnostic effort needs to be therefore, elucidation of what mechanism(s) is causing the pain in an individual patient and using this to identify which targets it offers for therapeutic intervention(36, 67). A simple illustration of this is that COX-2 is induced in macrophages early in inflammation and contributes to peripheral sensitization. Interestingly, COX-2 is also induced in neurons in the spinal cord where it contributes to central sensitization(68). In the absence of the peripheral and central induction, the target is not available and NSAIDS will have no on-target effect.

Analgesic target identification and analgesic development

The limited number of available analgesics is not for want of trying. In addition to those that are successful, there have been many analgesic target failures (Table 2), defined as attempts to develop analgesics based on putative analgesic targets, that failed in the clinic. Several explanations for this are possible; the wrong target was selected; the drug candidate may not have engaged the target to the required extent, location and duration, the wrong patients may have been selected in the efficacy trials and the outcome measure selected may have been too noisy and subject to confounders like placebo, to deliver a clear efficacy signal. All these factors may contribute, however, in this article the focus will be on target selection. There

are several drugs/drug classes undergoing clinical evaluation for efficacy at present (Table 3) that act on targets distinct from current (Table 1) or failed (Table 2) analgesics and we will need to watch the outcome of these trials.

How were the targets identified for the currently used analgesics; for those that failed and those undergoing clinical evaluation? Table 4 shows, as mentioned above, that many of the targets were initially discovered only after the clinical discovery of the analgesic activity of the drug - as for opioids, NSAIDs, voltage-gated sodium channels and the anti-inflammatory agent sulfasalazine which shows analgesia in rheumatoid arthritis and inflammatory bowel disease. For many, the target was only discovered after “analgesic” activity was shown to be present in preclinical models, including gabapentin, triptans, cannabinoids. More recently, the major way in which analgesic targets have been nominated has been based on elucidation of pain-related mechanisms in preclinical studies. However, this category also includes many of the analgesic target failures listed in Table 2, suggesting that reliance on this approach alone may not be enough to successfully identify clinically meaningful targets with high probability, perhaps both because of rodent/human species differences and that many of the current preclinical pain models are not true surrogates of human pain conditions and utilize insensitive and unreliable outcome measures.

There is no direct way to interrogate what an animal feels and in consequence most outcome measurements are based on elicitation of a reflex response to a defined stimulus - something that is not a characteristic however, of chronic human pain conditions, where spontaneous pain commonly predominates and where pain levels wax and wane over time such that making a snap shot measurement, as in preclinical models, may not capture complex pain dynamics. Behavioral studies typically only measure thresholds, which is a lower hurdle than the suprathreshold evoked and ongoing pain that patients typically suffer from. Neuronal activity and ongoing pain measures are used too rarely to capture these key elements of the patient’s pain phenotype and we need to build new measures and models for preclinical analgesic drug development.

One important issue that needs to be actively investigated and considered are gender differences in pain susceptibility and response to treatment. We need to understand the biological and genetic bases for such differences, and importantly, include them in our modeling and screening strategies.

The most recent approach to target selection has been based on human genetics, with Nav1.7 the poster child based on the very strong loss of pain phenotypes with loss-of-function mutations and the presence of pain syndromes with gain-of-function variants(69). However, so far this has not panned out in clinical trials for Nav1.7 selective channel blockers(70). Some pharmaceutical companies currently insist on human genetic validation before embarking on a drug discovery program, but a problem here is that the genetic variants contributing to pain are likely to be many, with each individually having only a small contribution as part of a large polygenic risk(71, 72), rather than the strong monogenic mendelian phenotypes industry would like. A further problem is that the effects gene variants may only be engaged in a disease setting, e.g. after nerve damage, and hence family histories are difficult to collect.

It would be useful and interesting to be able to assess the relative success and failure of target selection based on academic research, which is subject to peer review and where often a number of independent groups work on a single target, with internal studies within industry, where data and decision making is not shared or externally reviewed, and failures and the reasons for this when known, not published.

How can we most effectively find novel targets?

The conclusion is inescapable that the strategies used so far for the selection of analgesic targets has not been generally effective, efficient or successful, as reflected by how few targets there currently are, and how many failures there have been(73). How then to proceed? Continue just with either human genetic based targets or those nominated from preclinical studies of the molecular mechanisms of pain, or add additional approaches designed and selected to overcome their shortcomings and limitations?

My view is that while both the genetic and mechanistic approaches have value, they are not enough by themselves, and both have major problems that need to be confronted. For the genetic approach the problem is that there are no large well phenotyped patient cohorts with enough power to identify polygenic risk scores for pain, and reliance on rare loss or gain of function mutations will give us an incomplete picture, especially about chronic pain conditions. For the mechanistic approach the poor value of current preclinical models both to nominate or validate effective targets and to evaluate efficacy of drug candidates is a major problem, as is our incomplete knowledge of pain mechanisms in patients(73). There needs to be a greater appreciation for the possible need for a personalized medicine approach, including interventions designed to prevent pain, and most importantly, of effective pain biomarkers(74, 75). We need to critically assess what is missing in the standard analgesic target selection approach. This includes a lack of unbiased, genome-wide approaches for screening for targets and a focus only on developing drugs with action only on single targets rather than compounds with activity on those multiple targets selectively expressed by the cell or circuit of interest in a defined disease state.

Solutions to these problems will need to include full “o’mic” profiling of the cells and circuits involved in the generation of pain (e.g. single cell RNA-seq) to reveal specific expression of transcripts and proteins, in the relevant cell types, and especially of the changes in these that occur in the setting of inflammation or nerve injury(76). Study of the influence of genetic backgrounds that favor pain chronicity will also be needed as well as increased use of human neurons derived from stem cells for disease modeling and phenotypic screening, with enhanced focus on targeting activity in selective cell types(8, 77–80). In addition, an adoption of more sophisticated means to study the nervous system, including optogenetics to selectively activate or suppress defined neuronal populations(81–83) and the imaging of large neuronal populations in awake unrestrained animals as a readout of nociceptive circuit activity(84) will be vital. It is critical that we also adapt utilization of high spatial and temporal measures of behavior, with analysis based on machine learning and artificial intelligence to detect pain-related behaviors in an unbiased, observer-free and automated way(85). We also urgently need preclinical models that are better surrogates of human disease and utilize these at appropriate times; 14 days post nerve

injury is not, for example, chronic neuropathic pain and reduction in a noxious stimulus induced flexion reflex is not analgesia.

Combining these tools and approaches, together with mathematical modeling, will enable identification of those networks of targets that dynamically drive distinct pain conditions in different disease states. These targets/pathways can then be combined with gene targeting/editing and human neuron models for target validation, particularly including neurons differentiated from patient-derived induced pluripotent stem cells(86). The exploitation of human neurons for comprehensive disease-based phenotypic screens will need to be a key feature. It will be essential to achieve this to develop suitable assays for measuring/modulating pain-related phenotypes in responsible cells (for example hyperexcitable nociceptors after axonal injury or on exposure to tissue inflammation) for genome wide/chemogenomic screens to help elucidate target involved in establishing the disease phenotype. One can imagine a time when early “clinical trials” may be conducted on patient-derived neurons or organoids and where the best therapy for an individual patient is identified by screening activity of all possible therapeutics on their own stem cell derived nociceptive neurons. Development of accurate preclinical surrogate models of human disease to validate any development candidate is critical as well as identification of the multiple mechanisms contributing to diverse pain states in patients to ensure that the target(s) and new drugs are major contributors to defined sets of pains in identifiable patients.

This is a daunting task involving integration of genetics, cell and systems biology, *in vivo* system neurobiological analysis and careful patient phenotyping, but it’s one that needs to be embraced, together with all its complexity. We now have the technology and analytic tools to do so and I am therefore optimistic that we have the means to begin to make an impact on novel analgesic development, one that will lead to effective replacements for opioids, based on novel targets that will enable selective silencing or modulation of nociceptive circuits.

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Table 1.

Analgesic targets providing clinically validated efficacy

Target	Analgesic	Discovery of: Analgesic activity	Target
Mu Opiate Receptor	morphine/opioids	1806	(1973)
COX-2	NSAIDs/COX-2 inhibitors (Anti-inflammatory)	1899	(1975)
Sepiapterin reductase	sulphasalazine (Anti-inflammatory)	1948	(2011)
Voltage-gated sodium channels	carbamazepine (Anti-epileptic)	1964	(1982)
NMDA Receptor	ketamine (Dissociative anesthetic)	1965	(1983)
Cav2.2	ziconotide	1984	(1984)
Alpha2delta1	Ca2+ channel subunit gabapentin (Anti-epileptic)	1987	(1997)
5HT1B/D agonists	triptans (Migraine)	1988	(1988)
Serotonin-Norepinephrine Reuptake	duloxetine (Antidepressant)	1988	(1988)
CGRP	erenumab (Migraine)	2016	(1988)

Table 2.**Analgesic Target Clinical Failures**

<i>NK1</i> - substance P/tachykinin receptor antagonist
<i>TRPV1</i> - noxious heat/proton/capsaicin transducer antagonist
<i>Nav1.7</i> - voltage-gated sodium channel blocker/nociceptor excitability
<i>Cav3.2</i> - calcium channel blocker/synaptic transmission
<i>Kv7</i> - potassium channel opener/nociceptor excitability
<i>FAAH1</i> - enzyme inhibitor- cannabinoid enhancer
<i>CB1/CB2</i> - cannabinoid receptors agonists
<i>α2 adrenergic receptor</i> inhibitor
<i>p38</i> - intracellular kinase inhibitor
<i>CCR2</i> - chemokine antagonist

Table. 3**New Targets in Clinical Development**

NGF/TrkA reduction in nerve growth factor or its action on its receptor
Nav1.8 blockers of sodium channel expressed by nociceptors
Biased Opiate Receptor GPCRs attempt to differentiate analgesic and adverse effects of Mu receptor activation
Kappa Opiate Receptor - peripheralized agonists to avoid the central dysphoria
AT2R angiotensin 2 receptor - expressed in macrophages and contributing to immune activation of nociceptors
mPGES1 reduce prostanoid synthesis
P2X purinergic receptors block activation of nociceptors by ATP
GABA subtype-selective modulators - target GABA receptors in nociceptive circuits

Table 4.How were the targets discovered (*failed targets - italics*)?

Following clinical discovery of efficacy of drug
MOR/COX-2/VGSC/SPR
Following preclinical discovery of efficacy of drug
A2D/AT2R/KOR/5HT1/FAAH1/CB2/CB1/alpha2
Preclinical discovery of pain-related mechanisms
NMDAR/SNRI/Cav2.2/CGRP/NGF/Nav.18/P2X/GABA/NK1/TRPV1/Kv7/Cav3.2/p38/CCR2
Human genetics
<i>Nav1.7</i>

Table 5.

What do the analgesic targets do and where do they act?

Decrease inflammation (<i>peripheral</i>)
COX-2/SPR/CCR2/p38
Reduce nociceptor activation (<i>peripheral</i>)
NGF/P2X/AT2R/TRPV1
Reduce excitability (<i>peripheral</i>)
VGSC/Nav1.8/Nav1.7/Kv7
Increase inhibition (<i>central</i>)
MOR/KOR/SNRI/GABA/FAAH1/CB2/CB1/alpha2
Reduce synaptic transmission (<i>central</i>)
NMDAR/A2D/Cav2.2/CGRP/NK1/Cav3.2