

Professor Rita Levi-Montalcini on Nerve Growth Factor, Mast Cells and Palmitoylethanolamide, an Endogenous Anti-Inflammatory and Analgesic Compound

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Abstract

Professor Rita Levi-Montalcini discovered Nerve Growth Factor (NGF) in 1954, and many papers are published since, relating to this tremendously important milestone for the medical sciences. Much less is known about another milestone in molecular and clinical neurology she and her co-workers achieved. In the period 1993-1996 her group identified the mechanism of action of the anti-inflammatory and analgesic properties activity of the endogenous fatty amide palmitoylethanolamide (PEA).

PEA is a molecule with tissue-protective and anti-inflammatory activities, widely present in plants, animals and man. Rita Levi-Montalcini and her group discovered in 1993 PEA as a natural modulator of hyperactive mast cells, counteracting the pro-inflammatory actions of NGF. PEA however, has not been registered as pharmaceutical drug, due to the fact that patent protection of the pure and natural compound was impossible. Therefore, developed as a nutraceutical, it did not catch the attention of the medical community, which we hope to prove is incorrect. Based on Levi-Montalcini's work in the 90s PEA is now available as a nutraceutical for indications related to chronic pain and chronic inflammation. In the period 1970-1980 its safety and efficacy has been explored and documented in 6 double blind clinical trials in flu and respiratory infections in around 2000 patients. Triggered by the findings of Levi-Montalcini PEA has been evaluated since 1993 in a variety of pain indications such as sciatic pain, low back pain, diabetic pain, neuropathic pain, pain due to arthritis in a total of 2000 patients. PEA is therefore most probably the best-documented nutraceutical around, and its pharmacological profile has been described in more than 350 scientific papers. In this review we will discuss Levi-Montalcini's discovery of PEA's mechanisms of action and its clinical relevance.

Keywords: Palmitoylethanolamide; NGF; Levi-Montalcini; Mast cell; Pain; Inflammation

Introduction

The discovery of Nerve Growth Factor (NGF) by Prof. Rita Levi-Montalcini in the early 50s of last century, and her neurobiological work, which lead to the Nobel price in 1986, is widely known, and many papers were- and still are published related to this tremendously important milestone for molecular biology and pharmacology [1]. Much less is known about another milestone in molecular and clinical neurology she and her co-workers achieved. In the period 1993-1996 her group identified the mechanism of action of the anti-inflammatory and analgesic properties of the endogenous fatty amide palmitoylethanolamide.

Palmitoylethanolamide (PEA) is a food component known already for more than 50 years and since 2007 used in the clinic [2]. In the period 1957-beginning of the 80s of last century, slowly PEA started to be recognized as a molecule with tissue-protective and anti-inflammatory activities, widely present in invertebrates, vertebrates and man [3-7]. In the period 1957, since the first description and synthesis of PEA, until 1980 many papers were published on pharmacology and the clinical effects of this simple fatty amide. However, its mechanism of action was not understood and thus scientific and clinical interest waned. Rita Levi-Montalcini and her group discovered in 1993 that PEA acts as a natural modulator of hyperactive mast cells, counteracting the pro-inflammatory actions of NGF [8]. Since that hallmark paper, interest in PEA soared and many hundreds of publications emerged on PEA, its pharmacological profile, its mechanism of action and its value for treating many different chronic inflammation and pain states [2].

In this review we will discuss Levi-Montalcini's discovery of PEA's mechanisms of action and we will review the clinical relevance of PEA.

PEA as a Nutraceutical

Palmitoylethanolamide is synthesized and metabolized in

animal cells via a number of enzymes and it exerts a multitude of physiological functions, related to metabolic homeostasis. PEA is available for human use since 2007 [2]. PEA was introduced in 2007 as a nutraceutical in Italy and Spain under the brand name Normast. The Italian company Epitech produces it in Italy. Normast contains palmitoylethanolamide and a number of excipients, including sorbitol in one specific formulation. PEA is also under evaluation as special diet-treatment for Inflammatory Bowel Syndrome by CM&D Pharma Ltd and Nestlé in the USA. Since 2012 PEA is also internationally available as a nutraceutical under the brand name PeaPure, produced in the Netherlands by the company Russell Science Ltd. PeaPure contains palmitoylethanolamide only, without any excipients or sorbitol.

Birth of PEA

The history of PEA started in a chemical, non-medical environment in 1952, when chemists synthesized a number of acyl-ethanolamides, among which PEA, without understanding its biological properties and its value [9]. Some years later the anti-inflammatory properties of egg yolk were discovered and dried egg yolk preparations were introduced as a kind of 'pre-historical' nutraceutical. Egg yolk and peanut oil

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were found to possess anti-inflammatory activities, and PEA was discovered to be the carrier of these properties in 1957 [10-12].

The story of the emergence of insights in the biological roles and value of PEA after its identification in 1952 and the contributions of Rita Levi-Montalcini is worth telling, because it shows that plausible explanations of the mechanism of action of drugs are required before a treatment concept will be explored in more detail in science and in the clinic. Without a satisfactory explanation, even in the presence of clinical efficacy, as was the case for PEA, a new therapeutic concept will not be embraced by the scientific community. PEA research sunk into oblivion after the first surges of interest between 1960 and the mid 80s of last century, due to the fact that no mechanism of action was convincingly demonstrated. 1993 was the year of resurrection for PEA, due to Levi-Montalcini's paper [8].

PEA: From Discovery to Clarification of its Mechanism of Action by Prof. Levi-Montalcini

If we study the timeline of events related to PEA, we could define three periods: During the first period 1957-mid 80s. PEA was seen as an aspecific immunity-enhancer with anti-inflammatory properties [13-16]. Flu and respiratory infections were indications for the use of PEA, introduced in the clinic under the brand name Impulsin in Czechoslovakia by the pharmaceutical company Spofa. In this period PEA's safety and efficacy was evaluated in a number of clinical trials, resulting in a dose-recommendation of PEA 600-1800 mg/day in flu, common cold and respiratory infections [17,18]. Around 2000 adult volunteers and 400 children were entered in these trials [18]. All these clinical trials pointed in the same direction: PEA has clear treatment effects in respiratory infections, can be used as flu-prophylaxis and is safe in its use. 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" [18].

A second period, which we call the Silent Gap period, lasted around a decade, from the early 80s until 1993. As no mechanism of action could be detected, and PEA was seen as an unspecific immune enhancer, the scientific community lost interest.

In 1993 the third period started: Prof. Levi-Montalcini et al. clarified its mechanism of action in various papers. This clarification was related to her insights in the biological actions of NGF [8].

Discovery of PEA as an Anti-inflammatory Compound

The first real milestone was in 1957 when MSD scientists identified PEA as anti-inflammatory food-compound [11].

Kuehl et al. [11] isolated the anti-inflammatory factor in crystalline form in 1957 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 was identified as N-palmitoylethanolamide, i.e. N- (2-hydroxyethyl)-palmitamide. They also synthesized the compound, as well as various analogues, and attributed the anti-inflammatory activity to the ethanolamine moiety of the series of molecules they synthesized.

On 20 October of 1957 Kuehl and 4 colleagues reported:

"We have succeeded in isolating a crystalline anti-inflammatory factor from soybean lecithin and identifying it as N- (2-hydroxyethyl)-palmitamide. The compound also was isolated from a phospholipid fraction of egg yolk and from hexane-extracted peanut meal."

This was the first description of PEA and its biological activity as an anti-inflammatory agent. The identification was clear after

hydrolysis of the compound yielded palmitic acid and ethanolamide. Furthermore, PEA could be synthesized by refluxing ethanolamine with palmitic acid. This all permitted the identification of the inflammatory fatty compound as the known N- (2-hydroxyethyl)-palmitamide.

Bachur et al. [3] analyzed various tissues for the presence of fatty amides and found PEA present in several tissues of the rat and guinea pig and consistently in brain, liver, and muscle. However, they pointed out that PEA's mechanism of action remained a mystery: "The role of the fatty acid amides in metabolism is unexplained as yet" [3].

In 1967 and 1972 it was found that oral administration of PEA to mice decreased mortality caused by *Shigella dysenteriae* toxin, streptolysin O, or live group A *Streptococcus*, as well as the mortality rate resulting from traumatic shock [14]. The authors clearly pointed out that PEA could play a modifying role in the course of development of certain immunological processes, and stated that its mechanism of action has not been clarified and that further analytical studies were needed.

In 1975 the first supportive effects of PEA in cancer as a modulator of toxicity of chemotherapy was reported, based on an animal model [19]. In 2011, the research group of Professor Gruccu in Rome demonstrated the supportive effects of PEA in neuropathic pains and nerve damage after chemotherapy, totally in line with these early findings [20].

In 1975 also for the first time the results of a small pilot trial in rheumatic pain were published, supporting the analgesic properties of PEA [21].

In 1980 Dennis Epps, from the university of Minnesota, reported the accumulation of PEA in the infarcted myocardium, and stated this might be of physiological importance because of its anti-inflammatory properties. It was Epps who first suggested that these fatty molecules played a protective role during ischemia, and that its presence: "may signify a response of myocardial tissue to injury directed at minimizing damage and promoting survival" [22].

Meanwhile, more recent pharmacological studies all confirmed that the hypothesis of Epps et al. [22] was correct. PEA protects nervous tissue in various lesion-models related to spinal cord injury as well as in shock, stroke, MS and Alzheimer [23-28].

That the scientific activities focused on the physiological effects of PEA was clearly related to the absence of the pharmacological understanding of the receptor for this endogenous compound at that time. In the period 1957-1993 there were no clear mechanism of action studies that gave insight into how PEA could exert its physiological actions.

In 1993 this all changed, due to the work of Rita Levi-Montalcini and her co-workers [8]. Levi-Montalcini earned her Nobel Prize due to her work in the field of the nerve growth factor, NGF [1]. She pointed out the role of NGF during inflammation and its activating role on mast cells. The positive feedback of NGF on mast cell behavior could be modulated and inhibited by PEA and this was the first explanation of how PEA could inhibit inflammation. Hand in hand with this very relevant finding, she also was one of the first neurobiologist who pointed out that the mast cells are no Cinderella cells (her own words), but, and she quoted Galli, mast cells are rather 'master cells' [29].

PEA: Clarification of its Mechanism of Action as an Endogenous Modulator

So, clearly it was the research group of Prof. Levi-Montalcini who,

in the 1993 article titled 'A proposed autacoid mechanism controlling mastocyte behavior' presented evidence supporting 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 vivo* and her group coined in that paper a new acronym, ALIA [8].

Autocoid or autacoid is a rather old-fashioned term for a regulating molecule, locally produced and locally exerting its actions. An autocoid controls metabolism locally, whereas a hormone is produced locally but acts globally and also influences metabolism. In this case PEA is formed locally when inflammation or neurogenic pain occur, and increased PEA concentrations are based on the body-own mechanisms to cope with pain and inflammation. This is called: on-demand synthesis.

Prostaglandins are classical examples of autocoids. An ALIAMide is an autocoid synthesized in response to injury or inflammation, and acting locally to counteract such pathology. Thus, PEA is a classical example of an ALIAMide. The mast cell soon after the breakthrough paper of Levi-Montalcini was indeed shown to be an important target for the anti-inflammatory activity of PEA, and in the period 1993-2013 more than 30 papers were published on the impact of PEA on the mast cell [30].

Prof. Levi-Montalcini [30] started introducing the topic by defining the term ALIA:

"Evidence is provided here supporting the existence of a novel autacoid mechanism negatively modulating mast cell behavior in response to noxious stimuli *in vivo*; hence, the denomination "autacoid local inflammation antagonism" (ALIA). In particular, as lipid amides of the N-acylethanolamine type have been reported to accumulate in tissues in degenerative inflammatory conditions."

She put forward the following hypothesis:

"Tissue accumulation of free N-acylethanolamines has been reported to occur in pathological 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."

From another perspective one could state that this molecule is our natural defense molecule, or self-healing molecule, in case of over-active mast cell behavior, including activated glia cells, as present in many different painful and inflammatory disorders.

Professor Levi-Montalcini's focus was on NGF, and already as early as 1977 she pointed out that NGF was an irritative compound inducing mast cell degranulation [31]. The relation between mast cell and NGF, also related to their interactive function in diseases, were topics Rita Levi-Montalcini worked on for many years [32-37]. Her last paper on NGF was published in the year she died at the age of 103, in 2012 [38]. Her first paper leading to the discovery of NGF was published exactly seven decades earlier, in 1942, written together with professor G. Levi, soon to be followed by the first paper based on the cooperation with her American mentor, professor Victor Hamburger [39,40].

The Broadening of the ALIA Concept and the Role of PEA in Central Nervous Disorders

In 1994 Rita Levi-Montalcini reported the results of the work of her coworkers related to the protective effects of palmitoylethanolamide in central nervous system (CNS) damage. That was in a paper published in the Proceedings of the National Academy of Science [33]. She

stressed that activated NMDA receptors have been implicated in a variety of pathological states in the CNS leading to neuronal injury. She pointed out that little is known about endogenous molecules and mechanisms capable of modulating the NMDA induced excitotoxic neuronal death. In such CNS pathology the body prepares its own defense mechanism via saturated N-acylethanolamides like PEA. These protective compounds accumulate in ischemic tissues and are synthesized by neurons upon excitatory amino acid receptor activation. She summarized the research findings, pointing out that N-acylethanolamides, like PEA, and N-acylphosphatidylethanolamides accumulate in conditions involving degenerative changes to tissues, as in CNS and cardiac ischemia.

In addition to this, excitatory amino acids stimulate the synthesis of N-acylethanolamides and N-acylphosphatidylethanolamides in cultured central neurons. In a delayed post glutamate paradigm of excitotoxic death in cerebellar granule neurons, PEA appeared as an endogenous protective agent in case of NMDA induced neuron death. Prof. Levi-Montalcini extrapolated these findings and came to the conclusion that by providing the neuron with exogenous PEA, one might be making available quantities of its physiological modulator sufficient to restore cellular homeostasis in the face of an excitotoxic challenge.

In the 1996 paper on the protective effects of PEA in central neuron death, she broadened the concept:

"Palmitoylethanolamide, in reality, appears to exert a more broad local autacoid ant injury function, thus the acronym autacoid local injury antagonism for ALIA" [34].

In the same period she proved that mast cells could be sources of the synthesis of nerve growth factor, the base of the pathological immune system-CNS crosstalk. In an authoritative review article on nerve growth factors, in TINS 1996, she already asked attention for the therapeutic potential of PEA in neuropathic pain and multiple sclerosis [34].

In that article Prof. Levi-Montalcini wrote about the functional interaction between PEA and the mast cell:

"...Unregulated mast-cell activation constitutes a considerable risk to the health of the organism, and it is not unreasonable to expect that nature should have devised a means for the host to defend itself against such damage. It has recently been proposed that saturated N-acylethanolamides like palmitoylethanolamide, which accumulate in tissues following injury and which down modulate mast-cell activation *in vitro*, exert a local, autacoid, and anti-injury function via mast cells. Palmitoylethanolamide is orally active in reducing tissue inflammation and mast cell degranulation *in vivo*, in decreasing hyperalgesia that accompanies peripheral nerve compression, and in limiting the neurological deficits of experimental allergic encephalomyelitis. Moreover, palmitoylethanolamide appears to project against excitotoxic neuronal death *in vitro* and to be produced by cultured CNS neurons upon excitatory amino acid receptor activation. The mechanism of this action of N-acylethanolamides has been termed autacoid local injury antagonism (ALIA)."

The observed pharmacological effects of palmitoylethanolamide appear to reflect the consequences of supplying the tissue with a sufficient quantity of its physiological regulator of cellular homeostasis."

And concluding and how right she was:

"Conceivably, palmitoylethanolamide and its congeners ('ALIAmides') might play a role in modulating cellular defense

mechanisms by acting at non-CB1 cannabinoid receptors. The activation of such receptors might down-modulate deleterious cellular processes following pathological events or noxious stimuli in both the immune and nervous systems....”

In 1995 pupils of Rita Levi-Montalcini suggested that anandamide and PEA shared the same CB2 receptor, based on their findings that PEA could replace the binding of the high affinity cannabinoid agonist WIN 55-212-2 on white blood cells and mast cells, while arachidonic acid and ethanolamine were not effective [41].

In line with the ALIAmide line of thinking the authors concluded their paper with:

“...palmitoylethanolamide may behave as local autacoids capable of negatively modulating mast cell activation (ALIA mechanism). In keeping with this hypothesis, palmitoylethanolamide reduces mast cell activation associated with inflammatory processes. With these considerations in mind, the described pharmacological effects of palmitoylethanolamide could be mediated by interactions with CB2 receptors on mast cells.”

Subsequent studies never replicated these findings and the documented CB2 affinity of palmitoylethanolamide was most probably due to the absence of specificity of some pharmacological tools used.

Prof. Rita Levi-Montalcini is widely known for her work on NGF. Much less is known about two other formidable chapters she added to neurobiology: the central role of the mast cell in much pathology, and the modulating role of the endogenous lipid PEA via the mast cell. Based on her work in the 90s PEA is now available as a nutraceutical for indications related to chronic pain and chronic inflammation. PEA has been explored in a variety of indications such as sciatic pain, diabetic pain, neuropathic pain, pain due to arthritis and pain in multiple sclerosis in the period 1992-2010 and around 20 clinical trials have documented its safety and efficacy in these chronic pain states [2,42]. In the period 1970-1980 its safety and efficacy was already documented in a series of double blind clinical trials in flu and respiratory infections. PEA is therefore most probably the best-documented nutraceutical around, with pharmacological profile described in more than 350 scientific papers [2,42-44].

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