CHRONIC PAIN

PROF. ALBERT CILIA-VINCENTI

TWO TESTED NATURAL COMPOUNDS MAY BREAK PAIN CYCLE COULD THEY BE USEFUL IN NEURODEGENERATIVE DISEASE?

Chronic pain is a substantial medical concern because it is common, can be debilitating, and pain medications may be more dangerous than originally thought.

Analgesic drugs taken for even a few days are now claimed to increase myocardial infarction risk by 48%, using ibuprofen, and by 53% when using naproxen.[1] Chronic use of NSAIDs like ibuprofen is claimed to increase kidney function impairment by 32%.[2] Furthermore, the current opioid epidemic in the US is said to claim over 100 overdose deaths daily.

The challenge in pain control is both addressing the cause of the pain and switching off the pain signal. Is there a safe alternative? Two natural compounds are claimed to work together to reduce the underlying causes of pain. The first compound, **palmitoylethanolamide** (**PEA**), is an anti-inflammatory fatty acid derivative produced by the body in response to inflammation-inducing damage;[3] it acts at the site of tenderness, turning off the pain signal.[4,5] The second, **honokiol**, a Magnolia tree extract, modulates pain perception in the brain. These two compounds are claimed not to cause dependence because they do not act via opioid receptors.

The nature of PEA was first identified by Nobel Laureate Rita Levi-Montalcini, the co-discoverer of the nerve growth factor and the pain signal development and transmission mechanisms.[6-8] PEA is said to be an endocannabinoid, a natural neurochemical signalling molecule which does not bind to specific cannabinoid receptors, and which has no documented risk of dependency or adverse effects. This distinguishes it from most other chronic pain treatments.[9]

Several studies have established PEA as a powerful, peripherally-acting pain reliever.[4,5] One study was conducted on 636 sciatic pain sufferers randomly assigned to placebo or one of two doses of PEA (300mg or 600mg daily). After 3 weeks, both pain reduction and quality–of-life scores were significantly better than placebo, and the larger dose had better outcomes.[10,11]

In pain studies, determination of how many patients would need to be treated to achieve a 50% pain reduction is called the "number needed to treat". The standard number to treat for a useful pain intervention is less than 5, with 1 being statistically perfect (every treated patient achieves at least 50% pain reduction).

In this PEA study, the number needed to treat in the 600mg daily group was just under 3 at week 2 and only 1.5 at week 3.[10,12] A number needed to treat as low as 1.5 is virtually unknown in pain reduction, indicating such a high level of effectiveness which surpasses most pharmaceutical standards.

In another PEA study with carpal tunnel syndrome, subjects were randomly assigned to three groups, placebo, 600mg and 1,200mg daily for 30 days.[13] Nerve conduction measurements at the start and end of the study showed that PEA had slowed median nerve conduction. A faster nerve conduction indicates pain signals are being generated at the sore site. Therefore, this study indicated that PEA recipients' nerve conduction improvements matched their reduced symptoms compared to controls.

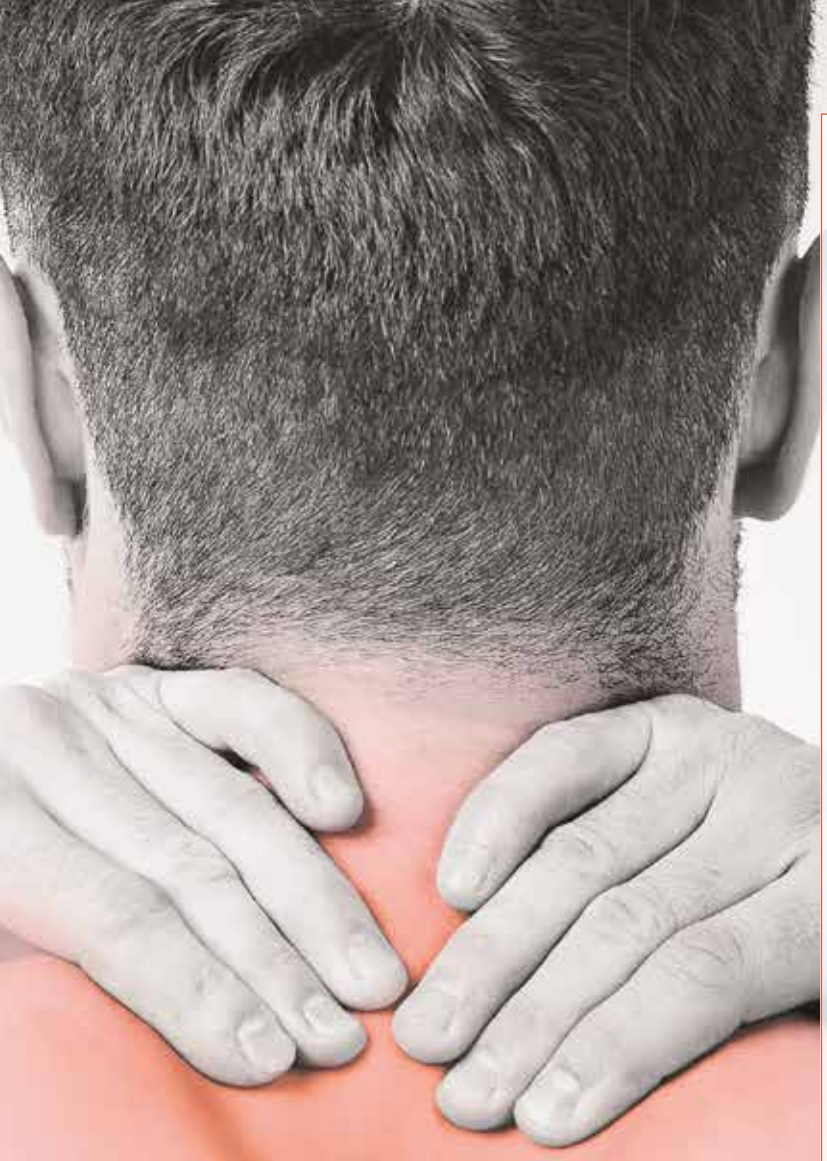
In a study on patients with temporomandibular joint pain, subjects were randomly assigned to 600mg ibuprofen 3 times daily for 2 weeks or 300mg PEA twice daily for 2 weeks. The PEA group experienced significantly greater decrease in pain.[14]

Another study showed that mice treated with morphine plus PEA were less prone to develop morphine tolerance compared with animals on morphine alone.[15] This suggests that PEA combined with an opioid could decrease the risk of tolerance and addiction.

Honokiol has been identified as the second compound that could approach pain reduction from a different aspect to provide deeper, complementary, more consistent relief. It operates in the central nervous system to affect how pain is perceived. It binds to GABA receptors, GABA being a neurotransmitter inducing calming, pain-dampening signals.[16,17]

Loss of GABA receptors and reduced GABA signalling is involved in the transition from acute to chronic pain, leaving the CNS exposed to continued stimulus from an old injury.[18-20] Honokiol mimicks GABA actions, interfering with the chronic pain cycle by restoring a central natural pain-dampening effect. This is being followed up by pharmaceutical companies.[21] Oral honokiol is quickly absorbed and distributed throughout the brain.[22-24]

An animal study has shown how capable honokiol is in its CNS pain-relieving action. Mice were injected with a variety of substances known to activate hyperalgesia receptors.[25] Then they were treated with either honokiol or a control injection.



For each pain-inducing substance the mice were timed on how long they spent licking the painful site, longer licking meaning more severe pain perception. They were then timed on how long they took to withdraw their paw from a hot water bath. In each case, the honokiol-treated animals showed significant reductions in licking time, and significant increases in paw withdrawal time from the hot bath. These actions indicated a reduction in pain and demonstrated how honokiol can help break the chronic pain cycle.

By inference, a honokiol-PEA combination could provide a complementary dual action approach to chronic pain, without the risks seen with conventional analgesic drugs.

Chronic inflammation in the CNS may be involved in the pathogenesis of neurodegenerative conditions such as Parkinson's and Alzheimer's diseases. In a study of 30 advanced Parkinson's patients being treated with levodopa, a cognitive test battery before and after receiving 1,200mg PEA daily for three months and 600mg daily for the rest of the year, found a significant and progressive reduction in both motor and non-motor symptoms.[26] PEA appears to have potential for some reversal of symptoms of chronic neurodegenerative diseases.

PEA is available in Europe under the trade name Normast®. A PEA-Honokiol combination product is marketed as ComfortMAX™ by *Life Extension Europe*, the European division of *Life Extension*, an American food supplement company.

REFERENCES

1. Bally M, Dendukuri N, Rich B et al. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. *BMJ*. 2017; 357:j1909.
2. Hsu CC, Wang H, Hsu YH et al. Use of Nonsteroidal Anti-inflammatory Drugs and Risk of Chronic Kidney Disease in Subjects with Hypertension: Nationwide Longitudinal Cohort Study. *Hypertension*. 2015; 66(3): 524-33.
3. De Filippis D, D'Amico A, Iuvone T. Cannabinomimetic control of mast cell mediator release: new perspective in chronic inflammation. *J Neuroendocrinol*. 2008; 20 Suppl 1: 20-5.
4. Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmokinetics, safety and efficacy. *Br J Clin Pharmacol*. 2016; 82 (4): 932-42.
5. Paladini A, Fusco M, Cenacchi T et al. Palmitoylethanolamide, a Special Food for Medical Purposes, in the Treatment of Chronic Pain: A Pooled Data Meta-analysis. *Pain Physician*. 2016; 19 (2): 11-24.
6. Leon A, Buriani A, Dal Toso R et al. Mast cells synthesize, store and release nerve growth factor. *Proceedings of the National Academy of Sciences of the United States of America*. 1994; 91 (9): 3739-43.
7. Aloe L, Tuveri MA, Caracassi U et al. Nerve growth factor in the synovial fluid of patients with chronic arthritis. *Arthritis & Rheumatism*. 1992; 35 (3): 351-5.
8. Levi-Montalcini R, Skaper SD, Dal Toso R et al. Nerve growth factor; From neurotrophin to neurokine. *Trends in Neurosciences*. 1996; 19 (11): 515-20.
9. Ryberg E, Larsson N, Sjogren S et al. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol*. 2007; 152 (7): 1092-101.
10. Guida G, De Martino M, De Fabiani A et al. La palmitoiletanolamida (Normast®) en el dolor neuropatico cronico por lumbociatalgia de tipo compresivo: studio clinico multicentrico. *Dolor Investrigacion Clinica & Terapeutica*. Vol 252010: 35-42.
11. Valat JP, Genevay S, Marty M et al. Sciatica. *Best Pract Res Clin Rheumatol*. 2010; 24 (2): 241-52.
12. Keppel Hesselink JM, Kopsky DJ. Palmitoylethanolamide, a neutraceutical, in nerve compression syndromes: efficacy and safety in sciatic pain and carpal tunnel syndrome. *J Pain Res*. 2015; 8: 729-34.
13. Conigliaro R, Drago V, Foster PS et al. Use of Palmitoylethanolamide in the entrapment neuropathy of the median nerve in the wrist. *Minera Med*. 2011; 102 (2): 141-7.
14. Marini I, Bartolucci ML, Bortolotti F et al. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. *J Orofac Pain*. 2012; 26 (2): 99-104.
15. Di Cesare Mannelli L, Corti F, Micheli L et al. Delay of morphine tolerance by Palmitoylethanolamide. *Biomed Res Int*. 2015; 2015: 894732.
16. Alexeev M, Grosenbaugh DK, Mott DD et al. The natural products magnolol and honokiol are positive allosteric modulators of both synaptic and extra-synaptic GABA (A) receptors. *Neuropharmacology*. 2012; 62 (8): 2507-14.
17. Squires RF, Ai J, Witt MR et al. Honokiol and magnolol increase the number of [3H] muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites. *Neurochem Res*. 1999; 24 (12): 1593-602.
18. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the central nervous system to damage. *Annu Rev Neurosci*. 2009; 32: 1-32.
19. Woolf CJ, Slter MW. Neuronal Plasticity: Increasing the Gain in Pain. *Science*. 2000; 288 (5472): 1765-8.
20. Kawasaki Y, Zhang L, Cheng JK et al. Cytokine mechanisms of central sensitization: Distinct and overlapping role of interlukin-1, interlukin-6 and tumor necrosis factor-α in regulating synaptic and neuronal activity in the superficial spinal cord. *Journal of Neuroscience*. 2008; 28 (20): 5189-94.
21. Rogawski MA, Loscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nature Medicine*. 2004; 10 (7): 685-92.
22. Jun-Jun W, Xiao-Lei M, Jing-Ya C et al. The Pharmacokinetics and Tissue Distribution of Honokiol and its Metabolites in Rats. *Eur J Drug Metab Pharmacokinet*. 2016; 41 (5): 587-94.
23. Liu Y, Wang D, Yang G et al. Comparative pharmacokinetics and brain distribution of magnolol and honokiol after administration of Magnolia officinalis cortex extract and its comparability with other herbal medicines in Zhi-Zi-Hou-Po Decoction to rats. *Biomed Chromatogr*. 2016; 30 (3): 369-75.
24. Wang X, Duan X, Yang G et al. Honokiol crosses BBB and BCSFB and inhibits brain tumor growth in rat 9L intracerebral gliosarcoma model and human U251 xenograft glioma model. *PLos One*. 2011; 6 (4): e18490.
25. Lin YR, Chen HH, Lin YC et al. Antinociceptive actions of honokiol and magnolol on glutamatergic and inflammatory pain. *J Biomed Sci*. 2009; 16: 94.
26. Brotini S, Schievano C, Guidi L. Ultra-micronized Palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease. *CNS Neurol Discord Drug Targets*. 2017.