EDITORIAL VIEW

# Glia as a new target for neuropathic pain, clinical proof of concept for palmitoylethanolamide, a glia-modulator

Jan M. Keppel Hesselink, MD, MS, PhD*

**Professor of Molecular Pharmacology, Department of Pharmacology and Toxicology, University of Witten Herdecke, Witten (Germany) and Institute of Neuropathic Pain, Bosch en Duin, (The Netherlands).*

**Correspondence:** Prof. Jan M. Keppel Hesselink, Department of Pharmacology and Toxicology, University of Witten Herdecke, Witten, Germany and Institute of Neuropathic Pain, Bosch en Duin, The Netherlands; e-mail: jan@neuropathie.nu

Glia cells play a much more important role in neuropathic pain, and probably in all kinds of chronic pain, as in general is perceived by the clinician. Glia seems to be so important that some scientists even prefer to speak about gliopathic pain as a synonym for neuropathic pain.[1]

Although many new clinical trials in painful neuropathy have been published since we entered the new millennium, sadly enough no new compounds entered the market with superior characteristics. Actually, it is a bit provocative, but since we started using amitriptyline for neuropathic pain half a century ago, no better drugs have been developed. Therefore, especially in this indication, we need to be open minded and think out of the box. It is time we need to start thinking about glia-modulators!

By combining analgesics with different mechanisms of action, including novel glia-modulators, we may achieve additive or even synergistic pain relief.

Such a multimodal pain relief schedule, may also permit use of reduced doses of each analgesic resulting in a decreased risk of adverse events while providing comparable or better analgesia than the individual components. Recent trials started to address the issue of the increased efficacy if one combines drugs from different classes. It is now a well-established fact that these combinations may lead to synergies, enabling the physician to treat patients more effectively with different drugs, and improve efficacy while reducing side effect, as individual drugs can be administered in lower dosages. In our hands we often see improvement of analgesia and reduction of side effects by adding the novel glia modulator palmitoylethanolamide (Normast) to the treatment schedule, and this has been seen in other clinics too.[2,3]

Microglia proliferation and activation occurs under several neuropathic pain conditions, for instance after spinal cord trauma and sciatic nerve compression. The activation results in clear changes in morphological phenotype of these cells. Activation of microglia result in increased production of inflammatory- and pain mediators. Several compounds targeting this microglia activation have been successfully tested in animal models of chronic pain. For instance minocycline, a non-selective microglia inhibitor attenuates neuropathic pain in the early phase of wind-up.[4]

Low-grade inflammation can also be seen in the dorsal horns of spinal cord and along the pain pathways to the thalamus and further even up to the parietal cortex after a peripheral nerve injuries.[5] We should actually understand that during the period in which an injury transforms into a chronic pain state, a wave of glia-activation and neuroinflammation from the peripheral parts of our body ascends to our brain.

Now, it is quite interesting to note that glia produce their own modulators we could even say, their own endogenous 'painkillers' and anti-inflammatory agents.[6] These modulators play an important role in decreasing winding up mechanisms in neuropathic pain. Anandamide and its sister molecule PEA are such modulators, and these molecules play an important role in 'winding down' chronic and neuropathic pain and neuroin?ammation. Both molecules are classical autacoids, and they fulfil the three criteria required for autacoids of lipid transmitters:

1. stimulus-dependent local production,
2. interaction with speci?c receptors and
3. enzymatic inactivation.

## Palmitoylethanolamide, a glia modulator with analgesic and anti-inflammatory characteristics

Palmitoylethanolamide ('PEA') is a body-own compound

and is since some years in Europe available for the treatment of chronic pain and chronic inflammation. Most clinical data have been gathered and published around its efficacy in neuropathic pain such as in post herpetic states, diabetes, carpal tunnel syndrome and sciatic compression. To date more then 30 clinical trials have been reported, many of these reports however, have been published in Italian medical journals and we will disclose here some of these impressive results.

PEA is an endogenous fatty acid amide and, and the last two decades the number of scientific papers on PEA's biological and clinical activity has soared to nearly 300. PEA binds to a receptor in the cell-nucleus (a nuclear receptor, PPAR) and influences a great variety of biological functions related to chronic pain and inflammation.[7] PEA therefore forms a new mechanism of action in the world of analgesics and its efficacy has been validated in a number of preclinical as well as clinical studies. PEA can therefore be seen as proof of principle (POP) as well as proof of concept (POC) for the fact that glia-modulation forms a new inroad for the treatment of chronic pain.

PEA has been shown to have anti-inflammatory, anti-nociceptive, neuroprotective, and anticonvulsant properties in a variety of animal models.[8,9] Its anti-inflammatory and analgesic properties can also be detected in animal models of central neuropathic pain, the King Charles model of syringomyelia.

In the Netherlands we conducted an open pilot trial and included 12 Cavalier kings Charles spaniels, all with MRI-scan positive syringomyelia and all suffering from behavioural abnormalities and objective signs related to syringomyelia and neuropathic pain.[10] Syringomyelia in dogs is also known as "neck scratcher's disease", because one of its common signs is scratching in the air near the neck. All dogs showed symptoms like these as well as other known behavioural abnormalities, such as scratching behaviour and scoliosis or lordosis, yelping, sitting with eyes closed, immobility, walking as on eggs, difficulty swallowing, tongue out of mouth, as well as symptoms of Primary Secretory Otitis Media (PSOM) and signs of conjunctivitis (excessive lacrimation). After 2 months of PEA use in these dogs, the results were the following. Of all the 12 dogs, based on the overall general impression, the owners could clearly detect relevant improvements within one week. This was not only based on the pain behaviour, but also on the inflammatory signs of the PSOM as well as the conjunctivitis, which vanished.[10]

We evaluated all clinical trials reported on the efficacy and safety of PEA in various pain states. One of the pivotal trials has been reported in 2010.[11] This was a three week placebo-controlled, double blind, randomised study in 636 patients suffering from sciatic pain (hernia), mean VAS 6.5-7 at study entry. There were three arms: placebo, PEA 300 mg/day, and PEA 600 mg/day. At endpoint pain decreased from a mean VAS 6.5 to 4.5 for placebo, VAS 6.5 to 3. 5 for PEA 300 mg and VAS 7.1 to 2.1 in the PEA 600 mg arm. 300 mg was significantly better compared to placebo, and 600 mg was significantly better compared to 300 mg as well as placebo. No relevant side effects were detected, nor any dropouts due to adverse events. The same significant improvement was seen in a functional back scale.

Canteri published a placebo-controlled, double blind, randomised study in patients suffering from sciatic pain (hernia), mean VAS 9 at study entry, in 111 patients.[12] Patients were treated either with placebo, PEA 300 mg/day, or PEA 600 mg/day. In each group half of all patients were further allowed to be treated with NSAIDS, while other half was treated with study medication only. Pain decreased from mean VAS 9 to 6 for placebo (both for NSAID users and NSAID virgins), VAS 9 to 3. 5 for 300 mg (both with/without NSAIDs) and VAS 9 to1.5 for 600 mg (for both groups with/without NSAIDs). Decrease of pain in both PEA arms compared to placebo was significant. Patients treated with PEA 600mg/day clearly responded best, with or without concomitant analgesia. There were neither relevant side effects nor drug interactions. We summarised all clinical trial data on the website of the Coalition for Chronic Pain.[13]

Glia-modulation might also play a role in other analgesics. For instance, even ketamine might have a mode of action related to inhibition of glia hyperactivity. The acute analgesic effects of ketamine are generally believed to be mediated by the inhibition of NMDA receptors in nociceptive neurons. However, parts of the analgesic effect of ketamine might now be understandable via its effects on spinal microglia. Ketamine in an animal model suppressed the nerve injury-induced development of tactile allodynia as well as the hyper activation of spinal microglia via the blockade of BK channels on this glia.[14]

Glia modulation seems an important new tool for treating our patients suffering from chronic and neuropathic pain. Proof of concept has been generated in a number of clinical trials in various pain states with the compound palmitoylethanolamide, which is available in Europe as a food for medical purposes.

## REFERENCES


1. Ohara PT, Vit JP, Bhargava A, Romero M, Sundberg C, Charles AC, Jasmin L.Gliopathic pain: when satellite glial cells go bad. Neuroscientist 2009;15(5):450-63
2. Desio,P et al. Efficacy of palmitoylethanolamide and oxycodon in patients with low back pain. Anesthesia and medicina critica (AMC) 2011;2:62-71
3. Desio P, Pregabalin and Palmitoylethanolamide in the treatment of neuropathic pain. Pathos 2010;l17:9-14
4. Echeverry S, Shi XQ, Zhang J. Characterization of cell proliferation in rat spinal cord following peripheral nerve injury and the relationship with neuropathic pain. Pain 2008;135:3747
5. Saadé NE, Jabbur SJ. Nociceptive behavior in animal models for peripheral neuropathy: spinal and supraspinal mechanisms. Prog Neurobiol. 2008 Sep;86(1):22-47. Epub 2008 Jun 18
6. Muccioli GG, Stella N. Microglia produce and hydrolyze palmitoylethanolamide. *Neuropharmacology* 2008;54(1):16-22.
7. Costa B, Comelli F, Bettoni I, Colleoni M, Giagnoni G. The endogenous fatty acid amide, palmitoylethanolamide, has anti-allodynic and anti-hyperalgesic effects in a murine model of neuropathic pain: involvement of CB(1), TRPV1 and PPARgamma receptors and neurotrophic factors. *Pain* 2008;139(3):541-50.
8. De Filippis D, Luongo L, Cipriano M, Palazzo E, Cinelli MP, de Novellis V, Maione S, Iuvone T. Palmitoylethanolamide reduces granuloma-induced hyperalgesia by modulation of mast cell activation in rats. *Mol Pain* 2011;7:3.
9. Scuderi C, Esposito G, Blasio A, Valenza M, Arietti P, Steardo L Jr, Carnuccio R, De Filippis D, Petrosino S, Iuvone T, Di Marzo V, Steardo L. Palmitoylethanolamide counteracts reactive astrogliosis induced by beta-amyloid peptide. *J Cell Mol Med.* 2011 Jan 21. doi: 10.1111/j.1582-4934.2011.01267.x.
10. Keppel Hesselink, JM Syringomyelia in Cavalier spaniels treated succesfully with palmitoylethanolamide (Normast). http://www.neuropathie.nu/research-development/syringomyelia-in-cavalier-spaniels-treated-succesfully-with-no.html
11. Guida, G, de Fabiani, A F. Lanaia, A. Alexandre, G.M. Vassallo, L. Cantieri, M. de Martino, M. Rogai, S. Petrosino La palmitoiletanolamida (Normast) en el dolor neuropatico cronico por lumbociatalgia de tipo compresivo: estudio clinico multicentrico. Dolor 2010;25:35-42.
12. Canteri L et al. Reduction of analgesics in patients suffering from lumbosciatic pain, treated with palmitoylethanolamide. Dolor 2010;25:227-234.
13. Keppel Hesselink JM. 2011 Overview all clinical trials with palmitoylethanolamide. http://www.chronicpaincoalition.com/1/24/502/normast-clinical-trial-overview. Accessed on
14. Hayashi Y, Kawaji K, Sun L, Zhang X, Koyano K, Yokoyama T, Kohsaka S, Inoue K, Nakanishi H. Microglial Ca2+-Activated K+ Channels Are Possible Molecular Targets for the Analgesic Effects of S-Ketamine on Neuropathic Pain. J Neurosci. 2011;31(48):17370-17382.