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Harnessing the anti-inflammatory potential of palmitoylethanolamide

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Palmitoylethanolamide (PEA) is a peroxisome proliferator-activated receptor alpha (PPAR-α) ligand that exerts anti-inflammatory, analgesic and neuroprotective actions. PEA is synthetized from phospholipids through the sequential actions of *N*-acyltransferase and *N*-acylphosphatidylethanolamine-preferring phospholipase D (NAPE-PLD), and its actions are terminated by its hydrolysis by two enzymes, fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine-hydrolysing acid amidase (NAAA). Here, we review the impact of PEA administration in inflammatory and neurodegenerative settings and the differential role of FAAH and NAAA in controlling PEA levels. Recent studies with NAAA inhibitors put forth this enzyme as capable of increasing PEA levels *in vivo* in inflammatory processes, and identified it as an interesting target for drug discovery research. Thus, PEA hydrolysis inhibitors could constitute potential therapeutic alternatives in chronic inflammatory and neurodegenerative diseases.

A brief overview of *N*-palmitoylethanolamine

N-Acylethanolamines (NAEs) constitute a family of endogenous bioactive lipids implicated in the regulation of several processes, from the modulation of food intake to pain and inflammation. Perhaps the most-studied NAEs are the endocannabinoid *N*-arachidonoylethanolamine (AEA), the anorexigenic compound *N*-oleoylethanolamine (OEA) and the anti-inflammatory and/or analgesic compound PEA.

NAEs share the same biosynthetic and degradation pathways (Fig. 1). They are synthetized on demand from membrane phospholipids by the sequential actions of an *N*-acyltransferase (to generate NAPEs) and a NAPE-PLD. Their actions are terminated by their hydrolysis by two enzymes, FAAH and the more recently described NAAA [1]. FAAH and NAAA have different catalytic properties and substrate specificity [2]. FAAH is a serine hydrolase that is active at neutral and alkaline pH, and has the highest reactivity against AEA, whereas NAAA is a cysteine amidase active at acidic pH (4.5–5), inactive at alkaline pH and is more efficient at hydrolyzing PEA [2].

Despite their shared metabolic pathways, NAEs constitute a diverse set of endogenous mediators, acting at different receptors and exerting a variety of effects. For instance, AEA is an endocannabinoid, classically exerting its actions by activation of two G protein-coupled receptors (GPR), the CB_1 and CB_2 cannabinoid receptors. It is also a known ligand for the ion channel transient receptor potential vanilloid receptor (TRPV1) and the PPAR nuclear receptors. OEA is an anorexigenic compound, known to exert its actions through activation of PPAR-α, GPR119 and TRPV1. Our focus here is on PEA, which is a known anti-inflammatory compound with analgesic, neuroprotective and antiallergic properties.

The receptors mediating the effects of PEA had been elusive until recently, with increasing evidence that the anti-inflammatory and nociceptive effects of PEA are mediated, at least in part, by PPAR-α activation [3–7]. Moreover, PPAR-α expression is downregulated in inflammatory settings and restored by PEA treatment [4].

It was postulated that PEA could bind to the CB_2 receptor [8]. However, this is not the case in other studies [9,10]. In addition, although the CB_2 antagonist SR144528 prevented the antinociceptive effects of PEA [11], it did not block its anti-inflammatory effects [12,13]. One explanation of these discrepancies is the possibility that SR144528 binds to a CB_2-like receptor [11]. Another explanation is that PEA could compete with AEA for FAAH-mediated hydrolysis, thus causing an increase in AEA levels, which

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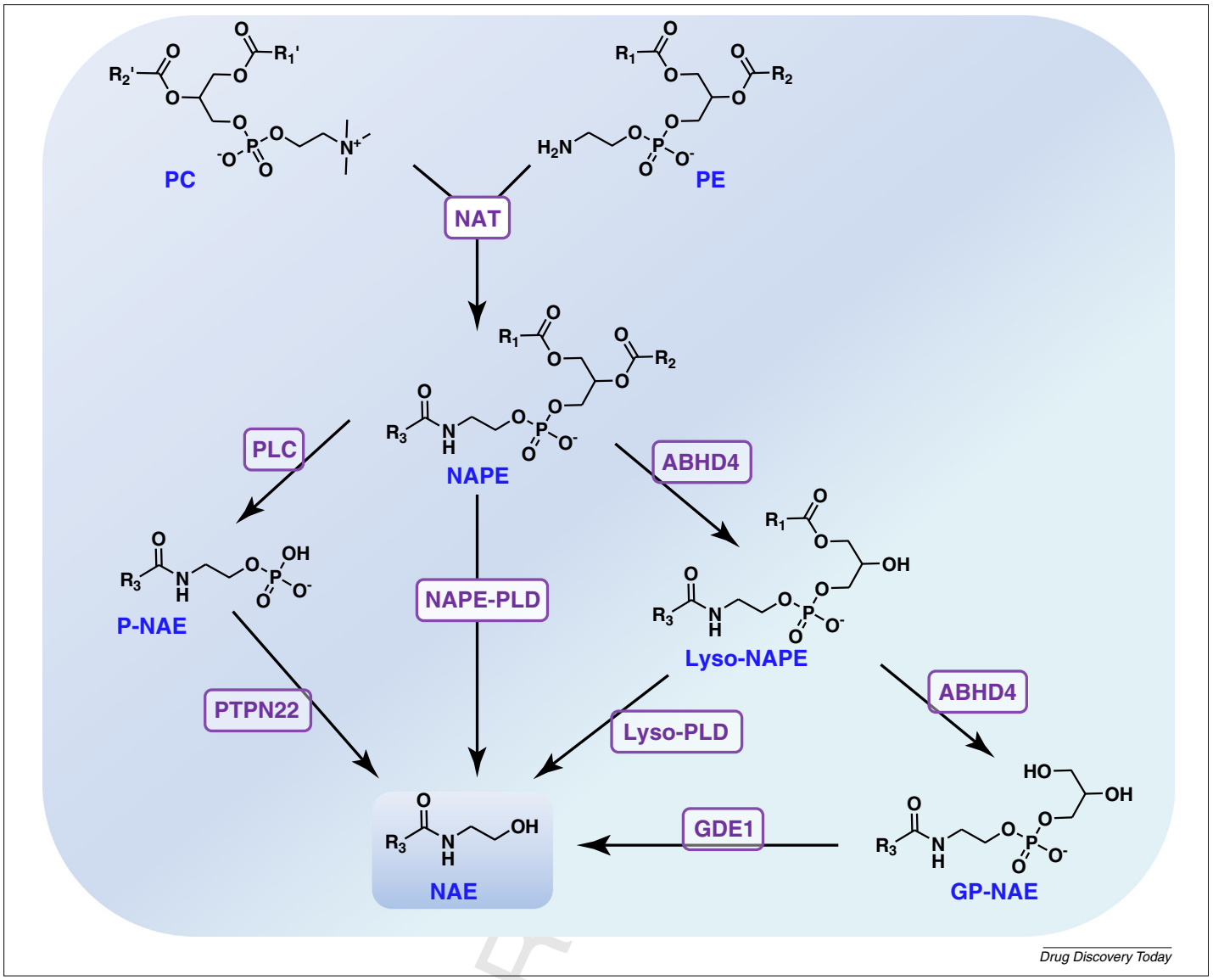

FIGURE 1

N-acylethanolamines biosynthesis. N-acylphosphatidylethanolamines (NAPE), the key precursors in the synthesis of N-acylethanolamines (NAE), are obtained from phosphatidylethanolamines (PE) and phosphatidylcholines (PC) via the action of a Ca^{2+}-dependent N-acyl transferase (NAT) [R′1 = R3]. Several routes have been described for the synthesis of NAE from NAPE. A N-acylphosphatidylethanolamine-preferring phospholipase D (NAPE-PLD) can directly release NAE from NAPE. Alternatively, phospho-N-acylethanolamine (P-NAE) can be obtained from NAPE via a phospholipase C activity (PLC), and the phosphate group subsequently removed by phosphatases, such as PTPN22. Lyso-NAPE, another intermediate in the synthesis of NAE, is obtained by the removal of one acyl chain from NAPE by the α/β-hydrolase domain 4 (ABHD4). Lyso-NAPE can be directly hydrolyzed by lyso-phospholipase D (lyso-PLD) to yield NAE, or by ABHD4 to yield a glycerophospho-N-acylethanolamine (GP-NAE), which is then converted to NAE by the glycerophosphodiesterase GDE1.

would then activate the CB_2 receptors. Moreover, PEA was shown to potentiate the affinity and potency of AEA for TRPV1. This was independent from the inhibition of its hydrolysis, because PEA was also able to potentiate the effect of low concentrations of resiniferatoxin and capsaicin, two other TRPV1 agonists [14]. This phenomenon was coined the 'entourage effect'. Interestingly, in one study, PEA administration decreased rather than increased AEA levels [3]. However, this was in an inflammatory setting and the authors did not report the effect of inflammation on AEA levels; therefore, the decrease in AEA levels could be the result of the anti-inflammatory effects of PEA.

Although it is now clear that PEA is a ligand for PPAR-α, some of its effects occur through as yet unidentified receptors. PEA was proposed as a putative ligand for the recently deorphanized GPR55 in contradicting pharmacological assays; however, there are few data so far to support this claim. In a human mastocytic cell line, HMC-1, the inhibitory effect of PEA on nerve growth factor release was abolished in the presence of GPR55 RNAi [15]. There is also evidence for an effect of PEA on cAMP accumulation in microglial cells through a $G_{i/o}$-coupled GPR, distinct from CB_1 and CB_2 [16]. Further studies are warranted for a better understanding of the receptors mediating the effects of PEA.

Impact of inflammation on PEA metabolism

Evidence suggests that PEA metabolism is disturbed during inflammation, and that a decrease in PEA levels contributes to the

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