

Evolution in pharmacologic thinking around the natural analgesic palmitoylethanolamide: from nonspecific resistance to PPAR- α agonist and effective nutraceutical

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Abstract: The history of development of new concepts in pharmacology is a highly interesting topic. This review discusses scientific insights related to palmitoylethanolamide (PEA) and its progression over a period of six decades, especially in light of the work of the science sociologists, Ludwig Fleck and Thomas Kuhn. The discovery of the cannabis receptors and the nuclear peroxisome proliferator-activated receptors was the beginning of a completely new understanding of many important homeostatic physiologic mechanisms in the human body. These discoveries were necessary for us to understand the analgesic and anti-inflammatory activity of PEA, a body-own fatty amide. PEA is a nutrient known already for more than 50 years. PEA is synthesized and metabolized in animal cells via a number of enzymes and has a multitude of physiologic functions related to metabolic homeostasis. PEA was identified in the 1950s as a therapeutic principle with potent anti-inflammatory properties. Since 1975, its analgesic properties have been noted and explored in a variety of chronic pain states. Since 2008, PEA has been available as a nutraceutical under the brand names Normast® and PeaPure®. A literature search on PEA meanwhile has yielded over 350 papers, all referenced in PubMed, describing the physiologic properties of this endogenous modulator and its pharmacologic and therapeutic profile. This review describes the emergence of concepts related to the pharmacologic profile of PEA, with an emphasis on the search into its mechanism of action and the impact of failing to identify such mechanism in the period 1957–1993, on the acceptance of PEA as an anti-inflammatory and analgesic compound.

Keywords: palmitoylethanolamide, sociology, science, paradigm, peroxisome proliferator-activated receptor-alpha, nutraceutical

PEA and the sociology of science

The history of palmitoylethanolamide (PEA) started in 1954 with a publication addressing the anti-inflammatory properties of egg yolk.¹ The finding that egg yolk appeared to be some sort of “protomedical diet food” and the fact that extracts from egg yolk and peanut oil had anti-inflammatory activity were discussed in that paper. That anti-inflammatory compound would later be known as PEA.

The history of the development of insights into the biological role of PEA after its identification in 1957 is worth telling because it demonstrates the close inter-relationship between the scientific context and the development of scientific facts. The importance of such studies has already been pointed out by the science sociologists, Ludwig Fleck and Thomas Kuhn. This analysis serves to add a new chapter to the sociology of medical and scientific knowledge. The paper demonstrates that



plausible explanations for the mechanism of action of drugs are required before a treatment concept can be explored in more detail in science and in the clinic, and before it can be accepted. Efficacy of a compound alone will not be enough to convince the scientific community. The case of PEA supports the validity of this scientific sociologic observation. Starting with the work of Rita Levi-Montalcini, a Nobel laureate, in the 1990s, more attention is being paid by the scientific community to the clinical relevance and usefulness of PEA in chronic pain and chronic inflammation.

Step by step emergence of insight

When studying the published papers relevant to PEA one can define four different periods leading to a step by step increase in insight into the pharmacology of this endogenous modulating fatty compound. These four periods are:

- 1954–1979, when PEA was found to be a nonspecific immunologic resistance enhancer, with anti-inflammatory properties and anti-influenza and anti-common cold indications
- 1980–1992, “a silent gap”, with unanswered questions related to the mechanism of action of PEA
- 1992–1998, due to the work of Levi-Montalcini, PEA was recognized as a mast cell modulator, and then (wrongly as it appeared later) as a CB2 cannabinoid agonist
- 1998 onwards, when PEA was identified as having high affinity for peroxisome proliferator-activated receptor alpha (PPAR- α), transient receptor potential vanilloid type 1, and the GRP 55 receptor.

First insights

The birth date of PEA can be identified as October 20, 1957, when Kuehl et al published a seminal paper clarifying its structure.² In that paper, they reported having isolated an anti-inflammatory factor in crystalline form from soybean lecithin as well as from a phospholipid fraction of egg yolk and hexane-extracted peanut meal. That product was tested using a local passive joint anaphylaxis assay in the guinea pig and identified as N-palmitoylethanolamine, ie, N-(2-hydroxyethyl)-palmitamide. They also synthesized the compound as well as various analogs, and attributed the anti-inflammatory activity to the ethanolamine moiety of the series of molecules they had synthesized.

This was the first description of PEA and its biological activity as an anti-inflammatory agent. Identification was clear after hydrolysis of the compound yielded palmitic acid and ethanolamine. Further, PEA could be synthesized by refluxing ethanolamide with palmitic acid. Kuehl et al pointed

out that PEA was a natural compound, and demonstrated that PEA could be identified in a variety of food products, such as soybean lecithin, egg yolk, and peanut meal.

A few years earlier, in 1954, the first scientific report of the anti-inflammatory activity of egg yolk, later attributed to PEA, was published by Coburn et al¹ who found the first food-related therapeutic effects, ie, that egg yolk and the alcohol-soluble fraction of egg-yolk could protect guinea pigs from anaphylactic arthritis.

Following the findings of Coburn et al in 1954, Long et al reported the results of testing of a specific antirheumatic compound in 1956.³ They showed that it slightly but significantly depressed the sensitivity of Bacillus Calmette-Guérin to tuberculin in infected guinea pigs. They found that the antiallergic activity was in the arachis oil in which the drug was suspended and not in the antirheumatic compound itself. They also showed that egg oil possessed antiallergic activity in a specific model. Further, they reported that the active substance appeared, in its chemical and biological properties, to be similar, if not identical, to the substance in arachis oil. In their opinion, it thus seemed probable that the antianaphylactic substance described by Coburn et al in 1954 was similar to or the same as the substance in arachis oil. Both egg oil and arachis oil were later on identified as important food sources of PEA.

In former Czechoslovakia, much clinical research was done in the 1960s and 1970s on PEA, formulated as tablets under the brand name Impulsin® (SPOFA United Pharmaceutical Works, Prague, Czechoslovakia). Its immunosupportive effects in influenza, respiratory disorders, and rheumatic fever were described in a number of papers.

Interesting preclinical findings fueled this first clinical chapter related to the anti-inflammatory properties of PEA. In 1967 and 1972, it was found that oral administration of PEA to mice decreased mortality caused by *Shigella dysenteriae* toxin, streptolysin O, and live group A streptococcus, as well as mortality resulting from traumatic shock.^{4,5} In 1958, Ganley et al confirmed that N-(2-hydroxyethyl)-palmitamide could decrease the intensity of several inflammatory and immunologic processes in experimental animal models.⁶ Step by step, the anti-inflammatory and analgesic properties of PEA became clear and were evaluated in various animal models.^{7–10}

In 1971, Perlík et al found that PEA had a definite prophylactic and therapeutic effect on the tuberculin reaction and on the secondary lesions of adjuvant arthritis, showing high potency and specificity for the inflammatory process in arthritis.⁶ They wrote: “If PEA does not act on the inflammatory process *per se*, its effect may be exerted on the delayed hypersensitivity

and/or on the subsequent processes which introduce the arthritic process.”¹¹ In 1973, the effects of PEA as an immunomodulator were described further by Perlik et al. In this publication, they commented on the absence of an understanding of the mechanism of action of PEA.¹² However, it would take more than two decades before science would understand how these fatty acids exert their powerful biological effects.

Natural occurring molecule with cytoprotective properties

In the period 1970–1990, one further specific property of PEA was described, but because of the absence of insight into its mechanism of action, was not taken up in the clinic. This was related to the protective properties of PEA in cells, neurons, and tissues. The prelude to this occurred in 1965 when Bachur et al analyzed various tissues for the presence of fatty acids and concluded that: “Palmitoylethanolamide was found in several tissues of the rat and guinea pig. The amounts found in liver were quite variable, but the ethanolamide was consistently found in brain, liver, and muscle.”¹³ However, at that time, the role of PEA remained enigmatic, and it was not until some years later that the first hints were published related to the protective properties of PEA.

In 1973, Obermajerova et al demonstrated that treatment with PEA produced characteristic changes in membrane lipids, with a marked increase in resistance of the membranes to various types of damage,¹⁴ leading Rakovfi et al to relate the efficacy of PEA to its detoxifying properties when investigating its protective properties in 1972.¹⁵ In 1975, the first supportive effects of PEA as a modulator of toxicity were reported in cancer.¹⁶ These authors reported that: “Repeated administration of PEA prolonged substantially survival of leukemic animals in the course of the treatment with cis-diamminedichloroplatinum(II) [cis-Pt(II)] in combination with cyclophosphamide, vincristine, and methotrexate respectively. The most advantageous combination used was the cis-Pt(II) with methotrexate and PEA administration even improved the treatment results. Long-term PEA treatment depressed first of all undesirable side effects and enabled use of a higher therapeutic dosage of chemotherapeutics and improved the final results.” In 2012, Truini et al demonstrated the supportive effects of PEA in neuropathic pain and nerve damage after chemotherapy, consistent with these early findings.¹⁷

In 1979, based on the early work of Kuehl et al² and Ganley et al,⁶ Epps et al, from the University of Minnesota, reported accumulation of N-acylethanolamines like PEA in infarcted myocardium, indicating that these findings might be of physiologic importance because of the reported pharmacologic

activities of these molecules, especially their anti-inflammatory activity.¹⁸ The amount of N-acylethanolamine, of which the C18 part was around 50%, was estimated to be 150 µg/g of wet tissue. It was Epps et al who first suggested that these fatty molecules had a protective role. In their discussion, Epps et al commented on the absence of insight into the catabolism and pharmacology of N-acylethanolamine, and put forward the following hypothesis.

“Our findings establish for the first time the accumulation of N-acylethanolamine under pathologic conditions. This accumulation may be a side effect of the degenerative changes induced by ischemia or it may signify a response of myocardial tissue to injury directed at minimizing damage and promoting survival.”

In 1990, this hypothesis was echoed by Schmid et al, who proposed that the production of PEA and related lipids under ischemic conditions: “may represent a defense mechanism aimed at minimizing the areas of irreversible injury and the ultimate size of the infarct.”¹⁹

Since the paper published by Epps et al, there has been other research reporting increased levels of PEA in damaged tissues *in vivo*, and increased formation of PEA was seen as an adaptive response to toxic stimuli.²⁰ Meanwhile, recent pharmacologic studies have all shown that the hypothesis advanced by Epps et al in 1979 regarding the possible protective effects of PEA is correct. PEA protects a great variety of tissues, including nervous tissue in various lesion models related to spinal cord injury, stroke, and Alzheimer’s disease.^{21–26} The importance of this protective effect has also been documented for painful neuropathy induced by chemotherapy.¹⁷

PEA: an inducer of nonspecific resistance?

All the early work pointed out that PEA increased resistance against infections and had important anti-inflammatory activity. Schmidt et al¹⁹ highlighted that PEA was a potent inducer of nonspecific resistance to viral and bacterial infection. They discussed that oral administration of PEA to mice decreased mortality caused by injecting *Shigella dysenteriae* toxin, streptolysin 0, or living group A *Streptococcus*. Furthermore that pointed out that PEA could decrease mortality rate caused by traumatic shock in pretreated mice compared to the control groups. they then concluded that this specific property, inducing non-specific resistance, and we quote:

[...] led to several clinical trials were repeated daily intake of N-palmitoylethanolamine (Impulsin, 30 mg/kg) reduced the incidence and severity of respiratory tract infections and

also markedly diminished the number of episodes of fever, headache, and sore throat.

This brings us to the Impulsin story, an exciting chapter in the history of the pharmacology of PEA.

A nonspecific immune enhancer in respiratory tract infections

After commercialization of PEA in the early 1970s, six clinical studies of the effects of Impulsin in the treatment of respiratory tract infections were published.

In 1974, Masek et al published the results of two double-blind, controlled trials including 1,345 healthy subjects, of which 41 failed to complete the trial.²⁷ The goal of these trials was to evaluate the efficacy of PEA in upper respiratory tract infections. The subjects were to take 600 mg PEA three times daily or placebo for 12 days.

In the first trial, 468 employees of the Skoda car factory, all suffering from influenza-like symptoms, such as fever, headache, sore throat, myalgia, nasal discharge, productive or dry cough, malaise, and fatigue were randomized to receive PEA 600 mg or placebo three times daily for 2 weeks. The second trial, which was prophylactic, included 918 volunteers aged 16–18 years and living in an army unit. Treatment was identical to that in the first trial for the first 2 weeks, after which a continuation dose of PEA 600 mg or placebo was administered once daily in a double-blind fashion. In total, 901 soldiers completed the trial.

The results of the first trial showed that the PEA group had fewer episodes of fever, headache, and sore throat compared with the placebo group ($P < 0.05$). In the second trial, the beneficial and prophylactic effect of PEA was apparent from the second week. The incidence of illness in the PEA group was 40% lower in week 6 of the trial and 32% lower in week 8 ($P < 0.0005$).

In 1974, a third randomized study was performed with 610 soldiers and, in 1975, a fourth randomized trial was done with 353 soldiers. The results of these trials were reported together in 1979 by Kahlich et al, including a fifth trial, and the authors compared the incidence of clinical endpoints and the titers of influenza virus between the PEA and placebo arm.²⁸ Evaluation of the results according to morbidity, regardless of etiology, showed a significant reduction in acute respiratory disease after administration of PEA. For instance, in one of these trials, in which 901 volunteers were included, 22.7% of subjects in the PEA group were found to have acute respiratory disease compared with 34.4% in the placebo group ($P < 0.0002$).

All these five clinical trials pointed towards the same conclusion, ie, that PEA had clear treatment effects in respiratory

tract infections, and that it could be used safely as prophylaxis against influenza. Side effects were not reported, and Kahlich et al explicitly stated: “No side effects were registered after several years of clinical testing of Impulsin in military and civilian communities.”

Another placebo-controlled study of PEA, this time examining the incidence of acute respiratory tract infections in children aged 11–15 years, was performed in 1976,²⁹ in which 457 children were allocated to receive 600 mg PEA tablets twice daily with an interval of 6 hours or placebo according to the same regimen. In total, 169 children were included in the PEA group and 224 children in the placebo group, and all received their tablets at school for 10 days, without administration of the study medication in the weekend. Sixty-four children were excluded for becoming ill in the first 5 days or not taking their study medication. Blood samples were taken before the study and 8 weeks later in 65% of the children. A microbiologic examination was performed on nasal samples. In the 8 weeks from the start of the study, children in the PEA group had a 15.7% lower rate of acute respiratory tract infection compared with the control group, and in children aged 11–13 years this difference was even more pronounced, at 25.5%. These differences were not statistically significant, probably because of the short trial duration and/or the study not being performed during the influenza season.

Mechanism of action proposed in early studies

With the emergence of pharmacologic concepts, a clear understanding of the mechanism of action appears to be important for acceptance of therapeutic activity by pharmacologists. In the period of research on PEA between 1950 and 1980, the mechanism of action of PEA remained unclear. Studies during this period could not pinpoint its mechanism of action, and this was the main reason why the scientific community lost interest in PEA until the work published by Levi-Montalcini.³⁶ Following her work, and supported by the discovery of anandamide (an endocannabinoid), the cannabinoid receptors CB1 and CB2, and the nuclear PPARs in 1992–2000, new interest in PEA emerged. In this first period, the effects of PEA were evaluated with regard to several proteins and the phagocytic activity of leucocytes.

In a study from 1978, a group of 50 children aged 4 years received PEA 30 mg/kg daily for 19 days,³⁰ with measurement of blood levels of albumin, orosomucoid, ceruloplasmin, transferrin, C3 and C4 complement, and immunoglobulins G,

A, M, and D before and after treatment with PEA. Phagocytic activity was measured using the photometric tetrazolium test. The authors reported a decrease in C3 complement and an increase in immunoglobulin G, which both were statistically significant ($P < 0.05$). The “spontaneous” metabolic activity of unstimulated neutrophilic granulocytes showed a significant increase after PEA. However, these results did not contribute to a further understanding of the biological activity of PEA.

In another study from this period, 18 children aged 5–7 years received PEA 30 mg/kg daily for 12 days,³¹ with measurement of B and T lymphocytes in the blood before and after treatment. PEA did not significantly affect absolute numbers of lymphocytes, but did change their percent proportions. The percent proportion of T lymphocytes was significantly reduced while that of B lymphocytes was increased.

Animal studies were also conducted to evaluate the biological effects of PEA, eg, in rats with leukemia, when administered in addition to chemotherapy. This animal study showed that PEA reduced the side effects of chemotherapy, enabling use of higher doses. PEA did not have a direct effect on cancer.³² Unfortunately, such studies also did not help to clarify the mechanism of action of PEA.

Identification as an analgesic agent for joint pain

In 1960, Coburn et al published data on PEA and rheumatoid arthritis.³³ The results were inconclusive. However, an observation made in this trial was that patients who received concentrated egg yolk daily for one month prior to infection did not develop symptoms of rheumatic activity. In a later study, the beneficial effects of this PEA-rich food were found to be less than those of acetylsalicylic acid. Therefore, some analgesic effects of PEA were already recognized in 1960, given that PEA was compared with acetylsalicylic acid at that time, even though the data were too limited and/or the dose administered was suboptimal.

In 1975, further details related to the analgesic action of PEA were published in *The Lancet*, when Czechoslovakian researchers reported the results of a clinical trial comparing the analgesic action of aspirin 3 g/day and PEA 1.8 g/day in patients with joint pain.³⁴ Although the results of this trial were not impressive, both agents were reported to improve joint movement and to decrease pain. The 1.8 g dose of PEA was the highest used in all the PEA studies, and was without side effects. Higher doses have not been evaluated in the context of clinical trials.

A publication on the active compounds in peanuts, also reported in *The Lancet*, was the reason for their report. In that paper, PEA was described as being biologically active as an inflammatory agent at a dose of 5 mg/kg bodyweight.³⁵ One year before the letter published in *The Lancet*, the painkilling properties of PEA had been described in the discussion of the results of a clinical trial assessing the efficacy and safety of PEA,³⁵ reported by Masek et al, who mentioned that pain had been reduced by 45.5% after PEA therapy ($P < 0.05$).²⁷ Thus, it is clear that the analgesic effects of PEA had been referred to in papers from 1960 and 1974, and outlined further in 1975. This early documentation of the analgesic effects of PEA remained unrecognized in literature.

Mechanism of action: from enhancer of nonspecific immunologic resistance to PPAR- α agonism

The scientific activity around the properties of PEA clearly relates to the pharmacologic understanding of the receptor for this endogenous compound. Between 1957 and 1993, there were no studies that gave a clear insight into how PEA might exert its physiologic actions. This changed in 1993 as a result of the work of Levi-Montalcini, who was awarded the Nobel prize for her work on the role nerve growth factor (NGF)³⁶ in inflammation and its activating role in mast cells, showing that positive feedback of NGF on mast cell behavior could be modulated and inhibited by PEA. This was the first explanation of how PEA could inhibit inflammation.

A second step forward in the understanding of the mechanism of action of PEA was the identification and isolation of anandamide as an endogenous lipid cannabis receptor agonist in 1992. As a result of this finding, more interest arose concerning endogenous ethanolamides and their respective physiologic roles. For a period of time, PEA was seen as an endocannabinoid, with affinity for the CB2 receptor.³⁷

After it became clear that PEA did not bind to the CB2 receptor, a new hypothesis emerged to explain its action, based on the so-called “entourage effect”. This was an unspecified activity via inhibition of the enzymes necessary for catabolism of endocannabinoids. However, it remained a hypothesis,³⁸ and became less popular after PEA was found to have high affinity for other receptors.

Several years after Isseman and Green identified the nuclear PPARs, data were presented in 1990 showing that PEA was an agonist for this receptor.³⁹ For several years,

Levi-Montalcini's line of thought that PEA was a modulator of mast cells ran in parallel with the PPAR story. The influence of these different pharmacologic chapters on the understanding of the mechanism of action of PEA are now discussed.

An aliamide and mast cell modulator?

In 1993, Levi-Montalcini's group was the first to present evidence indicating that lipid amides of the N-acylethanolamine type (such as PEA) are potential prototypes of naturally occurring molecules capable of modulating mast cell activation. In that paper, her group coined the term "autacoid local inflammation antagonism" (ALIA) and presented data "[...] supporting the possibility that lipid amides of the N-acylethanolamine type are potential prototypes of naturally occurring molecules capable of modulating mast cell activation *in vivo*."³⁶

An autacoid is a locally produced regulating molecule. Prostaglandins are classical examples of autacoids. An aliamide is an autacoid synthesized in response to injury or inflammation, and acts locally to counteract such pathology. PEA is a classic example of an aliamide. In this paper, Levi-Montalcini, based on her work with NGF, pointed out that PEA acts as a negative feedback loop on hyperactivated mast cells, and that PEA can therefore be seen as the biological counterpart of NGF.

Soon after the breakthrough paper of Levi-Montalcini, the mast cell indeed emerged as an important target for the anti-inflammatory activity of PEA. In the period 1993–2011, at least 25 papers were published on the various effects of PEA on the mast cell. Since 2005, we have come to understand that much of the biological effects of PEA on cells, including the mast cell, can probably be understood via its affinity for the PPAR. Levi-Montalcini et al introduced this topic by coining the new term, ie, ALIA, based on the somewhat outdated term, autacoid. Evidence is provided here supporting the existence of a novel autacoid mechanism negatively modulating mast cell behaviour in response to noxious stimuli *in vivo*; hence, the denominator "autacoid local inflammation antagonism."³⁶

Together with some of her coworkers, Levi-Montalcini put forward the following hypothesis, based on the work of Epps et al¹⁸ and Schmid et al¹⁹ already discussed and noting that tissue accumulation of N-acylethanolamines had been reported to occur in pathologic degenerative conditions:

As such conditions are known to be associated with inflammatory reactions, one attractive hypothesis is that

the production of these lipid metabolites may play an autacoid role in controlling mast cell behavior in pathological conditions.³⁶

The term "ALIA" was introduced to stipulate the physiologic mechanism of action of PEA in various inflammatory and painful states. The term "autacoid" is already found in the biological literature from around 1935. Examples of molecules acting as autacoids are nitric oxide, leukotrienes, and prostaglandins. An autacoid controls metabolism locally, whereas a hormone is produced locally but acts globally and also influences metabolism. PEA is formed locally at sites of tissue inflammation or, as Levi-Montalcini puts it, sites of neurogenic pain, and increased PEA concentrations are body-own mechanisms for coping with pain and inflammation.

From another perspective, one could state that PEA is a natural defense or self-healing molecule in the event of overactive mast cell behavior and activated glia cells, and occurs in many different pain and inflammatory disorders.

Levi-Montalcini's research focus was on NGF, and as early as 1977 she pointed out that NGF was an irritative compound inducing mast cell degranulation.^{40,41} Both mast cells and NGF were topics she worked on for many years. In an interview, when well into her 80s, she spoke of mast cells as "Cinderella" cells for chronic inflammation. She pointed out the very important role of these cells in a wide variety of autoimmune disorders, including multiple sclerosis. However, mast cells have always remained in a relatively dark corner in human pathogenesis, despite her work. In a paper on NGF published in 1995, she stressed the importance of NGF in inflammatory processes and autacoid regulation of mast cell hyperactivity.⁴²

Broadening of the ALIA concept and its role in CNS disorders

In 1995, Levi-Montalcini reported the results of research undertaken by her coworkers related to the protective effects of PEA against damage to the central nervous system (CNS).⁴² She pointed out that activated N-methyl-D-aspartate (NMDA) receptors have been implicated in a variety of pathologic states in the CNS leading to neuronal injury. She also pointed out that little was known about endogenous molecules and the mechanisms by which they are capable of modulating NMDA-induced excitotoxic neuronal death. In CNS pathology of this type, the body prepares its own defense mechanism via saturated N-acylethanolamides like PEA. These compounds accumulate in ischemic tissues and are synthesized by neurons upon activation of excitatory amino acid receptors.

In addition to this, excitatory amino acids stimulate the synthesis of N-acylethanolamides and N-acylphosphatidylethanolamides in cultured CNS neurons. In a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons, PEA was shown to be an endogenous protective agent in the case of neuron death induced by NMDA. Levi-Montalcini extrapolated these findings and came to the conclusion that, by providing the neuron with exogenous PEA, one might be making the available quantities of its physiologic modulator sufficient to restore cellular homeostasis in the face of an excitotoxic challenge. Given the fact that PEA was already shown by her group to stabilize mast cell hyperactivity in inflammation, she introduced the concept of ALIA.

In a 1996 paper on the protective effects of PEA in CNS neuron death, Levi-Montalcini broadened the ALIA concept to a more general local autacoid anti-injury function. In the same period of time, she pointed out the importance of NGF as an inflammatory mediator in neuropathic pain states, as well as in diseases such as multiple sclerosis. The mast cell was seen as an important player. She stressed the importance of mast cell activity in activated plaques in patients with multiple sclerosis, and the pathologic cascade of events triggered by these activated mast cells. She also demonstrated that mast cells can be the source of synthesis of NGF, ie, the basis of pathologic immune system-CNS crosstalk. Thus, by 1996, Levi-Montalcini had already drawn attention to the therapeutic potential of PEA in neuropathic pain and multiple sclerosis.⁴¹

In a series of articles on nutraceuticals in 2006, ALIA was again redefined, whereby aliamides were described as synthetic analogs of endogenous fatty acid amides behaving in a cannabimimetic fashion and accumulating in peripheral mammalian tissues exposed to various stressors. The authors pointed out that Aliamides are believed to be synthesized and released to protect neighboring cells from excessive propagation of the inflammatory and nociceptive response. "Aliamides are so called because of their mechanism of action, ie, decreasing mast cell degranulation via activation of both receptor-mediated and receptor-independent pathways."⁴³ Already at that time the authors could also state that there was a considerable body of evidence showing that aliamides have beneficial effects in inflammatory and/or nociceptive states.

PEA: an endocannabinoid?

Anandamide was the first endocannabinoid identified. Devane et al isolated a minute fraction of a lipid from 4.5 kg

of porcine brain,³⁷ and characterized its structure as arachidonylethanolamide, an ethanolamide of a C-20 fatty acid, which was confirmed via synthesis. The synthetic compound bound to the cannabinoid receptor with a K_i of 39 nM. Devane et al argued that anandamide might indeed be the neuromediator, given that three related fatty acids (one of which was PEA), did not bind to the CB1 cannabinoid receptor. In a 1992 paper, Devane et al pointed out the biological importance of the fatty acid amides, stressing the anti-inflammatory properties of PEA, as had been outlined since its isolation from egg yolk in 1957.³⁷

Following the observations of Devane et al, numerous other N-acylethanolamines have been found in mammals.⁴⁴ PEA in 1992, in the experiments of Devane et al, did not classify as a cannabinoid as its affinity for the cannabis receptor in their assay was absent, while anandamide had affinity for this receptor in the nanomolar range.

However, in 1995, Facci et al suggested that anandamide and PEA shared the same CB2 receptor, based on their finding that PEA could replace the binding of WIN 55-212-2, a high affinity cannabinoid agonist, on white blood cells and mast cells, while arachidonic acid and ethanolamine were not effective.⁴⁵ Consistent with the line of thinking about aliamide, these authors concluded that "... palmitoylethanolamide may behave as local autacoids capable of negatively modulating mast cell activation (ALIA mechanism)." They pointed out that PEA reduces mast cell activation associated with inflammatory processes. Some of the properties of PEA were by them contributed to the presumed interactions with CB2 receptors on mast cells.

Subsequent studies never replicated these findings, and the affinity of PEA for CB2 could not be found again. In 1999, Lambert et al tested a number of synthetic ethanolamides, and found no binding affinity between derivatives of PEA or PEA itself for either the CB1 or CB2 receptor.⁴⁶ They discussed their results and noted that there was a discrepancy between their findings and those of Facci et al, who demonstrated binding efficiency in RBL-2H3 and the biological activity of N-PEA.

Lambert et al⁴⁶ discussed comparable findings, all supporting questions related to the receptor-related effects of N-palmitoylethanolamide and its derivatives, and pointed out that this family of unsaturated fatty acid compounds may exert substantial receptor-independent effects in addition to receptor-dependent effects. CB2 receptor-independent pharmacologic effects started to be published during this period.⁴⁷ A putative CB-N receptor was proposed by Lambert and Di Marzo⁴⁸ in 1999 to explain the absence of

N-palmitoylethanolamide binding in CB1-CB2-transfected cells. The receptor for PEA again proved elusive.

Later, new targets and receptors were identified, and studies in knockout mice suggested the existence of new target sites for lipid ligands such as PEA, eg, transient receptor potential vanilloid type 1 and the nuclear PPARs.⁴⁹ The literature supporting PEA as a PPAR- α agonist has increased since then and has helped our understanding of the biological significance and importance of PEA in many clinical disorders.^{50–52}

For some years, PPAR agonism has generally been seen as one of the most important mechanisms of action of PEA, and use of the entourage effect to explain its biological actions has been less and less referred to and vanished from the modern literature around 2009.⁵³

Since the identification of PEA as a PPAR- α agonist, the results of a great number of clinical trials have been published. At least 6,000 patients with chronic pain and inflammation have been entered into clinical trials since the first clinical studies in the 1970s, and PEA is becoming recognized as an important therapeutic principle with an impressively positive risk/benefit balance.⁵⁴ Further, recent data support the hypothesis of deficient synthesis of PEA in pathologic states, such as fibromyalgia. The authors who described this deficient synthesis in the trapezius muscles in patients suggest that supplementation with exogenous PEA might be a useful therapeutic intervention in this chronic widespread pain state.⁵⁵

Emergence of new pharmacologic facts needing a scientific context

Ludwig Fleck (1896–1961), a Polish-Jewish microbiologist, was the first scientist to design a system for the sociology of science. Fleck used examples from microbiology and research on syphilis to demonstrate that creating scientific concepts is a collective activity, and only possible on the basis of a certain body of knowledge acquired from other scientists.⁵⁶ When clinicians and medical biologists start to create and exchange ideas, a so-called “thought collective” arises, resulting in a temporary construct of understandings and misunderstandings related to scientific facts. When a specific thought style becomes sufficiently sophisticated, new terms or explanations emerge, in this case, PEA as a non-specific immune enhancer. Fleck spoke of a “thought style” consisting of elements that shape ways in which members of the collective perceive medical observations, giving rise to scientific facts. However, according to Fleck, what we call facts are social constructs. Later this idea was taken over by

Thomas Kuhn, who introduced the “paradigm” concept for such a social scientific construct.⁵⁷

The history of PEA demonstrates how correct the concepts of Fleck and Kuhn are. PEA was first conceived of as a lipid with nonspecific immune-enhancing properties, reflecting the thought collective (paradigm) of that specific time period. However, this specific paradigm could not explain the biological activity or clinical effects of PEA, because there was no basic understanding related to the mechanism of action of PEA. Therefore, PEA did not penetrate into the clinic as a therapeutic principle, despite the presence of a number of pivotal double-blind and placebo-controlled trials supporting its efficacy and safety. Only after the emergence of insights in the mechanism of action, starting with the work of Levi-Montalcini in 1993, an understanding started to grow about how exactly PEA works.⁵⁸ This was supported by the emergence in the same period of other important biochemical findings, ie, discovery of the cannabinoid receptors and the endocannabinoid, anandamide. After identification of the nuclear factor PPAR- α as a receptor for PEA, the paradigm around PEA shifted again, in that the blueprint for understanding how PEA worked was now in place. Following on from this, new clinical data on the efficacy and safety of PEA as an analgesic were published, initially mostly in Italian and Spanish papers. Acceptance by the scientific community of the importance of PEA grew, and new clinical trials reported in the English literature further supported its efficacy and safety in a variety of chronic pain syndromes.^{57,62} In 2008, PEA became commercially available as a nutraceutical under the brand name Normast® (Epitech Group Srl, Milan, Italy) and in 2012 as PeaPure® (JP Russell Science Ltd, Nicosia, Cyprus), and thus a new chapter has opened in the treatment of chronic pain.

This paper demonstrates how a scientific concept, ie, PEA as an analgesic and anti-inflammatory compound with therapeutic value, has penetrated medical science. It has been shown that acceptance of a therapeutic principle, although clinical data are present and convincing, does not penetrate unless a clear mechanistic explanation for such a therapeutic intervention exists. PEA was demonstrated to be of clinical value in a wide variety of preclinical and clinical experiments in the period 1957–1992. However, PEA did not attract sufficient attention in the scientific community due to the absence of an explanation for its activity. New interest in PEA emerged only after Levi-Montalcini described the mechanistic effects of PEA in mast cells and identified PEA as an inhibitor of these cells when activated, and as an inhibitor of the pro-inflammatory actions of NGF. The fact that PEA is available

as a nutraceutical is the last hurdle for the medical community to take. Nutraceuticals are in general not patent-protected, so are not a focus for the pharmaceutical industry and therefore less studied, publicized, and recognized. However, a great body of evidence exists for PEA, comprising at least 40 clinical trials in around 6,000 subjects.^{54,60} This body of evidence shows a positive risk/benefit ratio for PEA, warranting much wider use of this compound by the medical community.

Disclosure

The author reports no conflicts of interest in this work.

References

- Coburn AF, Graham CE, Hanninger J. The effect of egg yolk in diets on anaphylactic arthritis (passive Arthus phenomenon) in the guinea pig. *J Exp Med*. 1954;100:425–435.
- Kuehl FA, Jacob TA, Ganley OH, Ormond RE, Meisinger MAP. The identification of N-(2-hydroxyethyl)-palmitamide as a naturally occurring anti-inflammatory agent. *J Am Chem Soc*. 1957;79:5577–5578.
- Long DA, Miles AA, Perry WL. Action of ascorbic acid on tuberculin-sensitivity in guinea pigs and its modification by dietary and hormonal factors. *Lancet*. 1951;1:1085–1088.
- Raskova H, Masek K. Nouvelles possibilites d'augmentation de la resistance non-specifique. [Novel possibilities of enhancing non specific resistance]. *Therapie*. 1967;22:1241–1246. French.
- Raskova H, Masek K, Linet O. Nonspecific resistance induced by palmitoylethanolamide. *Toxicon*. 1972;10:485–490.
- Ganley OH, Graeseli E, Robinson HJ. Anti-inflammatory activity on compounds obtained from egg yolk, peanut oil, and soybean lecithin. *J Lab Clin Med*. 1958;57:709–723.
- Benvenuti F, Lattanzi F, De Gori A, Tarli P. Activity of some derivatives of palmitoylethanolamide on carragenine-induced edema in the rat paw. *Boll Soc Ital Biol Sper*. 1968;44:809–813.
- Lackovic V, Borecký L, Kresáková J. Effect of impulsin treatment of interferon production and antiviral resistance of mice. *Arch Immunol Ther Exp (Warsz)*. 1977;25:655–661.
- Long DA, Martin AJ. Factor in arachis oil depressing sensitivity to tuberculin in B.C.G.-infected guineapigs. *Lancet*. 1956;270:464–466.
- Lackovic V, Borecký L, Kresáková J, Doskocil J. N[2-hydroxyethyl] palmitamide repeated administration effect on interferon production in mouse organism after phage double-stranded ribonucleic acid [ds-RNA] application. *Cesk Epidemiol Mikrobiol Imunol*. 1978;27:38–45. Slovak.
- Perlík F, Rasková H, Elis J. Anti-inflammatory properties of N-(2-hydroxyethyl) palmitamide. *Acta Physiol Acad Sci Hung*. 1971;39:395–400.
- Perlík F, Krejčí J, Elis J, Pekárek J, Svejcar J. The effect of N-(2-hydroxyethyl)-palmitamide on delayed hypersensitivity in guinea-pig. *Experientia*. 1973;29:67–68.
- Bachur NR, Mašek K, Melmon KL, Udenfriend S. Fatty acid amides of ethanolamine in mammalian tissues. *J Biol Chem*. 1965;240:1019–1024.
- Obermajerova H, Masek K, Seifert J, Buchar E, Havlik L. Structural and functional changes in liver mitochondria of mice fed palmitoylethanolamide (PEA). *Biochem Pharmacol*. 1973;22:2529–2536.
- Rakovfi H, Masek K, Linet O. Detoxicating properties of a simple lipid compound. Abstract presented at the Fifth International Congress of Pharmacology, July 23–28, 1992, San Francisco, CA, USA.
- Svec P, Béderová E, Svec F. The effect of long-term administration of N-(2-hydroxyethyl)palmitamide on the chemotherapy of RBA rat leukemia. *Neoplasma*. 1975;22:625–630.
- Truini A, Biasiotta A, Di Stefano G, et al. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. *CNS Neurol Disord Drug Targets*. 2011;10:916–920.
- Epps DE, Schmid PC, Natarajan V, Schmid HH. N-Acylethanolamine accumulation in infarcted myocardium. *Biochem Biophys Res Commun*. 1979;90:628–633.
- Schmid HH, Schmid PC, Natarajan V. N-acylated glycerophospholipids and their derivatives. *Prog Lipid Res*. 1990;29:1–43.
- Natarajan V, Reddy PV, Schmid PC, Schmid HHO. N-Acylation of ethanolaminephospholipids in canine myocardium. *Biochim Biophys Acta*. 1982;712:342–355.
- Ahmad A, Genovese T, Impellizzeri D, et al. Reduction of ischemic brain injury by administration of palmitoylethanolamide after transient middle cerebral artery occlusion in rats. *Brain Res*. 2012;1477:45–58.
- Ahmad A, Crupi R, Impellizzeri D, et al. Administration of palmitoylethanolamide (PEA) protects the neurovascular unit and reduces secondary injury after traumatic brain injury in mice. *Brain Behav Immun*. 2012;26:1310–1321.
- Di Paola R, Impellizzeri D, Torre A, et al. Effects of palmitoylethanolamide on intestinal injury and inflammation caused by ischemia-reperfusion in mice. *J Leukoc Biol*. 2012;91:911–920.
- Scuderi C, Valenza M, Stecca C, Esposito G, Carratù MR, Steardo L. Palmitoylethanolamide exerts neuroprotective effects in mixed neuroglial cultures and organotypic hippocampal slices via peroxisome proliferator-activated receptor- α . *J Neuroinflammation*. 2012;9:49.
- D'Agostino G, Russo R, Avagliano C, Cristiano C, Meli R, Calignano A. Palmitoylethanolamide protects against the amyloid- β 25–35-induced learning and memory impairment in mice, an experimental model of Alzheimer disease. *Neuropsychopharmacology*. 2012;37:1784–1792.
- Genovese T, Esposito E, Mazzone E, et al. Effects of palmitoylethanolamide on signaling pathways implicated in the development of spinal cord injury. *J Pharmacol Exp Ther*. 2008;326:12–23.
- Masek K, Perlík F, Klíma J, Kahlich R. Prophylactic efficacy of N-2-hydroxyethyl palmitamide (impulsin) in acute respiratory tract infections. *Eur J Clin Pharmacol*. 1974;7:415–419.
- Kahlich R, Klíma J, Cihla F, et al. Studies on prophylactic efficacy of N-2-hydroxyethyl palmitamide (Impulsin) in acute respiratory infections. Serologically controlled field trials. *J Hyg Epidemiol Microbiol Immunol*. 1979;23:11–24.
- Plesník V, Havrlantová M, Jancová J, Januska J, Macková O. Impulsin in the prevention of acute respiratory diseases in school children. *Cesk Pediatr*. 1977;32:365–369. Czech.
- Wiedermannová D, Wiedermann D, Lokaj J. Prophylactic administration of Impulsin to clinically healthy children. Effect on the serum proteins and metabolic activity of granulocytes. *Cas Lek Cesk*. 1978;117:1030–1034. Czech.
- Wiedermannová D, Lokaj J, Wiedermann D. Prophylactic administration of Impulsin to clinically healthy children. The effect on T and B lymphocytes in peripheral blood. *Cas Lek Cesk*. 1979;118:1249–1251. Czech.
- Svec P, Béderová E, Svec J. The influence of N-(2-hydroxyethyl)-palmitamide on virus-induced sarcomas in chickens and Rauscher leukemia in mice. *Neoplasma*. 1975;22:519–524.
- Coburn AF, Rich H. *Archs Interam Rheumatol*. 1960;4:498–515.
- Masek K, Perlík F. Letter: slow encephalopathies, inflammatory responses, and arachis oil. *Lancet*. 1975;2:558.
- Outram GW, Dickinson AG, Fraser H. Slow encephalopathies, inflammatory responses and arachis oil. *Lancet*. 1975;1:198–200.
- Aloe L, Leon A, Levi-Montalcini R. A proposed autacoid mechanism controlling mastocyte behaviour. *Agents Actions*. 1993;39 Spec No:C145–147.
- Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992;258:1946–1949.

38. Smart D, Jonsson KO, Vandevoorde S, Lambert DM, Fowler CJ. 'Entourage' effects of N-acyl ethanolamines at human vanilloid receptors. Comparison of effects upon anandamide-induced vanilloid receptor activation and upon anandamide metabolism. *Br J Pharmacol*. 2002;136:452–458.
39. Isseman I, Green S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature*. 1990;347:645–650.
40. Aloe L, Levi-Montalcini R. Mast cells increase in tissues of neonatal rats injected with the nerve growth factor. *Brain Res*. 1977;133:358–366.
41. Levi-Montalcini R, Skaper SD, Dal Toso R, Petrelli L, Leon A. Nerve growth factor: from neurotrophin to neurokin. *Trends Neurosci*. 1996;19:514–520.
42. Levi-Montalcini R, Dal Toso R, della Valle F, Skaper SD, Leon A. Update of the NGF saga. *J Neurol Sci*. 1995;130:119–127.
43. Miolo A, Re G, Barbero R, et al. Aliamides modulate skin mast cell degranulation in dogs and cats. *J Vet Pharmacol Ther*. 2006;29 Suppl 1:201–210.
44. Lambert DM, Fowler CJ. The endocannabinoid system: drug targets, lead compounds, and potential therapeutic applications. *J Med Chem*. 2005;48:5059–5087.
45. Facci L, Dal Toso R, Romanello S, Buriani A, Skaper SD, Leon A. Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. *Proc Natl Acad Sci U S A*. 1995;92:3376–3380.
46. Lambert DM, DiPaolo FG, Sonveaux P, et al. Analogues and homologues of N-palmitoylethanolamide, a putative endogenous CB(2) cannabinoid, as potential ligands for the cannabinoid receptors. *Biochim Biophys Acta*. 1999;1440:266–274.
47. White R, Hiley CR. The actions of some cannabinoid receptor ligands in the rat isolated mesenteric artery. *Br J Pharmacol*. 1998;125:533–541.
48. Lambert DM, Di Marzo V. The palmitoylethanolamide and oleamide enigmas : are these two fatty acid amides cannabimimetic? *Curr Med Chem*. 1999;6(8):757–773.
49. Fattore L, Melis M, Fadda P, Pistis M, Fratta W. The endocannabinoid system and nondrug rewarding behaviours. *Exp Neurol*. 2010;224:23–36.
50. Di Cesare ML, D'Agostino G, Pacini A, et al. Palmitoylethanolamide is a disease-modifying agent in peripheral neuropathy: pain relief and neuroprotection share a PPAR- α -mediated mechanism. *Mediators Inflamm*. 2013;2013:328797.
51. Paterniti I, Impellizzeri D, Crupi R, et al. Molecular evidence for the involvement of PPAR- δ and PPAR- γ in anti-inflammatory and neuroprotective activities of palmitoylethanolamide after spinal cord trauma. *J Neuroinflammation*. 2013;10:20.
52. Khasabova IA, Xiong Y, Coicou LG, Piomelli D, Seybold V. Peroxisome proliferator-activated receptor α mediates acute effects of palmitoylethanolamide on sensory neurons. *J Neurosci*. 2012;32:12735–12743.
53. Garcia Mdel C, Adler-Graschinsky E, Celuch SM. Enhancement of the hypotensive effects of intrathecally injected endocannabinoids by the entourage compound palmitoylethanolamide. *Eur J Pharmacol*. 2009;610:75–80.
54. Keppel Hesselink JM. New targets in pain, non-neuronal cells, and the role of palmitoylethanolamide. *Open Pain J*. 2012;5:12–23.
55. Ghafouri N, Ghafouri B, Larsson B, Stensson N, Fowler CJ, Gerdle B. Palmitoylethanolamide and stearoylethanolamide levels in the interstitium of the trapezius muscle of women with chronic widespread pain and chronic neck-shoulder pain correlate with pain intensity and sensitivity. *Pain*. 2013;S0304–S3959.
56. Fleck L. *Entstehung und Entwicklung einer wissenschaftlichen Tatsache. [The Genesis and Development of a Scientific Fact]*. Trenn TJ, Merton RK, editors. Chicago, IL: University of Chicago Press; 1979.
57. Kuhn TS. *The Structure of Scientific Revolutions*. Chicago, IL: University of Chicago Press; 1962.
58. Keppel Hesselink JM. Professor Rita Levi-Montalcini on nerve growth factor, mast cells and palmitoylethanolamide, an endogenous antiinflammatory and analgesic compound. *J Pain Relief*. 2013;2:114.
59. Keppel Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. *J Pain Res*. 2012;5:437–442.
60. Keppel Hesselink JM, de Boer T, Witkamp R. Palmitoylethanolamide: a natural body-own anti-inflammatory agent, effective and safe against influenza and common cold. *Int J Inflamm*. In press.

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