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The biological role of arachidonic acid-cyclooxygenase-prostaglandin (AA-COX-PG) pathway in various organ systems has been intensively investigated during the last fifty years. Particularly, the role of COX enzyme in generating PGs during AA metabolism following tissue injury and inflammation and subsequent PG-mediated peripheral and central sensitization in nociceptive processing has been extensively studied.

Non-steroidal anti-inflammatory drugs are well known COX inhibitors and are widely used in the treatment of fever, acute and chronic painful conditions associated with or without inflammation, and related disorders. However, their use is often limited by the gastrointestinal side effects particularly peptic ulcers. Of the three isozymes of COX identified, the physiological role of COX-1 and -2 have been well characterized. It has been demonstrated that suppressing PGs by constitutive COX-1 in stomach can result in ulcers and bleeding. COX-2 is not present constitutively but readily inducible by certain infections, nociceptive mediators like cytokines, and various inflammatory stimuli. During the last decade, the discovery of COX-2 led to a newer type of NSAIDs that selectively inhibits the COX-2 enzyme, which is associated with inflammation and pain and selective COX-2 inhibition effectively relieve pain with a reduced risk of ulcers. Thus, there is incessant development of newer selective COX-2 inhibitors with better safety profile.

Evidence indicates the elevated levels of cytokines are commonly observed in endotoxemia and following surgery, and the subjects show intense hypersensitivity to noxious stimuli. LPS, a well known endotoxin, when administered releases various proinflammatory cytokines and produces hypersensitivity. Neuropathic pain is the result of an injury or malfunction in the peripheral or central nervous system. The pain is often triggered by an injury, but this injury may or may not involve actual damage to the nervous system. Furthermore, it has also been reported that painful conditions affecting the trigeminal field of innervation (orofacial area) are of both inflammatory and neuropathic origins. Moreover, chronic pain conditions such as fibromyalgia are characterized by musculoskeletal pain. Recently, central sensitization and hypersensitivity in chronic musculoskeletal pain have also received significant attention. Relatively, less number of attempts has been made to unravel the underlying mechanisms in the pathophysiology of such painful conditions and such attempts have been hampered by the lack of animal models for such painful
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conditions. Nonetheless, the effectiveness of COX inhibitors, and the relative role of COX isozymes in these nociceptive conditions has not been well studied.

To reveal pathogenic factors, and thus to develop therapeutic strategies aimed at halting disease progression, there is a constant search of putative culprits in the neuropathology of various nociceptive conditions. Indeed, the role of the neuronal component in nociceptive transmission is well known, however in recent time, the non-neuronal cells of the CNS, such as glial (astrocytes and microglia) cells have gained importance and play an important role in the development of hyperalgesia. Both the glial cells release a variety of pro-inflammatory cytokines, neurotransmitters, and control upstream regulation of COX in AA-COX-PG pathway. This recent advance prompted us to unravel the exact role of glial cells, particularly microglia in the above disorders.

Balanced or multimodal analgesia involves the selective use of specific drugs in combination. The concept relies on using multiple analgesic drugs with different modes of action or via different routes of administration. There is now good evidence that this approach improves analgesia due to additive or synergistic effects. This permits the doses of the individual drugs to be reduced thereby reducing the incidence and severity of adverse effects. Though there are many analgesic choices for treating pain in general, there are fewer choices and more limitations when using analgesics in the management of acute and chronic debilitating painful conditions and also perioperative setting.

With this background, the present was undertaken to study establish animal models of lipopolysaccharide hyperalgesia, neuropathic pain of different etiologies, orofacial pain, and musculoskeletal pain, to study the involvement of COX isozymes and microglial cells, and to address the relative role of COX isozymes in these models of nociception. Attempts have also been made to investigate the potential beneficial antinociceptive interactions between NSAIDs and other commonly used analgesics in the management of painful conditions.

The present work is divided into 10 chapters and each chapter describes the investigations of one or two interdependent, but related pathophysiological mechanisms underlying and the effects of pharmacological interventions in various animal models of pain. The chapter 1 describes the pharmacological profile of a water soluble selective COX-2 inhibitor developed for parenteral administration in various behavioral paradigms of nociception along with its gastrotolerability. The role of
COX-2 in LPS mediated nociceptive hypersensitivity has been discussed in chapter 2. The possible role of COX isozymes in the development and maintenance of peripheral neuropathic pain has been explored in two different animal models of nerve injury and discussed in chapter 3 and 4. Chapter 5 discusses the possible role of COX isoforms in the development of diabetic neuropathic pain. The role of PGs and the relative role of COX isozymes in orofacial pain of trigeminal origin have been described in chapter 6. Chapter 7 deals with the possible role of microglial cells in the generation of hypersensitivity to nerve injury. Chapter 8 describes the development and characterization of LPS-induced bilateral muscle hyperalgesia and the possible role of microglia cells in such hypersensitivity has been discussed. Chapter 9 and 10 deals with the potential antinociceptive interactions between NSAIDs and tramadol or gabapentin using various behavioral paradigms of non-inflammatory and inflammatory pain.