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Palmitoylethanolamide and other Lipid Autacoids in the Treatment of Chronic Pain: A New Chapter in Pain Medicine

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Introduction

We gathered clinical experience since 2010 using an oral formulation of an endogenous lipid messenger, an autacoid, in a great many neuropathic pain disorders [1]. This compound palmitoylethanolamide (PEA), is the prototype of lipid autacoids, able to counteract chronic inflammation and chronic pain. PEA is available since 2005 as a supplement (nutraceutical) [2] (Figure 1). Currently there only two high quality and patent-based formulations clinically tested and available (without prescription needed), one product is developed in Italy (Normast, 300 and 600 mg tablets), and one in the Netherlands (PeaPure, 400 mg capsules). In our Dutch Institute for Neuropathic Pain we have worked with both formulations in patients suffering from a number of chronic pain disorders, mainly in neuropathic pain, and documented our findings in various case-report series [3,4]. Since 2 decades new lipid autacoids have been discovered. This will change the landscape of the treatment of chronic pain, especially since these classes are devoid of the troublesome side effects we know from classical analgesics.

Inhibition of Neuroinflammation by 'following where Nature Leads'

Chronic pain and chronic (neuro-)inflammation go hand in hand. Inhibiting chronic inflammation often has a positive impact on pain symptoms in chronic pain. However, there are only corticosteroids and NSAID's (non-steroidal anti-inflammatory drugs) available for the clinician to inhibit chronic inflammation and both classes are fraud with side effect problems.

Lipid autacoids are endogenous molecules, fit for various oral and parenteral formulations to treat chronic pain and inflammation via influencing natural existing biochemical pathways in our body. While PEA is already available and has been clinically tested as tablet, capsule, suspension and cream, other lipid autacoids are more difficult to administer orally and are in need for more research and development work at the moment.

It was already in 1986 that the eminent neuroscientist professor Erminio Costa (1924 - 2009) delivered a keynote lecture in Washington: 'To follow where nature leads'. Costa pointed out how nature itself can become our tutor in developing new therapeutic inroads, in so far as we can trigger and activate endogenous repair and defense mechanisms of the body by administrating the endogenous molecules related to these pathways [5]. The modern lipid autacoids, such as the lipoxins, resolvins, the protectins, the maresins as well as the N-acyl-ethanolamides to which PEA belongs, are classes of compounds activating nature in its action, and their mechanism of actions has been perfected during many millions of years evolution in animals and plants [6].

The first molecule entering the clinic from this group of lipid autacoids and which was developed according to Costa's vision was PEA [7]. It was the famous Nobel laureate professor Rita Levi-Montalcini (1909-2012) who identified the anti-neuroinflammatory activity of PEA [8,9]. Levi-Montalcini and her group demonstrated

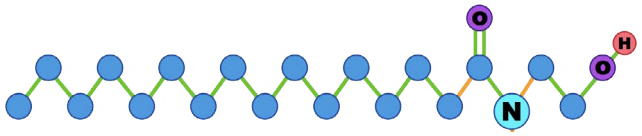

Figure 1: Molecular structure of palmitoylethanolamide, first determined in 1957.

that lipid amides of the N-acyl-ethanolamine type (such as PEA) are naturally occurring molecules capable of modulating immune cells such as the mast cells [10]. In 2002 this concept of local anti-inflammatory autacoids was 'rediscovered' for a different class of lipid-autacoids called the resolvins [11]. Up to the beginning of this century it was general thought that inflammatory processes are slowly phasing out, once the inflammatory trigger is vanished. The work on the modulatory effects of PEA on overactive mast cells created the base of a new paradigm in inflammation biology and pain medicine. The leading idea of Levi-Montalcini was that tissue accumulation of N-acyl-ethanolamines is a biological significant response during pathological degenerative conditions in order to control such inflammation. Since this millennium we know that PEA indeed acts as a negative feedback molecule preventing escalation of neuro-inflammation via its activation of the nuclear receptor PPAR-α [12,13].

Lipid Autacoids of Aliamides: Brakes on Pathological Inflammation

Autacoids are a locally produced modulating factors, influencing locally the function of cells and/or tissues, which are produced on demand and which subsequently are metabolized in the same cells and/or tissues [14]. There are different classes of lipid autacoids: the N-acyl-ethanolamides (NAEs), lipoxins (Lxs) protectins (Pts), resolvins (Rvs) and maresins(Mss) currently seem the most important. The key function of these molecules is to inhibit overactive and activated immune cascades and thus act like a 'stop' signal in inflammation processes otherwise becoming pathological, a break. Such autacoids are referred as '*nature's way to resolve inflammation*', clearly supporting the concept of 'to follow where nature leads' Costa introduced in 1986 [15].

N-acyl-ethanolamides are derived from membrane phospholipids, N-acylphosphatidylethanolamine (NAPE) [16]. PEA is one such

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N-acylethanolamide. Resolvins are metabolites of the polyunsaturated omega-3 fatty acids: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). The metabolites of EPA are termed E resolvins (RvEs), those of DHA are termed D resolvins (RvDs), and those of DPA are termed resolvins D (RvDsn-3DPA) and resolvins T (RvTs) [1]. Protectins (Pts) and Maresins (Mss) are also derived from omega-3 fatty acid docosahexaenoic acid (DHA). Lipoxins are synthesized from arachidonic acid [17].

It is now generally known that cells convert ω-3 polyunsaturated fatty acids into highly potent, short-lived, anti-inflammatory autacoids that control the duration and magnitude of inflammation [18]. Some companies are developing new formulations of ω-3 fatty acids in order to locally boost the synthesis of for instance the resolvins. Another possibility is to adapt diet in such a way that its lipid profile enhances lipid autacoid synthesis.

Importantly, most of the lipid autacoids are effective in the nanomolar range, and for many the upstream targets have been identified [19]. In a number of models for central neuro-inflammation lipid autacoids proved to have a clear anti-inflammatory effect. This also holds true for the precursors, such as docosahexaenoic acid (DHA). DHA treatment in an inflammation paradigm, could reduce the inflammation induced activation of microglia, phosphorylation of p38 mitogen-activated protein kinase (MAPK), and reduce the production of proinflammatory cytokines, such as TNF-α and interleukin-1β - IL-1β) [20].

Conclusion

In many chronic pain states there is a disturbed balance between over activated inflammatory factors and inflammation resolving and inhibiting factors. Recently more insight is gained into the natural inhibitors for these overactive inflammation processes. The body can synthesize a series of lipid inflammation-resolving and inhibiting endogenous factors. In line with the vision of professors Costa and Rita Levi-Montalcini more attention has been given recently to these natural corrective mechanisms based on autacoids. These are endogenous molecules, produced on demand, and acting directly in tissue was they were produced. There are a number of relevant families of these autacoids: the N-acylethanolamides to which PEA belongs, the lipoxins, resolvins, protectins and maresins. Relevant (high) dosages of polyunsaturated ω-3 precursors are supposed to stimulate enhanced synthesis of some of these autacoids. Low dose aspirin seems to boost its synthesis. The N-acyl-ethanolamides are formed from membrane phospholipids. PEA is a prototype and available as a food supplement. PEA can be dosed easily and up to 2400 mg/day (for instance 3 times 2 capsules), and troublesome side effects nor drug-drug interactions are unknown, while the compound has been evaluated in a number of RCTs, in a population over 5000 patients [1].

Lipid autacoids might become an important new inroad in treating chronic pain. Boosting endogenous lipid autacoid synthesis with high dose and high quality ω-3 formulations seems possible and logical. New formulations of these molecules are underway.

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