

Autacoids: A New Fundament for Pain Medicine of the 21th Century

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Abstract

Autacoids are endogenous signaling molecules, synthesized and released locally, influencing local biological processes and metabolized locally. Since 1990 new insights in the biology of pain emerged related to the special roles these autacoids can play. Especially the signaling lipids amongst the autacoids have been found to play crucial roles in chronic inflammation and pain and possibly in a variety of other disorders, such as asthma, rheumatic disorders, glaucoma, neurotrauma, and neurodegenerative disorders.

Since 2010 we gathered much experience with the autacoid palmitoylethanolamide in many thousands of patients suffering from chronic pain. The compound is available as a food supplement, and has been explored in many clinical trials in more than 5000 patients. Palmitoylethanolamide is reported to have a favorable side effect profile, a well documented efficacy in neuropathic pain, and its ease of administration and absence of drug-drug interactions support its use as part of any multi-modal therapy for chronic pain. We will discuss the emergence of autacoid pain medicine and present two cases from our clinic to illustrate the putative role of autacoid therapy in pain medicine.

Keywords: *Autacoids; Palmitoylethanolamide; Pain; Neuropathic pain; Analgesia*

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Introduction

It is clear that current treatments of chronic pain still have many shortcomings. Tolerability and side effects often limit its use over an extended period of time, and the efficacy of many drugs need to be much improved. Even the effects of often prescribed drugs such as pregabalin or opioids are disappointing for patients suffering from neuropathic pain. Furthermore, some classes of analgesics might decrease pain, but can also negatively interfere with our body repair systems, such as the non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase (COX) inhibitors. While it is widely known these last compounds inhibit pro-inflammatory cascades in many chronic pain states, much less it is known that the same inhibition impairs the biological activity of endogenous repairing and protecting molecules such as the lipoxins and the resolvins [1]. Towards the end of the 20th century many explorations to find new targets in the treatment of chronic pain focused on inhibiting 'pro-inflammatory' processes to dampen pathological inflammation, as present in many states of chronic pain [2,3]. During the latter part of last century a new concept appeared: 'active resolution' of inflammation. Inflammation was recognized as a biological process that not slowly dampens out, but inflammation is an active process orchestrated and modulated by a number of endogenous molecular components, the autacoids. These autacoids have 'pro-resolving' properties. NSAIDs inhibit the synthesis of many autacoids and thus do not contribute to resolving chronic inflammation and repair injury. NSAIDs thus inhibit the synthesis

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of the 'good guys and the bad guys'. It is not only the NSAIDs negatively influencing inflammatory resolution, opioids are also increasingly recognized as pro-inflammatory compounds and opioid-induced glial activation and its proinflammatory consequences is regarded as a factor for failure of analgesia as well as a pathogenetic base for the emergence of opioid tolerance [4,5]. In all these cases analgesics negatively interfere with endogenous autacoid repair and anti-inflammatory processes [6]. To find new inroads in the treatment of chronic pain via the autacoids therefore seems a promising way of identifying new analgesic compounds, acting via endogenous healing mechanisms. It seems indeed quite logical to make use of endogenous repair and homeostasis mechanisms, already available in the body. It was the famous professor Erminia Costa who already pointed out in the 80s of last century that we need 'to follow where nature leads', while designing new therapies. Autacoid Pain Medicine follows this principle and might therefore become one of the new fundaments for the design of the 21st century pain medicine.

Autacoids: endogenous produced factors inhibiting inflammation and reducing pain

Let us start giving a formal definition: 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. There are a number of classes of lipid autacoids: the N-acyl-ethanolamides (NAEs), lipoxins (Lxs) protectins (Pts), resolvins (Rvs) and maresins (Mss) [7]. The key function of autacoids belonging to these classes is to inhibit hyper-activated immune cascades and thus act like a 'stop' signal in inflammation processes otherwise becoming pathological. In 1993, the Nobel laureate Rita Levi-Montalcini (1909-2012) was working on the inhibiting and modulating role of palmitoylethanolamide in overactive mast cells. Based on her findings, she developed the concept of 'aliamides' derived from the acronym ALIA: Autacoid Local Inflammation Antagonist [8,9]. The term was subsequently used only in the field of N-acetyethanolamides autacoids such as palmitoylethanolamide (PEA) [10]. Although 'aliamide' was defined by Levi-Montalcini as a container concept for all lipid inhibiting and modulating mediators the term did not further gain wide acceptance [11]. Other lipid messengers, such as the lipoxins, resolvins, protectins and marisins also belong to the class of aliamides. All these unsaturated lipids are derived from the polyunsaturated omega-3 fatty acids: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA).

The last 6 years we gathered much experience in our clinic advising patients to use the anti-inflammatory autacoid palmitoylethanolamide (PEA), we reviewed all clinical data, and published a number of review articles and case collections [12,13].

Autacoid palmitoylethanolamide formulations and experience

Currently there only two high quality patent-based and GMP produced formulations developed and available as supplements (without prescription needed). One product is developed and produced in Italy (Normast, 300 and 600 mg tablets), and one in the Netherlands (PeaPure, 400 mg, excipient free capsules). It is important to note that since few years some uncontrolled me-too PEA formulations have been aggressively marketed based on empty claims and sadly enough without any clinical data to support the efficacy and safety. In our Dutch clinical for neuropathic pain since 2010 we have worked only with GMP produced and patent-based PEA products in many thousands of patients suffering from a number of neuro-inflammatory disorders, mainly neuropathic pain. We will describe 2 cases which illustrate the possibilities of autacoid therapy in pain medicine. The first patient was suffering from chronic idiopathic axonal neuropathy, and was treated with 400 mg PEA capsules (PeaPure, JP Russell Science). The second patient suffered from diabetes type 2, and was treated with a new combination capsule consisting of 400 mg PEA combined with a range of low dose vitamins from the B complex family PeaPlex, JP Russell Science (SKIP global).

Cases illustrating the approach of Autacoid Pain Medicine

A 63-year-old Caucasian female (born in 1948) visited our clinic in 2011. She suffered from neuropathic pain symptoms since many years based on a severe sensory and motor axonal neuropathy, diagnosed via EMG by a neurologist. She complained about numbness and tingling combined with severe burning pain in both feet (anesthesia dolorosa), suffered from instability, with a positive sign of Romberg, and there were signs of a moderate pareses of feet and toe extensors (Medical Research Council grade 4). We started treating with 1200 mg PEA daily, and pain decreased from 7 on the NRS score to a mean score of 3. Side effects were not reported. The reduction of pain of more than 50% remained for more than a year, after which we lost patient for follow-up.

A 51-year-old Caucasian female (born in 1964) visited our clinic in 2016, suffering from neuropathic pain symptoms since some years due to diabetes mellitus type 2, treated with metformin 500 mg three times daily. He complained about numbness, tingling, burning pain in both feet and suffered from severe insomnia due to allodynia induced by the contact with bed sheets. We started treating with 1200 mg PEA daily, and pain decreased from 8 on the NRS score to a mean score of 5 within a few weeks after start therapy. The effect seemed to level off and we changed PEA into the combination of PEA and low doses vitamins B, especially since it is known that metformine can impair the cobalamin status [14,15]. Many patients with DM are using multivitamins for compensating such impairment select high doses of vitamin B6 (pyridoxine), which in itself can impair nerve function and induce neuropathic pain, while low doses are in general recommended for neuropathy [16]. This helped to decreased the pain below NRS score 4 and patient reported for the first time since years undisturbed sleep. Side effects were not reported. During the last consultation patient made the remark that it was 1000 times better than before; he continued taking the PEA-B-complex supplement.

These are two illustrative cases of the many neuropathic pain patients we have treated in our clinic suffering from neuropathic pain, either with oral palmitoylethanolamide, or with various topical creams containing analgesics, such as ketamine 10%, amitriptyline 10%, baclofen 5% and palmitoylethanolamide 1%. Our experiences with these topical analgesia we have described elsewhere [17-19].

Autacoids: promising new compounds for pain medicine

Autacoids seem promising new therapeutic inroads for the treatment of chronic inflammatory disorders as well as chronic (neuropathic) pain [20,21]. Oral, as well as topical formulations of natural autacoids such as palmitoylethanolamide, and its derivatives and prodrugs, offer options for the treatment of chronic pain, including nerve compression syndromes [22]. For topical administration, one needs to take into account the penetration degree of the active compound in the various compartments of the skin. Most probably many autacoids will have good tolerability, given the fact that these molecules are endogenous compounds. We have gathered much and positive experience with the autacoid palmitoylethanolamide, both as oral formulation, as well as components in a topical analgesic formulation. Palmitoylethanolamide belongs to the class of N-acyl-ethanolamides, and other promising classes of lipid autacoids for pain medicine will in future be developed from the families of the resolvins, lipoxins, maresins and protectins. The fact that since few years the literature on these lipid signaling compounds is expanding vast, will help to quicker integrate the idea and the results of autacoid pain medicine into mainstream medicine.

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