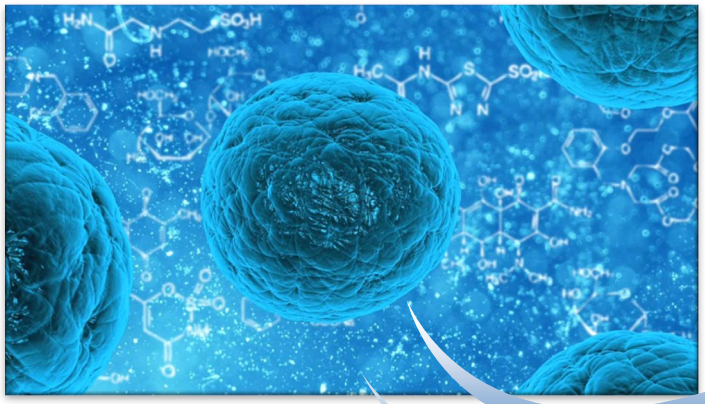
Immunity Boosting via anti-inflammatory effect: Palmitoylethanolamide (PEA)

Inflammation and Immunity

Inflammation is the first biological response – the first immune mechanism to an external aggression of physical such as injury, toxic, chemical, or biological (virus and bacteria) agents. The duration of the inflammation depends on the time that is required to eliminate these harmful causes and repair the damage. The pain that accompanies this natural process thus does not interfere with the quality of everyday life (Peritore, 2019). However, at times, inflammation becomes pathological due to an imbalance in the relationship between pro-inflammatory and anti-inflammatory mediators in a sort of adaptive mechanism to a person's permanent exposure to stress factors, attaining a stage of chronic inflammation (Graziottin et al., 2014). Chronic inflammation not only affects the infected organs, but also can be the cause of various comorbidities and disabilities. Treatment with synthetic anti-inflammatory drugs may be useful, however, routine use of such drugs poses the danger of addiction and worsening the general condition of the body. In this regard, endogenous and naturally occurring food/dietary supplements can offer an excellent alternative to the traditional drugs that can also prevent the situation from becoming chronic in the first place by boosting the overall immunity of our body.



What is Palmitoylethanolamide?

Marketed as a food supplement in the western world since 2008, Palmitoylethanolamide (PEA or N-(2-hydroxyethyl) esadecanamides) is an endogenous fatty acid amide, that via modulation of mast cells and spinal glial cells activation on peripheral and central nervous system neurons have demonstrated to be effective against various inflammatory mechanisms that develop and maintain chronic pain state (Hesselink, 2012). It is ubiquitously expressed in almost all bodily tissues and produced on-demand from cell membrane lipid-bilayer, exerting its action locally. Based on the foundation of its anti-inflammatory effects PEA is well-recognised with over 350 Papers documenting its wide range of therapeutic effects such as anti-allergic, analgesic, neuroprotective, anti-influenza and modulation of immune response in both animal and human studies (Hesselink et al., 2013). This multifaceted immune response of PEA is due to its unique mechanism of actions that targets multiple pathways at different sites, which works synergistically to produce its therapeutic effects (Petrosino, 2015). The most relevant mechanism of actions of PEA related to immunopathology are PEA's affinity toward orphan cannabinoid receptor (GPR55 and GPR11), the vanilloid receptor TRPV1 and the nuclear Peroxisome proliferator-activated receptor-α (PPAR-α) (Hesselink et al.,2013).

Discovery of PEA

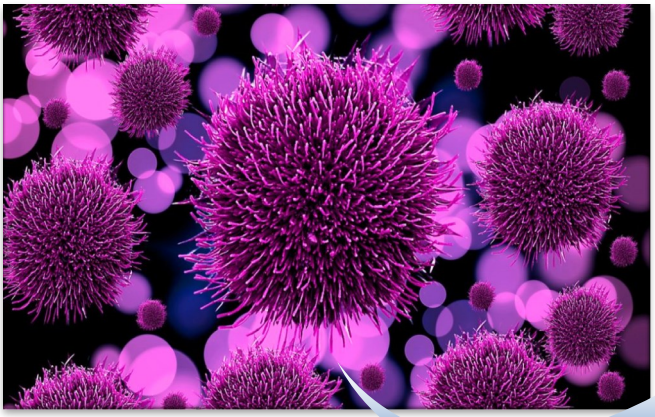
The discovery of PEA was accompanied with the discovery of its anti-inflammatory and anti-allergic properties in various infection. In the 1930s, bacteriologists Coburn and Moore found that feeding dried egg yolk to children susceptible to streptococcal infection in New York prevented the occurrence of rheumatic fever (Coburn and Moore, 1939). Subsequent investigations in 1957 into the specific anti-inflammatory compounds in egg yolk as well as soybean lecithin led to the isolation of PEA (Kuehl et al., 1957; Coburn, 1960). In the 1960s, PEA was first introduced in the market under the brand name "Impulsin" as prophylactic treatment for influenza and the common cold. In the 1970s, research into PEA's efficacy against influenza heightened with the publication of six clinical trials. These trials demonstrated and corroborated the beneficial effects of PEA on influenza symptoms and incidence of the disease. Based on previous animal Studies, it was postulated that PEA's prophylactic action was due to a nonspecific mechanism at play i.e PEA like many other lipid compounds increased our body's nonspecific resistance to bacteria and virus infection along with increase in lung macrophage activities (Kahlich et al., 1979).

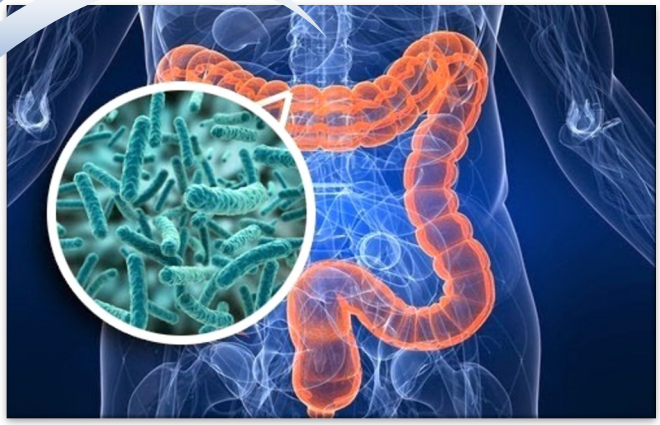
Mechanism of Action - Regulation of Macrophage and cytokines via PPAR-α

The activation of macrophage is a result of a cascade mechanism initiated by the binding of PEA to PPAR-α. More recently however, a more specific mechanism of action has been elucidated. Increased production of specific inflammatory cytokines, such as the tumor necrosis factor (TNF)-α, interleukin- (IL-) 1, IL-6, and IL-10, is characteristic during an influenza infection, resulting in a "cytokine storm" (Liu et al., 2016). The increased production of proinflammatory cytokines, hypercytokinemia, causes a state of hyper-inflammation which is the key player in the increased morbidity and mortality by influenza and other virulent infections (Bermejo-Martin et al., 2009). Initial research to elucidate PEA's mechanism of action revealed its limitation of mast cell migration and degranulation, a key first stage of the onset of inflammation. Further research has shown PEA's ability to bind to the nuclear receptor peroxisome proliferator-activated receptor-α (PPAR-α) (Hesselink, 2013). When PEA binds to this receptor in immune cells, it initiates a cascade of events which results in the reduced production of pain and inflammatory signals. To date, there are more than 60 PubMed indexed Papers discussing the anti-inflammatory activities of PEA. Its inhibitory action on TNF- α secretion is sufficiently documented (Cerrato et al., 2010). But PEA has a much wider modulating effect on interleukins. For instance, recently PEA was shown to significantly attenuate the degree of intestinal injury and inflammation and to inhibit proinflammatory cytokine production (TNF-α, IL-1β), adhesion molecules (ICAM-1, P-selectin) expression, and NF-κB expression (Di Paola et al., 2012). As PEA down modulates a number of proinflammatory cytokines, this could very well be the reason for the decreased influenza and common cold symptomatology in individuals treated with PEA.

Mechanism of Action - Mast Cell Regulation

Another mechanism of Action that concerns PEA's anti-allergic and anti-inflammatory properties is mast cell regulation as mentioned above. Mast cells play a critical role in Immune regulation and inflammation. In an in vivo study it was shown that exogenous administration of PEA attenuates intestinal radiation injury via preventing mast cell degranulation and migration (Wang et al., 2014). Therefore, PEA is likely to be highly effective in boosting our immunity against virus infection and inflammatory conditions.





PEA on Gut Microbiota - Mechanism of Action via PPAR-α

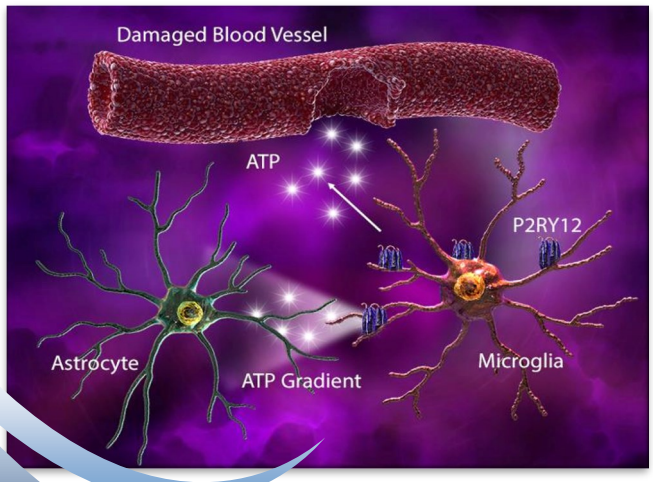
Due to the presence of PEA virtually in all the tissues of the body and its anti-inflammatory properties, PEA is an I interesting therapeutic substance which holds great promise for the symptomatic relief for a number of (auto) immune disorders concerning inflammation (Hesselink et al., 2013). Certain disorders cause prolonged inflammation of all or part of the GI tract resulting in the malfunction of Gastrointestinal organs as well as alteration in the gut microbiota. In turn, this alteration in gut microbiota could result in increased gut permeability, resulting in further inflammation and further changes to the gut microbiota. In addition to this, changes to the normal gut flora may result in opportunistic infections, further increasing inflammation (Russo et al, 2018). Exogenous administration of PEA can serve to relieve inflammatory symptoms of such disorders through its action on PPAR-α in the colon, which therefore prevents alterations of the gut microbiota as well as, prevent behavioral changes that is caused as a result of an alteration of gut microbiota. Gut microbiota are also indispensable in the development of the innate immune system and are essential in shaping adaptive immunity. Therefore, PEA is potentially a beneficial Endogenous biodome mediator that can contribute to correcting the effect of dysbiosis and shape the immune system. PEA is becoming an increasingly popular area of research in Probiotic Studies and its overall effect in strengthening the overall immunity of our body.

Mechanism of Action - Bacterial resistance through Microglial Cells Phagocytosis

PEA not only acts as a gut microbiota mediator, but also, it potentially protects our body in exogenous bacterial invasion. Prolonged chronic inflammations may predispose individuals to neurological or neurodegenerative disorders through cytokines released into the bloodstream (Russo et al, 2018).

One in vivo Study demonstrated the prophylactic efficacy of PEA in prolonging the survival rate and decreasing detrimental effect of inflammation in the absence of antibiotics in aged mice with bacterial meningitis. In the early phase of infection, PEA pre-treated mice also showed lower bacterial titers in spleen, liver and blood than control mice (Heide et al., 2018). The Study also Reports that PEA pre-treatment increased the survival rate and bacterial clearance of immunocompetent young mice challenged with E. coli (Heide et al., 2018). Studies have also shown PEA's capability to increase resistance against systemic bacterial infections in vivo (Loria et al., 2008, Ribes et al., 2010).

The ability of PEA to increase bacterial resistance can be explained by its regulation of microglia and macrophages. Microglial cells are the resident immune cells and key effectors in the resolution of Central Nervous System (CNS) infections (Mcmahon and Malcangio, 2009). They are also the professional phagocytes in the CNS, responsible for eliminating apoptotic cells, myelin debris and bacteria (Sierra et al., 2014). In vitro Studies have confirmed that PEA stimulated the phagocytosis of pathogens via macrophages and microglia. Short term exposure (30 mins) stimulates E.coli uptake in macrophages and microglia (Redlich, 2012). One Study showed that PEA was involved with Cannabinoid receptor 2 (CB2) in inducing microglia changes associated with increased migration and phagocytic activities via PPAR-α activation (Guida et al., 2017). The proposed mechanism of action is PEA's 'Entourage effect' – An increase in PEA enhances the physiological effects of endocannabinoids such as Anandamide (AEA) by preventing their enzymatic-mediated hydrolysis. This results in consequence of TRPV1 and CB2 stimulation i.e. activation of macrophages, neutrophils and other immune cells (Klein, 2005). Therefore, it is suggested that PEA may prevent some forms of brain infections and consequently, exert its immune modulatory effect in inflammatory neurodegeneration via promoting microglial phagocytosis.

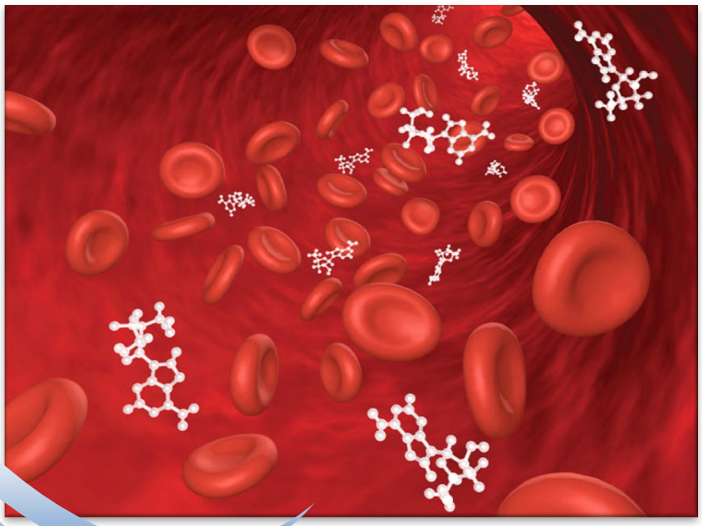


Summary

All in all, the multifaceted effects of PEA via multiple targets and the fact that PEA is a naturally occurring compound makes it a perfect candidate as an important regulator of inflammatory conditions and mediator of interactions between the nervous system, and immune system to boost the overall immunity. However, the onset of the inflammatory state causes a decrease in the production of PEA. Thus the administration of exogenous PEA can replenish endogenous levels and restore its anti-inflammatory and immuno-modulatory potential.

Overcoming Challenges

PEA, being a fatty acid derivative, has poor absorption and bioavailability in the aqueous medium of our digestive system. While literature regarding PEA's pharmacology is scarce, it has been found to be short-lasting in the body, with its levels returning to baseline just 2-3 hours after oral administration (Costa et al., 2008). Levagen+™ is a Trademark form of PEA manufactured by Gencor Pacific Limited. Using its Sister Company Pharmako Biotechnologies's LipiSperse® delivery system, Levagen+™ demonstrates increased bioavailability and format versatility, especially in liquid. LipiSperse® delivery technology reduces surface tension and eliminates the size absorption problem of PEA particles. Thus, they can freely disperse in water, have improved bioavailability and greater dose-efficacy. Our pharmacokinetics Study revealed that Levagen+™ had 1.8 times more bioavailability compared to standard PEA. Moreover, it is backed by Halal and Kosher statements from the manufacturers, non-GMO, allergen free and vegan.



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