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THE ROLE OF 5-LIPOXYGENASE IN PATHOPHYSIOLOGY AND MANAGEMENT OF NEUROPATHIC PAIN

Pascanus Lamsihar PT*, Faldi Yaputra, Jimmy FA Barus△ and I Putu Eka Widyadharma**,1**

*Department of Neurology, Provincial Mental Hospital, West Borneo, Indonesia., **Department of Neurology, Faculty of Medicine, Udayana University-Sanglah General Hospital, Bali, Indonesia., △Department of Neurology, Faculty of Medicine, Atma Jaya Catholic University, Jakarta-Indonesia.

ABSTRACT Neuropathic pain (NP) is a pain caused by lesions in the nervous system. Several causes of NP are traumatic, metabolic disorders, ischemia, toxins, infections, immune-related, and hereditary. The pathophysiology of NP is very complicated and unknown entirely. Therefore the treatment of NP is still unsatisfactory. Recent studies believed the critical role of primary inflammatory mediators in the pathophysiology of NP especially leukotrienes (LTs). The 5-lipoxygenase enzyme (5-LOX) is an enzyme that plays a role in the metabolism of arachidonic acid into LTs. Leukotrienes (LTs) are the essential inflammatory mediators in the pathophysiology of NP. Leukotriene B4 (LTB4) can cause chemotaxis on neutrophils, lowering nociceptors threshold and may contribute to NP. Several studies believed the administration of 5-LOX inhibitors or LTs receptor antagonists could be useful in the management of NP. The purpose of this review is to summarize the involvement of 5-LOX enzyme as an essential role in the pathophysiology and management of NP.

KEYWORDS 5-lipoxygenase, leukotrienes, pathophysiology of neuropathic pain, inflammatory mediators, management of neuropathic pain

1.INTRODUCTION

Pain is an unpleasant sensory and emotional experience related to actual or potential tissue damage or described by the damage. Pain is classified into two categories, nociceptive pain and NP [1]. Neuropathic pain (NP) occurs due to lesions of the nervous system [2]. So, any diseases or injuries in the nervous system may lead to NP [3]. The prevalence of NP in developed countries estimated 1% - 7% of populations [1]. Until now, the most effective treatment for NP is still unavailable [4].

Pain is commonly associated with inflammation and part of the first four classic signs of inflammation together with redness, tumour, and heat. Inflammation is a homeostatic response of vascularization to eliminate noxious agents and restore their standard functions [2]. There is increased activation of peripheral immune cells in nerve injury-induced NP [5]. They are recognized as elicited nociceptive neurotransmitters and mediators (glutamate, substance P, adenosine triphosphate, fractalkine, etc.) that are released from sensitized primary afferent terminals and activate spinal microglia and astrocytes [6].

There are two critical enzymes in the inflammation process, cyclo-oxygenase (COX) enzyme, and 5-LOX enzyme. Many previous studies have focused only on the COX pathway, and most of the anti-inflammatory drugs work only by blocking the COX pathway. the 5-LOX enzyme is not less critical than COX enzyme in the inflammation process. Both enzymes metabolize arachidonic acid into prostaglandins (PGs) by COX [7] and into LTs by 5-LOX [9]. Prostaglandins (PGs) and LTs are pro-inflammatory mediators that induce pain symptoms [8]. Some studies indicate inhibition of the COX pathway may even increase arachidonic acid metabolism via the 5-LOX pathway that releases more of LTs [7]. Therefore, by inhibiting the COX pathway alone does not seem to be able to relieve pain completely. The objective of this review is to summarize the function of 5-LOX based on various studies in pathophysiology and management of NP.

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[1]Department of Neurology, Faculty of Medicine, Udayana University/ Sanglah General Hospital, Bali- Indonesia; Email: eka.widyadharma@unud.ac.id

2.RISK FACTORS AND CAUSES

There are several risk factors and causes of NP. Neuropathic pain (NP) is associated with neurological disorders of both peripheral and central nervous system. It manifests as a persistent burning pain with spontaneous and worsening exacerbations upon normal causing an impact on the quality of life [10]. The damaged nerve can develop into NP [11]. The mechanism of NP is very complicated, and it is difficult to determine what conditions could be a definite cause of NP. The leading causes of NP include traumatic, metabolic disorders, ischemia, toxins, infections, immune-related and hereditary [12].

The prevalence of NP increases with age and severity of underlying disease [13]. Purwata et al. were reported the higher prevalence of NP in 41-60 years old (n=1,030;57,9%) [14]. Several studies have found a significant association between the incidence of NP with worse physical, mental and social health. In France, Smith et al., were reported a decreased quality of life, sleep and increased the incidence of psychiatric disorders such as anxiety and depression in patients with NP [15]. Widiastuti et al., study 50 patients with 66% proportion of woman with mean age 67,40 ± 6,80 years old. The proportion of NP 44% and 58% have poor sleep quality. They reported, 42% of the samples have NP with poor sleep quality, there is a significant relationship between NP and poor quality of sleep in the elderly [16]. In diabetic patients with smoking habits, hypertension, hypercholesterolemia, obesity and long duration of diabetes increase the risk of peripheral diabetic neuropathy (PDN). Risk factors for the occurrence of postherpetic neuralgia (PHN) include elder subjects of herpes zoster infections, immunocompromised and severe herpes zoster infections. The risk of PHN has decreased by prevention of herpes zoster infection; Zoster vaccine administration reduced the incidence of PHN by up to 66%. The prevention of HIV infection through education and sexual health promotion are vital to reducing the occurrence of HIV-associated peripheral sensory neuropathy (HIV-SN) [15].

3.MAJOR INFLAMMATORY MEDIATORS AND ANTI-INFLAMMATORY CYTOKINES IN PATHOPHYSIOLOGY OF NP

Several studies believed the involvement of inflammatory conditions behind the occurrence of NP [17,18]. Nowadays many researches are focused on the role of inflammatory mediators such as lipid mediators (PGs and LTs), chemokines and cytokines in the pathophysiology of pain. In the peripheral nervous system, after nerve injury, inflammatory mediators are hyper-regulated by resident cells and infiltrate leucocytes that induce peripheral sensitization. In the central nervous system, glial cells in spinal cord activated by inflammatory mediators induce central sensitization [2].

Inflammatory mediators are released both by infiltrative and resident immune system cells and by glial cells with immune function, which activate or sensitize nociceptors, leading to aberrant nociceptive system activity. Chemical pro-inflammatory mediators may act on adjacents glial cells and increasing migration of immune system cells, inducing the distant release of more mediators. Painful phenomenon increasing list of inflammatory mediators including bradykinin, eicosanoids (PGs and LTs), adenosine triphosphate (ATP), histamine, cytokines inflammatory, chemokines, neurotrophins and oxygen reactive species. Inflammatory chemical mediators are released in injured tissue by activated cells which coordinate the inflammatory response process [2]. Anti-inflammatory mediators such as immune cell-derived endorphins, anti-inflammatory cytokines (interleukin-10, IL-10 and transforming growth factor beta, TGFB), and some neurotrophic factors (glial neurotropic factor, GNF) show antagonist effects to inflammatory pain mediators [2].

4.THE ROLE OF 5-LOX IN PATHOPHYSIOLOGY OF NP

The 5-lipoxygenase (5-LOX) enzyme is an enzyme that metabolizes arachidonic acid into LTs [3]. Leukotrienes (LTs) are known to be involved in the pathogenesis of inflammatory pain [19]. We will review the functions of the 5-LOX enzyme and their association in the pathophysiology of NP. The 5-lipoxygenase (5-LOX) enzyme can be found on inflammatory cells such as leucocytes, basophils, mast cells, polymorphonuclear, and macrophages. When cell damage occurs, it activates the phospholipase A2 enzyme thereby releasing arachidonic acid from phospholipid membrane. After the arachidonic acid is released, it will be metabolized by two significant enzymes, COX enzyme, and 5-LOX enzyme. The 5-lipoxygenase (5-LOX) enzyme is activated first by 5-LOX activating protein (FLAP), which metabolizes arachidonic acid into leukotriene A4 (LTA4) [2]. LTA4)hydrolase will metabolize leukotriene A4 (LTA4) into LTB4 or by leukotriene C4 (LTC4) synthase into LTC4. Leukotriene C4 (LTC4) will be converted into leukotriene D4 (LTD4) and leukotriene E4 (LTE4). Leukotriene C4 (LTC4), LTD4, and LTE4 are called cysteinyl leukotrienes [9].

Leukotrienes (LTs) action with specific receptors in the glial cells and several immune cells. BLT1 is receptors with high affinity for LTB4, while BLT2 binds LTB4 and other LTs as lower affinity, CisLT1 and 2 binds CystLTs as a selective receptor. Leukotriene B4 (LTB4) had a chemotactic response of neutrophils and indicated the involvement of LTB4 in the pathophysiology of inflammatory diseases. Several LTs are released such as 8R and 15S-diHETE that produce hyperalgesia by intraplantar LTB4 injections, which lowering nociceptors threshold and may contribute to NP [2]. The rats spared nerve injury (SNI) have been shown the increasing of LTs synthesis and expression on CystLT1 receptors in the spinal microglia, which may lead to NP. Administration of CystLT receptor antagonists can inhibit microglia activation [6].

5. THE ROLE OF 5-LOX IN MANAGEMENT OF NP

Most people with NP experienced life-long pain; this is because the pathophysiology of NP is very complicated and not yet fully known [3]. Neuropathic pain (NP) often do not respond to conventional analgesics treatment. Drugs that are commonly used in treating NP include nonsteroidal anti-inflammatory drugs (NSAIDs), narcotic analgesics, opioid, anticonvulsants, and tricyclic antidepressants [20].

Leukotrienes (LTs) can cause symptoms associated with inflammation including pain, so inhibitors of 5-LOX and LTs receptor antagonists may have therapeutic value in pain management. The pain models have proven the administration of zileuton (active inhibitor of 5-LOX) [19] and montelukast (LT receptor antagonists) can reduce the symptom of pain in NP. Administration CystLT receptor antagonists can cause inactivation of microglia, thus lowering LTs synthesis and expression on CystLT1 receptors [6]. Pranlukast (cysteinyl-leukotriene receptor-1 antagonists) can decrease inflammation in the dorsal root ganglia (DRG) in patients with PHN. Montelukast may decrease hyperalgesia in children and adolescents accompanied by dyspepsia and duodenal eosinophilia [21].

Prostaglandins (PGs) and LTs have a synergistic effect on the occurrence of pain symptom. The administration of both inhibitor of 5-LOX (zileuton) and NSAIDs (indomethacin) also synergistically decrease hyperalgesia compared to either alone [21]. So the combined inhibitors of both prostaglandin and leukotriene would have benefits over existing drugs.

Eicosanoids are numerous family of compounds with high potency and broad biological activity spectrum. Arachidonic acid, one of the constituents of cell membranes, is the most important precursor of eicosanoids. After released from cell membranes, the arachidonic acid will be amenable to oxygenated. A state of injury or degeneration may increase the likelihood of arachidonic acid to be metabolized, and the metabolites outcome is a sign that noxious or potentially noxious stimuli. There are four central pathways in arachidonic acid metabolism, i.e., by COX, LOX, isoprostane, and epoxygenase [2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics are widely used to treat pain, but there are many adverse side effects. Many studies have researched to find safer analgesic and anti-inflammatory drug formulations [7]. The researches are developing an alternative natural medicine. Some medicinal plants are believed to have analgesic and anti-inflammatory potential even with or without small side effects [22]. Some of which are Curcuma longa rhizome extract and Boswellia serrata extract. Both of those medicinal plants have anti-inflammatory effects with a slightly different way of pharmacodynamics. Curcuma longa rhizome extract works as a COX-2 blocker, which inhibits the formation of prostaglandins. Boswellia serrata extract inhibits the release of inflammatory mediators such as LTs. Both of those medicinal plants have been used to manage NP [23]. In the future, natural medicine treatment is necessary to be considered in NP management related to the absence of adverse side effects, but it still needs further researches on the usefulness.

6. CONCLUSION

Neuropathic pain (NP) is commonly associated with inflammation. The pathophysiology of NP is very complicated and unknown entirely. Due to its complex pathophysiology, therefore the treatment of NP is still unsatisfactory. It has been known that LTs (LTB4, LTC4, LTD4, LTE4) play a role in the pathophysiology of NP. Leukotriene B4 (LTB4) can cause chemotaxis to neutrophils and produce hyperalgesia which decreases of nociceptors threshold and may contribute to NP. Some clinical studies have proven the administration inhibitors of 5-LOX and antagonists receptor of LTs can decrease hyperalgesia. Based on the involvement of 5-LOX to produce LTs in the pathophysiology of NP, maybe in the future the 5-LOX and LTs inhibitors can be a useful alternative therapy for patients with NP. Some medicinal plants are known to have anti-inflammatory effects such as Curcuma longa rhizome extract and Boswellia serrata extract. The advantage of using natural anti-inflammatory in NP treatment is the absence of side effects compared to other chemical drugs. So the need for natural anti-inflammatory in NP treatment is necessary. Some medicinal plants have been used in the treatment of NP, but still, need further research on its usefulness.

7. COMPETING INTERESTS

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