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Editorial

New therapeutics for pain—an overview

1. Introduction

The International Association for the Study of Pain defines *pain* as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Spacek [2] further defines *pain* as "an individual, multi-factorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope." It has also been noted that the inability of an individual to communicate does not exclude the possibility that pain is present and the need for pain relief. "Pain of recent onset and probable limited duration" is considered to be *acute pain*, and *chronic pain* is considered to be "pain that persists beyond the time of healing of an injury and frequently there may not be a clearly identifiable cause" [3].

We have now come to realize that acute and chronic pain could represent a continuum in which untreated acute pain may convert to chronic pain. *Neuropathic pain* (NP) is defined as "pain caused by primary dysfunction of the nervous system [4] that affects between 2-4% of the world population but consumes a disproportionate amount of health resources" [5]. Commonly recognized NP conditions are as follows: painful diabetic neuropathy, postherpetic neuralgia, central poststroke pain, phantom limb pain, pain arising from the nervous system, some cancer pain, multiple sclerosis, and HIV infection. The pathogenesis of NP is complex. It may arise from altered sensitivity and expression of various channels (vallinoids, sodium, and calcium), receptors (excitatory amino acids, neurokinins), and proteins (nitric acid synthetase, protein kinase) [6]. Activation of neuroglia may also play a role [6]. With such diverse targets, a comprehensive and combined strategy is required that includes the following: enhancing inhibitory neurotransmitters directly (via γ-aminobutyric acid, opioids, and cannabinoids) or indirectly (via epinephrine, 5-hydroxytryptamine, and acetylcholine); reducing neurotransmission at receptors (*N*-methyl-D-aspartate, neurokinin antagonists); and modulating calcium, sodium, and potassium channels.

The 3 main categories of drugs currently prescribed for the treatment of NP are anticonvulsants, tricyclic antidepressants, and local anesthetics. All of these appear to modulate voltage-gated sodium channels and, in this way, exert their therapeutic effect. Sodium channel blockers have been in widespread use for several decades for the treatment of pain, and some "sodium channel blockers affect calcium-signaling and modulate neutrophil immune response" [7]. Recently, we have seen a rapid expansion in our knowledge and understanding of the roles, modulation, and regulation of sodium channels in nociceptive information processing. There has been a growing disposition recently to develop new pain therapies that use sodium channels as targets. Several new clinical models have validated this trend and have demonstrated significant advantages over current treatments [7].

2. Overview of supplement

The articles in this Supplement to *Metabolism* build on recent achievements in pain research and development and explore selected key themes in pain management.

Johanne Tremblay and Pavel Hamet ("Genetics of pain, opioids, and opioid responsiveness") discuss the potential of genomics to contribute to therapeutic advances, including such promising approaches as use of small interfering RNA in the control of NP. Knowledge of the genetic factors that affect opioid efficacy, metabolism, and adverse effects has the potential for personalizing treatment of both acute and chronic pain, and for the design of more useful opiate pain medications, with lower adverse event profiles.

Bruce S. McEwen and Madhu Kalia ("The role of corticosteroids and stress in chronic pain conditions") examine new scientific and clinical evidence that demonstrates the direct role steroids play in the generation and clinical management of chronic pain. They discuss new findings demonstrating the fact that steroids and related mediators produce paradoxical effects on pain such as analgesia, hyperalgesia, and even placebo analgesia. In addition, they examine the physiologic effect on pain of stress, high allostatic load, and idiopathic disease states such as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and burnout.

JoAnn Manson ("Pain: sex differences and implications for treatment") focuses (1) on the fact that women have a higher prevalence than men of several clinical pain conditions, (2) on the sexual dimorphism of certain inflammation-mediated disorders, and (3) on the evidence for sex differences in

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sensitivity to experimental pain and in the response to analgesics. Manson discusses sex differences in the opioid, dopaminergic, serotoninergic, and other pain-related systems as well as differences that are most pronounced during the peak reproductive years. Given the important role of inflammation in mediating pain, Manson reviews the potential role of moderate- to high-dose vitamin D and omega-3 fatty acid supplements that modulate the inflammatory response. These nutritional interventions, which influence cytokine, leukotriene, and prostaglandin pathways, may be of particular benefit to women owing to their higher prevalence of inflammatory chronic pain disorders.

James P. O'Callaghan and Diane B. Miller ("Spinal glia and chronic pain") describe the role of nonneuronal elements in pain following recent findings that implicate glial-derived signaling molecules as in pain signaling in the spinal cord. Glial proinflammatory mediators within the dorsal horn of the spinal cord appear to contribute to self-perpetuating pain. They discuss recent evidence that suggests that opioid tolerance and withdrawal hyperalgesia may be initiated and maintained via actions of microglia and astroglia. The authors suggest that these recent findings suggest that glia will serve as novel therapeutic targets for the treatment of chronic pain. To fully exploit glia as therapeutic targets will require a greater understanding of glial biology, as well as the identification of agents able to control the glial reactions involved in chronic pain, without interfering with beneficial glial functions.

Stylianos Nicolaidis ("Neurosurgical treatments of intractable pain") provides a practical update of neurosurgical techniques available to treat intractable pain. Neurosurgery can affect pain's pathways from the receptor up to the "centers" of its reception and perception, either by destroying or by stimulating them. Ablative procedures are able to suppress or alleviate pain; however, in most cases, such ablations have only remained effective for a few months or, at best, a few years. Therefore, a better understanding of the mechanism of pain-inspired development of electrical and chemical neuromodulation procedures at every level of the nociceptive system (peripheral nerve, cord, thalamic, periventricular/aqueductal gray, and cortical centers) is required. The indications for undertaking an ablative vs a neurostimulative procedure, as well as selection of the anatomical target, depend largely on whether pain is nociceptive or neuropathic, given that most of these indications overlap to some extent. And because the published outcomes are not based on universal criteria, it is difficult for the attending physician to select the type of procedure most suitable to the pain problem.

Theodore VanItallie ("Gout: epitome of painful arthritis") discusses gout, the most common cause of inflammatory arthritis among men and postmenopausal women and which is notable for the agonizing nature and unique pathogenesis of the pain it generates. He discusses genetic variants within a newly identified transport gene, SLC2A9, that have been associated with a low fractional excretion of uric acid and the presence of gout in several population samples. Based on a large population study, it has been estimated that at least 10% of all gout cases in white people may be attributable to a single nucleotide polymorphism causal genetic variant. Of the various categories of arthritis, the crystal-induced arthropathies, gout and pseudogout, are manifested by acute inflammation and tissue damage arising from deposition in joints and periarticular tissues of monosodium urate, calcium pyrophosphate dehydrate, or basic calcium phosphate crystals. Usually, gout can be diagnosed by medical history, physical examination, and presence of hyperuricemia (urate >416 μmol/L). However, a urate concentration less than 416 μmol/L does not by itself rule out gout. Confirmation of the diagnosis by identification of typical monosodium urate crystals in aspirated synovial fluid is definitive. Analysis of joint fluid is mandatory to rule out septic arthritis, which can rapidly become lethal. Because of its special ability to identify and quantitate urate deposits in peripheral tissues, dual-energy computed tomography should prove valuable in the differential diagnosis of gout. Gout mimics a variety of illnesses; for example, spinal gout may masquerade as metastatic cancer, epidural abscess, and nerve compression syndrome.

Richard Wurtman ("Fibromyalgia and the complex regional pain syndrome: similarities in pathophysiology and treatment") focuses on the pain of fibromyalgia, which usually is not preceded by an injury to the involved tissue, and complex regional pain syndrome. He points out the fact that, although complex regional pain syndrome usually starts at a site of prior trauma or surgery, both disorders may share a common mechanism—pathologic sensitization of brain mechanisms that integrate nociceptive signals. Both apparently respond to treatment with ketamine, an anesthetic-analgesic agent whose actions include blockade of *N*-methyl-D-aspartate receptors. Ketamine's widespread illegal use as a recreational agent probably precludes developing it as a general treatment of centrally mediated pain disorders; however, its efficacy suggests that related, to-be-discovered agents could be useful.

Claude Lenfant ("Chest pain of cardiac and noncardiac origin") discusses chest pain—one of the most common symptoms driving patients to a physician's office or the hospital's emergency department. In approximately half of the cases, chest pain is of cardiac origin, either ischemic cardiac or nonischemic cardiac disease. The other half is due to noncardiac causes, primarily esophageal disorder. Pain from either origin may occur in the same patient. In addition, psychological and psychiatric factors play a significant role in the perception and severity of the chest pain, irrespective of its cause. Chest pain of ischemic cardiac disease is called *angina pectoris*. Stable angina may be the prelude of ischemic cardiac disease; and for this reason, it is essential to ensure a correct diagnosis. In most cases, further testing, such as exercise testing and angiography, should be considered. The more severe form of chest pain, unstable angina, also requires a firm diagnosis, as it indicates severe coronary disease and may be an early manifestation of acute myocardial infarction. Once a diagnosis of stable or unstable

angina is established and if a decision is made not to use invasive therapy, such as coronary bypass, percutaneous transluminal coronary angioplasty, or stent insertion, effective medical treatment of associated cardiac risk factors is a must. Acute myocardial infarction occurring after a diagnosis of angina greatly increases the risk of subsequent death. Chest pain in women warrants added attention because women underestimate their likelihood to have coronary heart disease. A factor that complicates the clinical assessment of patients with chest pain (both cardiac and noncardiac in origin) is the relatively common presence of psychological and psychiatric conditions such as depression or panic disorder. These factors have been found to cause or worsen chest pain; but unfortunately, they may not be easily detected. Noncardiac chest pain represents the remaining half of all cases of chest pain. Although there are a number of causes, gastroesophageal disorders are by far the most prevalent, especially gastroesophageal reflux disease.

Gerard Plante and Theodore VanItallie ("Opioids for cancer pain: the challenge of optimizing treatment") discuss the role of opioids in the treatment of cancer pain. During 2010, at least 8.2 million Americans (about 70% of the US residents who currently suffer from invasive cancer) will experience pain sufficiently severe to require chronic opioid treatment. Cancer-induced pain is usually described under 3 headings: acute pain, chronic pain, and breakthrough pain (BTP). Among patients with chronic, persistent cancer pain controlled by around-the-clock analgesics, there is a high prevalence of BTP—often precipitated by some form of physical activity. Breakthrough pain seems best treated by a powerful, fast-acting opioid such as intravenous morphine or transmucosal fentanyl. At present, opioids are virtually the only analgesics capable of controlling moderate and severe cancer pain. In recent years, a veritable arsenal of opioids with a wide range of pharmacologic properties has become available for use in different pain situations. The World Health Organization has developed a 3-step "analgesic ladder" to guide management of cancer pain based on the pain's severity, estimated by means of a 1 to 10 numeric rating scale. As the severity of the pain escalates, more potent (World Health Organization step III) opioids are used. When faced with a difficult case of cancer pain, the physician must choose—from an array of options—the safest and most effective opioid analgesic and the most appropriate delivery system. Such decisions require an adequate understanding of the available opioids and experience with their use. The pharmacodynamic response to a given opioid depends on the nature of the receptor to which the opioid binds and its affinity for the receptor. Morphine activates the μ-opioid receptors, resulting in not only analgesia and sedation, but also euphoria, respiratory depression, constipation, and pruritus. The existence of a number of opioid receptor subtypes, each with its own repertoire of responses, has given rise to the hope (as yet unrealized) that an opioid can be found (or engineered) that will selectively produce adequate analgesia and sedation without, at the same time, causing unwanted adverse effects. Furthermore, suitable neurostimulatory or neuroinhibitive methods involving the central nervous system are being sought that can amplify the analgesic action of opioids. In the search for antinociceptive agents as efficacious as currently available opioids, but without their troublesome adverse effects, the endogenous opioids, such as the endomorphins, are being examined as offering possible solutions to the adverse effect problem.

3. Summary

The clinical diagnosis and treatment of pain have been particularly challenging because of the variety of mechanisms that underlie the condition and the fact that the response to the same therapeutic approach differs from patient to patient. The challenge for the clinician for intervention of all 3 different types of pain is to seek out the most suitable medication(s) available with the most acceptable adverse effects [4]. A recent study using different drug combinations [6] suggests that clinicians should consider co-prescribing gabapentin and opioids at the onset of NP for optimal relief. Other studies that test the effects on pain of different drug combinations will be helpful in optimizing pharmacotherapy for the management of pain.

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