SHORT COMMUNICATION

Role of PEA in Reduction of Opiate Tolerance

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DESCRIPTION

Despite the strength and effectiveness of morphine, the development of tolerance to the anti-nociceptive effect restricts its clinical use for chronic persistent pain. The extensive and poorly understood cellular and molecular pathways underlying morphine tolerance. Recently, it has been proposed that the phenomena may be influenced by the activation of glial cells and the release of pro inflammatory mediators from these cells. An endogenous substance called N-palmitoylethanolamine (PEA) has anti-nociceptive properties that can lessen glial activation.

Compared to the vehicle, morphine group, PEA therapy dramatically slowed the onset of tolerance and increased the number of days that morphine was effective as an anti-nociceptive. In contrast, PEA had no effect on the morphine-dependent rise in spinal TNF-α level. PEA suppressed the growth of microglia and astrocyte cell numbers in the dorsal horn. However, the immunohistochemistry study showed much more TNF-α immune reactivity in the astrocytes of rats protected by PEA, pointing to a PEA-mediated reduction in astrocyte cytokine release. The endogenous component PEA intervenes in the neurological changes that result in the absence of morphine's anti-nociceptive effects; it is claimed that opioid-based therapies may benefit from using this substance[1,2].

Opioids continue to be a crucial component of medical pain management. Although opioids are frequently effective in acute settings, long-term use of these drugs may be associated with declining levels of analgesic response that are not immediately related to the progression of underlying disease, necessitating dose escalation to control pain. Tolerance to analgesics has been used to explain the opioid effectiveness that had decreased over time. This undesired manifestation considerably lowers quality of life in chronic pain sufferers, coupled with additional side effects brought on by increasing doses (such as over sedation, respiratory depression, and constipation).

Multiple lines of evidence have shown that many processes, mostly involving neural mechanisms of adaptation and sensitization, are known to be involved in morphine tolerance. Contrarily, long-term morphine therapy stimulates spinal and cortical glial cells, which aid in the growth of anti-nociceptive tolerance. The increased production of numerous substances, including free radicals, nitric oxide, pro inflammatory cytokines and chemokines, prostaglandins, complement proteins, neurotoxins, neurotrophic factors, and excitatory amino acids, as a result of direct and indirect morphine-evoked signals, actively counteracts the analgesic effects of morphine and aids in the development of tolerance.[3].

It has been discovered that administering the glial metabolic inhibitor fluorocitrate lessens the emergence of morphine tolerance. In naive mice as well as in a model of neuropathic pain, minocycline, propentofylline, and pentoxifylline dramatically inhibited the development of morphine tolerance. Because of the decreased perioperative cytokine response, patients on pentoxifylline had longer patient-controlled analgesia trigger intervals and require less morphine overall. However, the negative effects of these substances prevent their extended use in situations involving chronic pain.

The amide formed naturally between ethanolamine and palmitic acid is called N-palmitoylethanolamine (PEA), and it is a member of the family of lipid mediators known as Fatty Acid Ethanol amides (FAEs). Several animal models have shown that PEA has anti-nociceptive effects. Numerous clinical trials focusing on the treatment of pain states have demonstrated its safety and effectiveness, including those for diabetic neuropathy, carpal tunnel syndrome, temporomandibular joint pain, dental pain, post-herpetic pain, and chemotherapy-induced neuropathic pain. Additionally, PEA guards against neurotoxicity and neurodegeneration, reduces peripheral inflammation, and blocks mast cell degranulation in neuropathic circumstances.

PEA also decreased the activation of astrocytes and microglia. In both the formalin-induced inflammatory pain paradigm in rats and the spinal cord injury model in mice, PEA normalised the activation of spinal microglia and astrocytes. In a rat brain model of Parkinson's disease produced by 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP), PEA treatment decreased microglial activation and the number of astrocytes and prevented reactive gliosis. The anti-nociceptive effect of repeated administration of the alkaloid was assessed over time during PEA administration on the basis of the idea that the glial cell modulator PEA may affect the development of morphine tolerance.[4].

CONCLUSION

Multiple characteristics of PEA combine to interact with morphine evoked signals. The fact that PEA delays the onset of tolerance to morphine's anti-nociceptive effects raises the possibility of using this endogenous substance in opioid-based therapeutics. The transient receptor potential vanilloid type 1 (TRPV1) and cannabinoid receptors may be indirectly stimulated by PEA. It's interesting to note that morphine can alter endocannabinoid levels. The amounts of 2-arachidonoylglycerol (2-AG) and arachidonoylethanolamide (anandamide, AEA) in the brain following morphine administration.

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