

Editorial

Smoking-Induced Nociception

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The association between smoking and pain is extremely complex (1-3). In a recent review Shi et al (4) described multiple potential factors whereby smoking may contribute to pain. Smith (5) has postulated a potential novel mechanism whereby smoking may contribute to inflammatory pain via its inhibitory actions on an enzyme known as leukotriene A4 hydrolase (LTA4H), --- an action on the peptidase site of LTA4H revealed by Snelgrove et al(6).

Epidemiologic studies have reported an association between smoking and low back pain (7,8). Leboeuf-Yde et al (9) performed a systematic literature review on the association between smoking and low back pain based on 47 studies published between 1974 and 1996. Many, but not all, studies find a positive association between smoking and low back pain. Goldberg et al. reviewed publications from 1976 through mid-1997 on the association between smoking and nonspecific back pain and also found that smoking is associated with nonspecific back pain in some, but not all, of the studies (10). Other studies suggest that among those with chronic pain, smokers complain of greater pain intensity and an increased number of painful sites (11,12).

Shi and colleagues have noted that many factors may influence the relationship between smoking and chronic pain including: 1) smoking-induced altered processing of pain, chronic exposure to cigarette smoke (chronic smoke exposure may change pain perception in smokers compared with nonsmokers)) (Smokers may perceive a given stimulus as more painful (at least while deprived of cigarettes) and may smoke to relieve increased pain perceptions caused by incipient nicotine withdrawal when nicotine blood levels fall (e.g., during sleep) 2) smoking-induced neuroendocrine system modulation of pain perception; 3) smoking-induced structural damage to other systems/processes [interference with bone and connective tissue homeostasis, interference with wound healing, interference with oxygen delivery]; 4) smoking-induced mood changes [association with depression]; 5) smoking associated psychosocial factors, and/or 6) smoking associated opioid use and interaction with opioids or opioidergic systems/pathways. [Opioid-related pathways may modulate both the analgesic effects of nicotine and the reinforcing properties of smoking that contribute to addiction] (Exposure to cigarette smoke may also alter the pharmacokinetics of opioids) (4).

Although the review of Shi et al. concentrates on nicotine-modulation of pain they appropriately point out that "any of the approximately 3,000 other constituents of cigarette smoke may also be involved in the development of painful conditions (4). "Chronic exposure to carbon monoxide increases the level of heme oxygenase (13,14); thus "the possible involvement of the heme oxygenase-carbon monoxide system in the susceptibility of smokers to chronic pain deserves further study" (4). Smith has proposed a novel potential mechanism in which smoking may facilitate inflammatory pain that appears to be unrelated to nicotine or carbon monoxide (5).

Leukotriene B4 (LTB4) is largely derived from the action of 5-lipoxygenase on arachidonic acid in leukocytes (15,16). LTB4 may evoke profound hyperalgesia on intradermal injection into the dorsum of the rat's hindpaw (17). LTB4 induced-hyperalgesia is distinguished from that of PGE2 by a dependence

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on polymorphonuclear leukocytes (PMNLs) and a lack of effect of the cyclooxygenase inhibitors (17,18).

LTB₄ may facilitate pain in certain pain states via its chemoattractant activities but LTB₄ also seems to possess inherent pro-nociceptive qualities. Neutrophil accumulation may fuel inflammation as well as nociception certain inflammatory painful conditions. It appears that certain factors which may be key in bringing about neutrophil accumulation in inflammatory pain states, may also be important in contributing to or facilitating pain. Previous studies demonstrated that PMNLs could be recruited locally by mediators such as formyl-methionine-leucine-phenylalanine (fMLP), LTB₄, complement C5a, and NGF (17-20). Injection of these mediators induced pain (i.e., mechanical or thermal hyperalgesia) that was attenuated by PMNL depletion. Rittner and colleagues found that hyperalgesia, local PGE₂ production, and spinal c-Fos expression occur after CFA-induced inflammation but not after CXCL1- or CXCL2/3-induced, selective PMNL recruitment; suggesting that PMNLs may be less important in certain inflammatory hyperalgesic states than

in others (21). Guerrero and colleagues showed that LTB₄-induced hypernociception depends on the additional release of endogenous leukotrienes (LTs) as well as neutrophil recruitment and/or prostanoids (22).

Normally matrix metalloproteinases are evolved during various inflammatory processes. Matrix Metalloproteinases enzymatically generate the tripeptide proline-glycine-proline (PGP) and its more potent acetylated form (N- α -PGP) from extracellular matrix proteins (e.g. collagen) (23-25). PGP and N- α -PGP are strong selective neutrophil chemoattractants that seem to be involved in processes of neutrophil accumulation (6). Direct instillation of PGP or N- α -PGP into rodent's lungs induces neutrophil accumulation and inflammation (23). Leukotriene A₄ hydrolase (LTA₄H) has been considered a proinflammatory enzyme since via its hydrolase activity (acting as an epoxide hydrolase), LTA₄H generates the chemoattractant leukotriene B₄ (LTB₄) (26,27). Under normal circumstances, it is likely that PGP and N- α -PGP, which may be generated in various inflammatory states, are degraded by the peptidase activity of LTA₄H (6) (Fig. 1).

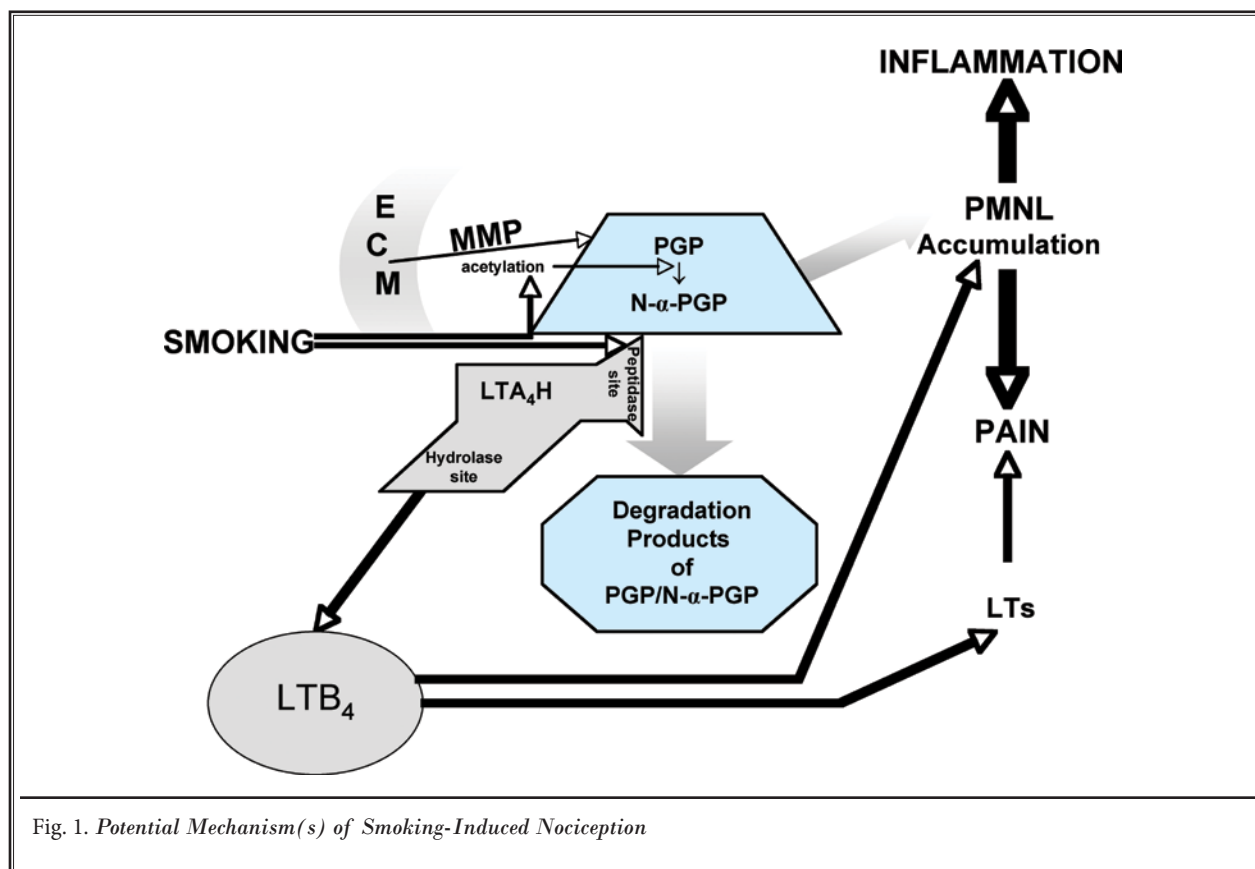


Fig. 1. Potential Mechanism(s) of Smoking-Induced Nociception

Snelgrove and colleagues revealed that cigarette smoke extract (possibly via acrolein — an extract component) may increase acetylation of PGP (thereby increasing its chemotactic capacity) and inhibit the peptidase activity of LTA4H (without affecting its hydrolase activity), thereby blocking the normal degradation of PGP and N- -PGP, leading to increased levels of these potent neutrophil chemoattractants PGP and N- -PGP. Thus,

neutrophil chemotaxis may be increased and prolonged by cigarette smoking, due to increased levels of PGP and N- -PGP. Therefore, smoking may facilitate an increase and persistence of inflammation and potentially pain as well in certain conditions. Since smoking does not inhibit the hydrolase activity of LTA4H; normal or perhaps increased levels LTB4 may still be generated with smoking, which also may facilitate inflammation/pain.

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