

● PERSPECTIVE

Combining fatty acid amide hydrolase (FAAH) inhibition with peroxisome proliferator-activated receptor (PPAR) activation: a new potential multi-target therapeutic strategy for the treatment of Alzheimer's disease

Alzheimer's disease (AD) is a widespread pathology described for the first time by Alois Alzheimer in 1907. It can be classified as a neurodegenerative disease consisting in a progressive loss of memory and cognitive functions, whose prevalence is estimated to grow due to the increasing life expectancies all over the world. To date, the only treatments available for this disease are symptomatic and no actual effective cure is available. The main effect of the drugs commonly used in therapeutic protocols is to temporarily delay the onset of the disease and to slightly improve the patients' cognitive capabilities (Piemontese, 2017) (Figure 1).

The main difficulty in the development of a cure for AD is that its underlying causes are not yet clear. The general consensus on the nature of AD is that it is a multifactorial pathology, with both genetic and environmental components, and the dysregulation of many signalling and metabolic pathways seems to be involved in its pathogenesis. Another important aspect of this pathology is that the neurodegenerative processes begin much earlier than the manifestation of symptoms; because of this, treatment is usually initiated at an already too advanced state of the disease. For these reasons, multi-target agents are currently one of the main lines of research for the therapy and prevention of AD. In this context, the most common targets of recent research have been cholinesterases, monoaminoxidases,

beta-secretase and the N-methyl-D-aspartic acid receptor. Other desired effects of investigational compounds are chelation of heavy metal ions (Cu, Fe, Zn, and Al), inhibition of beta amyloid aggregation, inhibition of *tau* protein hyperphosphorylation and antioxidant activity (Hiremathad and Piemontese, 2017; Piemontese, 2017; Piemontese et al., 2018).

Unfortunately, despite numerous efforts of both public and private institutions involved in the research of new multi-functional therapeutic agents, none of the candidate drugs is even close to be introduced in therapy. The investments of pharmaceutical companies are decreasing and researchers are in urgent need to find new routes to reverse this dangerous trend.

Therefore, the design of an effective multi-target compound should consider pharmacophore groups able to simultaneously act on different targets, both established and innovative. The control of metabolism, achieved through the action of different pathways, is particularly attracting as it can result in an indirect modulation of neuroinflammation and in the inhibition of beta amyloid accumulation (Piemontese, 2019).

Following this approach, in the last decade, the cannabinoid system has been the object of growing interest for the treatment of AD. This signaling system is strongly affected by AD patients, with the cannabinoid receptor CB1 being underexpressed and CB2 being selectively expressed in the astrocytes and microglia associated with neuritic plaques. The concentrations of endocannabinoids like anandamide (N-arachidonoyl-ethanolamine) are also particularly low in the central nervous system of AD patients. This is a result of N-arachidonoyl-ethanolamine's main catabolic enzyme, fatty acid amide hydrolase (FAAH), being in turn upregulated. Accordingly, treatment with synthetic cannabinoids (mostly active on CB1, such as WIN55,212-2) and inhibitors of FAAH showed promising results in animal models of AD (Basavarajappa et al., 2017).

When compared to direct cannabimimetics, the main advantage of FAAH inhibitors is that they often allow a modulation of the endogenous cannabinoid system free of the usual psychotropic side effects commonly associated with the use of Cannabis as a recreational drug (Panlilio et al., 2013). Additionally, endocannabinoids can be considered intrinsically multi-target agents. Indeed, the cannabinoid system includes many other receptors in addition to the canonical CB1 and CB2, including peroxisome proliferator-activated receptors (PPARs) (Bedse et al., 2015; Fernández-Ruiz et al., 2015). PPARs are a class of metabolic receptors, activated by saturated and unsaturated fatty acids, comprising subtypes PPAR α , PPAR γ and PPAR δ (Piemontese et al., 2015, 2018); in the central nervous system their activation exerts neurotrophic and anti-inflammatory effects and it has been shown to decrease the rate of deposition of beta amyloid protein aggregates (Bedse et al., 2015; Fernández-Ruiz et al., 2015; Agarwal et al., 2017; Piemontese, 2017). Other than N-arachidonoyl-ethanolamine, FAAH also hydrolyzes other endocannabinoid-like amides, known as N-acyl-ethanolamines, such as N-oleoyl-ethanolamine and N-palmitoyl-ethanolamine. These compounds are not properly endocannabinoids, as their activity on the CB receptors has not been proven; on the other hand, they are active as PPAR α (N-palmitoyl-ethanolamine and N-oleoyl-ethanolamine) and PPAR δ (N-oleoyl-ethanolamine) agonists (Panlilio et al., 2013).

PPAR agonists have different effects depending on the specific target subtype: PPAR α agonists, such as fibrates, are hypolipidemic agents that have been used for the therapy of dyslipidemias and obesity, while PPAR γ agonists, namely thiazolidinediones,

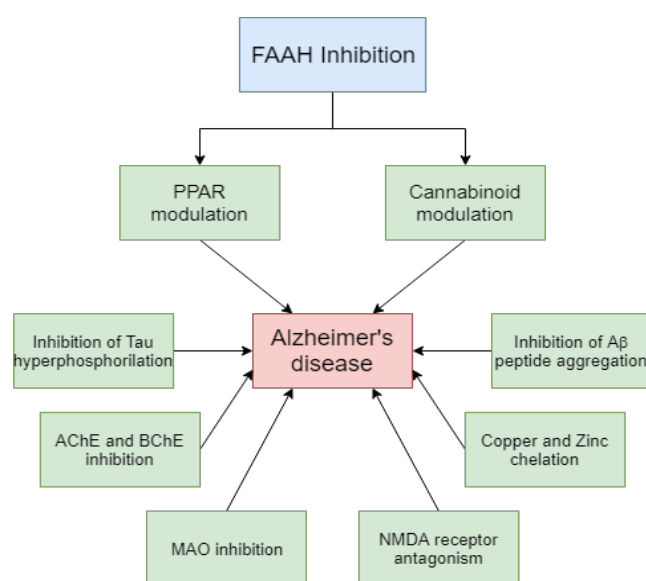


Figure 1 Fatty acid amide hydrolase (FAAH) inhibition in the context of Alzheimer's disease therapy.

A β : Beta amyloid; AChE: acetylcholinesterase; BChE: butyrylcholinesterase.

have been used as insulin sensitizers in the therapy of type 2 diabetes mellitus (Piemontese, 2017), although their therapeutic use is somewhat limited by the undesired side effects of full PPAR γ agonism such as weight gain and bone fragility. In the recent years, researchers have been focusing on the synthesis and optimization of PPAR α/γ dual agonists, PPAR $\alpha/\gamma/\delta$ pan-agonists, or even selective PPAR modulators capable of showing a different activity profile characterized by gene and tissue selective effects (Piemontese et al., 2015, 2017).

Moreover, it was recently proposed that insulin resistance localized in the central nervous system might figure among the various pathogenic factors that contribute to the development of AD. The molecular causes of this can be found in the regulation of the *tau* gene, mediated by insulin and insulin-like growth factor signalling cascades. At the same time, type 2 diabetes mellitus seems linked to cognitive impairment, with improved cognitive performance in experimental models and even humans with AD after treatment with insulin sensitizers. These results are corroborated by epidemiologic evidence of significant associations between type 2 diabetes mellitus and AD; obesity seems similarly linked to AD (Agarwal et al., 2017; Piemontese, 2019). A logical conclusion to this is that antidiabetic and anti-obesity agents, such as PPAR agonists, could aid in the therapy of AD or at least lower its incidence in obese or diabetic patients treated with them (Piemontese, 2019).

In addition to this, a body of experimental evidence supports the idea that N-acyl-ethanolamines, acting via both canonical CB receptors and PPARs, can control the activity of various signalling pathways, like mitogen-activated protein kinase, nuclear factor- κ B, Notch1 and Wnt/ β -cat, through which they reduce neuroinflammation, hinder the formation of beta amyloid plaques and neurofibrillary tangles, resulting in an improvement of synaptic structure, synaptic plasticity and learning and memory deficits (Bedse et al., 2015; Fernández-Ruiz et al., 2015). From this point of view, dual acting compounds, active as inhibitors of FAAH and agonists of PPAR α/γ (or even PPAR pan-agonists) could emulate and enhance the effects of endogenous N-acyl-ethanolamines by optimizing the existing synergies between the effects mediated by CBRs and those mediated by PPAR activation. The potential of such an activity profile was explored a few years ago, and there is a remarkable possibility of synergy between the two signalling systems. However, a class of compounds capable of exploiting this synergy has yet to be found and studied (Panlilio et al., 2013).

At the same time, targeting an amide hydrolase which is greatly overexpressed in the AD patient's brain could also be a solution to finally achieve centrally active PPAR agonists via pro-drug design. To this day, most known PPAR agonists are either acids or strongly polar molecules, a fact that severely hinders their capability to cross the blood-brain barrier. This novel approach was successfully put into practice by Meinig et al. (2017), who synthesized primary and secondary amides of thyromimetic Sobetirone ("sobetiramides") that could cross the blood-brain barrier and were then metabolized to their acidic, active form by FAAH. Various known PPAR agonists show some structural similarity to Sobetirone and can be classified as 2-substituted phenoxyacetic acids, the main difference being some degree of steric hindrance on the alpha position of the carboxylic group (Piemontese et al., 2017). Therefore, the design of amides of these PPAR agonists could be an effective strategy to obtain central nervous system-directed pro-drugs of these compounds.

In light of these observations, the design and investigation

of novel candidate drugs with this pharmacological profile is a promising, yet unexplored, line of research that could yield very fascinating results in the coming years.

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