

METHODS FOR TREATING PAIN

This application claims benefit of the filing date of the U.S. Provisional Application No. 60/520,536, filed Nov. 13, 2003, hereby incorporated by reference.

FIELD OF THE INVENTION

In general, the invention features methods for diagnosing, treating, reducing, or preventing pain.

BACKGROUND OF THE INVENTION

The sensation of pain is a common symptom that may be indicative of an underlying disease or injury, or the expression of an abnormal function within the nervous system. Pain is often the primary incentive for which treatment is sought.

Pain can take a variety of forms depending on its origin. Pain may be described as being peripheral neuropathic if the initiating injury occurs as a result of a complete or partial transection of a nerve or trauma to a nerve plexus. Alternatively, pain is described as being central neuropathic following a lesion to the central nervous system, such as a spinal cord injury or a cerebrovascular accident. Inflammatory pain is a form of pain that is caused by tissue injury or inflammation (e.g., in postoperative pain or rheumatoid arthritis). Following a peripheral nerve injury, symptoms are typically experienced in a chronic fashion, distal to the site of injury and are characterized by hyperesthesia (enhanced sensitivity to a natural stimulus), hyperalgesia (abnormal sensitivity to a noxious stimulus), allodynia (widespread tenderness, associated with hypersensitivity to normally innocuous tactile stimuli), and/or spontaneous burning or shooting lancinating pain. In inflammatory pain, symptoms are apparent, at least initially, at the site of injury or inflamed tissues and typically accompany arthritis-associated pain, musculo-skeletal pain, and postoperative pain. Nociceptive pain is the pain experienced in response to a noxious stimulus, such as a needle prick or during trauma or surgery. Functional pain refers to conditions in which there is no obvious peripheral pathology or lesion to the nervous system. This particular form of pain is generated by abnormal function of the nervous system and conditions characterized by such pain include fibromyalgia, tension-type headache, and irritable bowel syndrome. The different types of pain may coexist or pain may be transformed from inflammatory to neuropathic during the natural course of the disease, as in post-herpetic neuralgia.

Although one approach for the treatment of pain is the removal of the causative or etiological agent (disease modifying therapy), the pain often outlasts the duration of the initiating cause. Accordingly, symptomatic control is essential. In cases in which the sensation of pain becomes unbearable, rapid and effective analgesia is imperative (e.g., postoperative state, burns, trauma, cancer, and sickle cell crisis). Currently, there exist a wide variety of analgesic agents useful for the management of pain, including for example non-steroidal analgesic agents (NSAIDs), anticonvulsants, and opioid analgesics. Despite their efficacy, the chronic use of such agents is often not recommended because of the potential debilitating side effects, such as gastric irritation, toxicity to the liver, respiratory depression, sedation, psychotomimetic effects, constipation, nausea, tolerance, dependence, and the risk of abuse. Also, these agents are sometimes sub-optimal, particularly for neuropathic and functional pain.

Thus, better therapeutic strategies are required for the treatment and management of pain.

SUMMARY OF THE INVENTION

In general, the present invention features methods for the diagnosis, treatment, reduction, and prevention of pain or of endogenous mechanisms that further increase a traumatic, metabolic or toxic peripheral nerve lesion in a mammal. According to this invention, a mammal (e.g., a human) is administered a composition (e.g., methotrexate) that reduces tetrahydrobiopterin (BH4) biological activity such that pain is reduced, prevented, or treated. Alternatively, pain may be reduced in the mammal being treated by decreasing the levels or activity of any one of the enzymes involved in the synthesis of BH4, i.e. BH4 synthetic enzymes. In this regard, BH4 synthesis may be reduced by decreasing the biological activity of at least one, two, three, or more than three of the following enzymes: sepiapterin reductase (SPR), Pyruvoyltetrahydropterin Synthase (PTPS), GTP cyclohydrolase (GTPCH), Pterin-4 α -carbinolamine dehydratase, and dihydropteridine reductase (DHPR). Such activity may be reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% 95%, 99%, or even 100% relative to an untreated control. Alternatively, BH4 biological activity may be reduced by increasing the expression or GTPCH-binding or other biological activity of GTP cyclohydrolase feedback regulatory protein (GFRP). GFRP biological activity may be increased by administering a BH4 or phenylalanine analog that specifically binds to GFRP or a GTPCH:GFRP complex. Traumatic nerve lesions include those caused by mechanical insults and compressive injuries. Compressive injuries may be caused by external trauma or injury, or from internal conditions and disease states, such as a compression resulting from an infiltrative tumor. Metabolic nerve lesions amenable to treatment using the methods of this invention include, for example, diabetic peripheral neuropathies, heritable neuropathies, or neuropathies caused by infectious agents such as the human immunodeficiency virus (HIV). Toxic nerve lesions include, for example, those cause by other therapeutic agents (e.g., chemotherapeutics), or chemicals and environmental toxicants (e.g., heavy metals and organic solvents).

According to this invention, a reduction in pain may result, for example, from changes in the function of primary sensory neurons or neurons within the dorsal horn of the spinal cord, in the brainstem, or in the brain. Such changes may result, for example, from a reduction in the synthesis of BH4, leading to a reduction in the activity of various enzymes (e.g., nitric oxide synthase) that utilize BH4 as a cofactor and to a reduction in the activation of membrane-bound BH4-binding receptors following its release from cells. BH4 action on BH4-binding receptors may be inhibited or reduced by means of competitive or non-competitive BH4-like receptor antagonists. BH4 action on enzymes which use BH4 as a cofactor may be inhibited by means of BH4-like competitive antagonists. Such binding or activity may be reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% 95%, 99%, or even 100% relative to an untreated control.

Furthermore, levels of tetrahydrobiopterin (BH4), its precursors, or its metabolites may be measured in a biological sample obtained from a mammal (e.g., plasma, tissue sample, cerebrospinal fluid, synovial fluid, or tissue exudates) and, in turn, serve as diagnostic tools and as biomarkers of pain or nerve injury. Methods for measuring BH4 are described, for example, in Powers et al. (1988) *J Chromatogr* 432:321-328; Blau et al. (1994) *Clin Chim Acta* 226:159-169; Ponzzone et al. (1994) *Eur J Pediatr* 153:616; Zorzi et al. (2002) *Mol Genet Metab* 75:174-177; and Shiraki et al. (1994) *Eur J Pediatr*