● REVIEW

An innovative approach for the treatment of Alzheimer's disease: the role of peroxisome proliferator-activated receptors and their ligands in development of alternative therapeutic interventions

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Abstract

Alzheimer's disease is a multifactorial pathology, for which no cure is currently available. Nowadays, researchers are moving towards a new hypothesis of the onset of the illness, linking it to a metabolic impairment. This innovative approach will lead to the identification of new targets for the preparation of new effective drugs. Peroxisome proliferator-activated receptors and their ligands are the ideal candidates to reach the necessary breakthrough to defeat this complicate disease.

Key Words: *Alzheimer's disease; multifunctional drugs; peroxisome proliferator-activated receptors; type 3 diabetes; innovative therapies; type 2 diabetes mellitus; metabolism; neuroinflammation*

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Alzheimer's disease (AD) is one of the main socioeconomic problem in the Western countries, when we consider the growth of the incidence of the pathology (mainly due to the increasing of life expectancy) and the high costs related to drugs and assistance for the National Health Systems (Piemontese, 2017).

At the present time, only a limited number of drugs are available for AD therapy; unfortunately, these molecules are just able to temporary improving the cognitive ability of the patients (Piemontese, 2017). The main issue in the research of new routes for the treatment of this disease is a deeper understanding of its pathogenesis and onset. This could be the expected breakthrough in order to direct the physicians to new and relevant drug strategies, able to combat the pathology.

To date, the most common theory followed by the scientists to clarify the AD are the cholinergic and the amyloid hypotheses (Orhan and Senol, 2016; Piemontese, 2017).

The impairment of cholinergic neurons and the subsequent loss of acetylcholine activity, indeed, is commonly linked with AD onset. Therefore, the acetylcholinesterase was the first target to be investigated for the treatment of the pathology and, as a consequence, four up the five internationally approved drugs against AD (namely tacrine, donepezil, galantamine and rivastigmine) are inhibitors of this enzyme. Recently, it was demonstrated that butyrylcholinesterase as well plays an important role in cholinergic neurotransmission, in particular in normal central nervous system, and several studies suggest that a non-selective cholinesterase inhibitor should lead to better clinical results (Daoud et al., 2018).

The acetylcholinesterase seems to play a role in the deposition of β-amyloid peptides (Aβ) in the extracellular environment of brain in AD patients as well (Daoud et al., 2018). The Aβ are produced by cleavage operated by proteolitic enzymes such as β- and γ-secretase from the membrane-anchored β-amyloid precursor protein. They are neurotoxic themselves and are also involved in the formation of amyloid plaques. Heavy metals such as copper (II), and zinc (II) are in general included in the structures of these complexes (Piemontese, 2017; Chaves et al., 2018). The Aβ toxicity seems to begin outside the cells and end inside them, through the production of oxygen radicals, lipid peroxidation, increasing intracellular calcium levels, mitochondrial dysfunction, and neuronal inflammation (Rivera et al., 2018). New effective drugs will be useful in fighting the accumulation of these aggregates through inhibition of the formation (using metal chelators (Piemontese, 2017; Chaves et al., 2018) as well as blocking the action of secretases)

and the removal of the complexes already present in the extra-synaptic environment.

In the last decade, even if numerous industries funded researches in this important field, very few new entities joined the clinical trial steps, but they failed to be introduced in therapy. But, as assumed above, it is widely recognized that the only possibility for researchers to reach new goals is to better the knowledge of the pathology, assuming that it is probably due to a multi-factorial origin (Piemontese, 2017). Recently, a new perspective about AD is taking hold, starting from the analysis of different studies reporting several pathophysiological changes, such as particular signalling pathways, neuronal stress signalling and inflammatory pathways that are strictly linked to both type 2 diabetes mellitus (T2DM) and AD (Kandimalla et al., 2017).

T2DM is a chronic pathology, characterized by hyperglycaemia and insulin resistance (reduced sensitivity to insulin of metabolic active tissues) (Fracchiolla et al., 2012; Laghezza et al., 2015; Piemontese et al., 2015; Kandimalla et al., 2017). There are numerous features connected with AD that are frequently found in T2DM patients: both pathologies can show insulin resistance and a modification of the insulin growth factor and glycogen synthase kinase 3β signalling mechanism (Kandimalla et al., 2017). Furthermore, an abnormal inflammatory response joined with oxidative stress prove common in either conditions, as well as changes in acetylcholinesterase activity regulation, and increasing in formation of Aβ and neurofibrillary tangles. Therefore, several researchers designed the particular co-occurrence of these conditions as type 3 diabetes (Kandimalla et al., 2017).

The insulin resistance and the unavailability of glucose in neurons leads to a lack in the energy production and a subsequent cognitive loss. Therefore, an impaired glucose metabolism can be strictly linked with AD, at least as an additional risk factor for the development of the pathology (Kandimalla et al., 2017). As a matter of fact, it can lead to typical pathological features of neurodegenerative diseases, such as insoluble the accumulation of extracellular plaques and/or intracellular neurofibrillary tangles, loss of hippocampal neurons (linked to memory defeat), and decrease in acetylcholine system regulation (Correia et al., 2012; Kandimalla et al., 2017).

Considering these findings, the use of anti-diabetic agents may prove an innovative approach for the treatment of neurodegenerative disease (Piemontese, 2017). Consequently, peroxisome proliferator-activated receptors (PPARs), have been recently been identified as innovative targets in the research of new active

drugs for AD. There are three different subtypes of these nuclear receptors, namely PPARα, PPARβ/δ, and PPARγ, that are expressed in all the districts of the organism, including central nervous system (Laghezza et al., 2015; Piemontese, 2017). Classical drugs that are known to activate PPARs are fibrates and glitazones (Fracchiolla et al., 2012; Laghezza et al., 2015; Piemontese, 2017). These molecules have been used over the years in the therapies of atherosclerosis and diabetes, and many efforts have been made in the last twenty years with the aim of obtaining a single ligand able of acting on hyperlipidemia and T2DM through the synthesis of dual PPARα/γ- or pan-agonists (Fracchiolla et al., 2012; Piemontese et al., 2015).

Numerous recent studies highlighted the involvement of PPARs at the onset of neurodegenerative diseases (Agarwal et al., 2017). In particular, PPARα expression levels have been reported to significantly decline during the aging process (Cheng et al., 2015). The administration of PPARα agonists increases the expression of the receptor, thereby contributing to the prevention of the apoptotic signals induced by Aβ toxicity, which is, in turn, strictly linked to the neuronal degeneration due to the pathways involving pro-apoptotic proteins apoptosis-inducing factor and Endo G from mitochondria (Cheng et al., 2015; Hiremathad and Piemontese, 2017). The activation of PPARγ, instead, seems to enhance the degradation of Aβ by microglia, and to inhibit pro-inflammatory gene expression. This subtype is also responsible for the anti-inflammatory action, which inhibits the microglial activation and reduces the expression of pro-inflammatory mediators (Yamanaka et al., 2012; Hiremathad and Piemontese, 2017).

The role played by PPARs on the regulation of the TOMM40-ApoE-C1 genes cluster is also very important. The overexpression of certain types of ApoE, indeed, seems to increase a person's risk of developing AD (Subramanian et al., 2017). Finally, PPARs are able to restore the impaired blood-brain barrier function in AD patients, and to balance the energy status in the brain through regulation of metabolic pathways of lipids and glucides (Zolezzi and Inestrosa, 2013; Agarwal et al., 2017).

For these reasons, the preparation of new small molecules able to suitably modulate PPAR activity can be useful to further investigate the important role played by these receptors as new therapeutic targets for AD, as already experimented in the recent past with only a few natural and synthetic molecules (Agarwal et al., 2017; Godoy et al., 2017; Hiremathad and Piemontese, 2017; Wang et al., 2017). The modulation of these receptors and the relative influence

on the regulated pathways is for sure an important alternative for the preparation of multi-target derivatives (Hiremathad and Piemontese, 2017; Piemontese, 2017). Moreover, the possibility for patients to be treated with anti-diabetics already in therapy is for sure very attractive as well. Several of these drugs, such as pioglitazone or insulin itself, are already studied in clinical trials (Cummings et al., 2017) but we cannot yet predict if and when they can be used in AD therapy.

The comprehension of new disease modifiable risk factors connected with AD is critical in the development of alternative therapeutic interventions (Kandimalla et al., 2017). In particular, this innovative approach, in which the metabolic control results in an indirect control of neuroinflammation and in the inhibition of Aβ accumulation, could really be the breakthrough that we were waiting for.

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