Bioorganic & Medicinal Chemistry Letters 26 (2016) 1103–1119

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Digest paper

New approaches to treating pain

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ARTICLE INFO

Article history:
Received 10 September 2015
Revised 28 December 2015
Accepted 29 December 2015
Available online 30 December 2015

Keywords:
Pain
Opioids
Non-opioids
NSAIDs
Analgesics

ABSTRACT

Pain is the most common reason for patients seeking medical care resulting in an estimated world market for analgesics of more than USD 50 billion. Pain is a highly complex, heterogeneous and dynamic process characterized by specific patterns of phenotypic sensory neuronal change. Current treatment options for pain include opioids and non-opioid analgesics, acetaminophen and non-steroidal anti-inflammatory drugs and other drug classes such as antidepressants and anticonvulsants and a combination thereof. Novel approaches are focusing on the optimization of side-effect profiles of opioid based analgesics, the improvement of selectivity for specific opioid receptors, or by addressing molecular gateways implicated in pain. Promising candidates in development target various types of voltage-gated ion channels and receptors for capsaicin and analogs. Currently, after decades of pain research it has to be stated that the assessment, prevention and treatment of pain in industrialized countries as well as in low-income and middle-income countries are neither adequate nor equitable. Further research is needed so that specifically chronic pain control can be improved and individualized.

Introduction: Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'.[1] Pain is a subjective experience that is learned by the individual through experiences relating to injuries in early life. The experience of physical pain is familiar to everyone; however, the intensity, character and tolerability of each person's pain is subjective. How patients perceive and react to pain is influenced by social, cultural and psychological factors.[2] Different types of pain have different 'molecular signatures'. That is, they are characterized by specific patterns of phenotypic sensory neuronal change.[3] Despite being a universal problem, disparities exist—globally and nationally—in the management of pain. For example, Knaul and colleagues noted that high income countries, which represent less than 15% of the global population, accounted for 94% of morphine use to ease pain.[4] As a vital physiological function, pain constitutes the body's mechanism of self-preservation. The same sensation, however, has the potential to evolve into a debilitating disease under certain pathological conditions such as inflammation, cancer, viral infection, diabetes and other acute and chronic diseases.[5] Pain is a highly complex, heterogeneous and dynamic process that involves multiple interrelated neurotransmitter and neuromodulator systems in the spinal cord, ascending and descending spinal pathways and supraspinal sites.[6] Thus, detailed examination as to the character (e.g., dull, throbbing, stabbing), location and intensity of pain, how and when it occurs and the effects of pain is needed in order to recommend appropriate interventions.

Classification of pain types: Pain may be acute or chronic.[7] When it occurs as a normal, predictable response to trauma (chemical, thermal or mechanical injury) or an acute illness, pain is considered acute. Moreover, acute pain is generally associated with an identifiable cause, resolves after the removal of the cause, responds to treatment and lasts less than 1–3 months.[8] Therefore, acute pain is defined as associated with a sudden stimulus (e.g., accident or surgery)[9] and is generally expected to resolve as the injury heals. Pain that does not have a clear cause, or that lasts longer than 1–3 months after the initial injury heals, is considered chronic pain.[10] Chronic pain can be further subdivided into nociceptive chronic pain, resulting from ongoing tissue damage, as in the case of cancer or osteoarthritis and neuropathic chronic pain, which is an abnormal form of pain that continues to persist long after the resolution of tissue damage or even in the absence of a causative illness or injury.

Neuropathic pain is associated with a functional abnormality of the nervous system. Changes in the nervous system cause it to continue sending pain signals in a pointless and detrimental fashion, until the pain itself rather than the predisposing condition becomes pathological.[11,12] Neuropathic pain severity, however, is not correlated with the amount of damage and symptoms can persist long after tissue damage from an antecedent injury resolves.[9] Clinical features of neuropathic pain include the presence of an

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http://dx.doi.org/10.1016/j.bmcl.2015.12.103
0960-894X/

abnormal, unpleasant sensation (dysesthesia) that frequently has a burning or electrical quality with an occasional paroxysmal, brief, shooting or stabbing quality. Pain may be felt in a region of sensory deficit.

Human neuropathic pain is commonly associated with the phenomena of allodynia, hyperalgesia and causalgia. Allodynia is the perception of pain following a stimulus that would not normally be painful, such as mild brushing against the skin. Hyperalgesia is an enhanced response to a mildly noxious stimulus. Causalgia is a chronic burning pain that persists in the absence of an obvious noxious stimulus.[13]

Chronic non-cancer pain can develop as a result of persistent stimulation of or changes to nociceptors due to localized tissue damage from an acute injury or disease (e.g., osteoarthritis) or damage to the peripheral or central nervous system or both (e.g., painful diabetic neuropathy, post stroke pain, spinal cord injury). There is a wide range of treatments available to physicians for neuropathic pain, some of which have specific indications and some of which are used off-label.

Pain is further categorized according to the neural and biochemical mechanisms they work. Nociceptive pain is the normal physiological response to a noxious stimulus such as injury or inflammation. The stimulus causes nociceptors to release the neurotransmitters glutamate, calcitonin gene-related peptide and substance P, which transmit the signal to second-order neurons in the spinal cord. These second-order neurons form the ascending spinothalamic tract that leads to the thalamus, where they synapse with third-order neurons that project to the sensory cortex, where the pain is perceived.[14] Pain signals are modulated by release of endorphins and enkephalins in the midbrain. These neurotransmitters interact with specific opioid receptors in descending modulatory neurons that synapse with the primary or second-order pain-transmission neurons. Descending neurons release norepinephrine and serotonin (5-Hydroxytryptamin; 5-HT), which directly inhibit the release of pain transmitters and inhibit the activity of the second-order pain transmission neurons.[14]

Some types of chronic pain include cancer pain. This may be acute or chronic, neuropathic pain (e.g., diabetic neuropathy, AIDS neuropathy, carpal tunnel syndrome), trigeminal neuralgia. Other types of neuropathic pain are caused by damage to the trigeminal nerve, post herpetic neuralgia, phantom and stump pain, fibromyalgia, myofascial pain syndromes, central pain syndrome, complex regional pain syndrome (CRPS), psychogenic pain, headache disorders, arthropathic pain in patients with rheumatoid arthritis or osteoarthritis, chronic low back pain, visceral pain including chronic abdominal pain and/or discomfort, burn pain and many others.

Pain afflicts a significant proportion of cancer patients, ranging from 25% at time of diagnosis to 75% or more patients in advanced stages of the disease and has a tremendous impact on quality of life.[15] In spite of the high incidence of cancer pain, undertreatment is a well-documented reality.[16] Cancer pain syndromes include bone pain from metastases, acute nerve compression or spinal cord compression, neuropathic pain somatic and visceral nociceptive syndromes, among others.[17,18] In addition to cancer itself, chemotherapeutic drugs, radiation therapy and surgical procedures used in its treatment may contribute to symptoms of pain.[15,17]

The mainstay symptomatic treatment for cancer pain is opioid-based pharmacotherapy. Effective opioid treatment depends on appropriate selection of a drug and route, individualization of the dose, consideration of so-called rescue dosing for breakthrough pain and treatment of common opioid side-effects. In addition, non-steroidal anti-inflammatory drugs (NSAID) to opioid treatment can be helpful, especially in some painful conditions, but the gastrointestinal, cardiovascular and renal risks of these drugs should be weighed against their benefits on a case-by-case basis. Adjuvant analgesic drugs, such as glucocorticoids, antidepressants and anticonvulsants, have many uses as auxiliary analgesics when opioid treatment is not sufficient.[18]

Chronic pain burden: Worldwide, chronic pain afflicts more than 1.5 billion individuals.[19] In 2013, pain was in the top ten list of causes of years lived with disability (YLD) in 188 countries. Low back pain accounted for more than a mean of 72 million YLD, neck pain more than 34 million YLD and migraine more than 28 million YLD.[20] Pain has a considerable economic impact at the individual and societal levels. The economic burden associated with persistent pain, which includes healthcare utilization, quality of life and impact on productivity, absenteeism and risk of leaving the labor market, is comparatively greater than most other health conditions.[21,22] In the USA the estimated financial cost of treatment and loss of productivity as a consequence of chronic pain is USD 560–635 billion per year. Nevertheless, for many people pain treatment is not satisfactory.[23]

Pharmacological treatment options: The analgesic effect is one of the most important objectives of treatment in terms of improving quality of life. The world market for analgesics in 2009 was estimated more than USD 50 billion. The seven major markets (USA, Japan, France, Germany, Italy, Spain and the UK) alone accounted for more than half of that, USD 27 billion.[24] Sales of drugs to treat neuropathic pain in the seven major markets totalled USD 2.4 billion in 2010. This figure is expected to increase to USD 3.6 billion by 2020.[25] Pharmacological treatment for pain includes non-opioid analgesics, such as salicylates, acetaminophen and NSAIDs, opioids and other drug classes, including antidepressants and anticonvulsants.[7] The structural diversity of analgesics is shown in Figure 1.[26]

Opioid medications mimic the actions of endorphins by interacting with opioid receptors in the brain and spinal cord. Activation of mu-opioid receptors (MOR) in ascending pathways may work to inhibit nociceptive signals.[14] Increase in the effect on ascending pathway activity of opioid receptors may activate the modulating descending neural pathways and produce relief of pain.[14] However, opioids are associated with the potential for abuse and addiction[2] and are generally indicated for moderate to severe acute pain. The many drawbacks associated with long-term opioid therapy (adverse effects, tolerance, dependency and strict regulatory limits imposed on their use) have spurred the development of non-opioid therapeutics that are effective in the long-term therapy of chronic pain states.[27] The classification 'non-opioid analgesics' encompasses a widespread collection of compounds with analgesic effects, including NSAIDs, voltage-gated ion channel (VGIC) modulators, cannabinoids, antidepressants and more. Non-opioid oral medications are recommended for mild to moderate acute pain and most are available over the counter or by prescription. Therapy with NSAIDs is associated with potentially serious side effects, the risk of these is increased by higher doses and longer-term use.

Combination therapy: An alternative approach involving the use of drug combinations with additive analgesic effects, but without additive toxicities, has emerged in recent years.[28] The use of drug combinations incorporating an opioid plus adjuvant medications is called multimodal or balanced analgesia.[29] Several combinations incorporating an opioid and an NSAID, more than one opioid in a single formulation or an anti-inflammatory plus a gastro protectant are in development. Some of these are listed in Table 1. Raffa et al. describes the mechanistically based determination and application of fixed-dose analgesic combinations for treating multimodal pain.[30] When the pathophysiology of a medical condition is multimodal, that is, related to multiple physiological causes or mediated by multiple pathways, the optimal strategy can be to use a drug or a combination of drugs that contribute multiple