● PERSPECTIVE

New approaches for prevention and treatment of Alzheimer's disease: a fascinating challenge

The prevention and treatment of neurodegenerative diseases is the new challenge for pharmaceutical industry, but also for public institutions, physicians, patients, and their families. The spread of these pathologies is, in fact, a real social problem, especially in the Western Countries where the population age is increasing and chronic diseases are more and more common. For several of these pathologies, only few drugs have been available for therapies over the years. Alzheimer's disease (AD), for instance, has only five "symptomatic" approved drugs: four of them (tacrine, donepezil, rivastigmine, galantamine) are acetylcholinesterase inhibitors, while memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist (Santos et al., 2016). These molecules are able to delay the onset of the disease for a few years and, if administered in time, can improve cognitive abilities of the patients. Unfortunately, nothing more seems useful at the moment. So, it is urgent to find new ways for the treatment of this wide number of patients, in order to limit the high costs of public health systems and alleviate the suffering of the families.

AD is widely recognized as a multifactorial disease. For this reason, the multiple origin of the pathology suggests that a possible solution to win the battle against this kind of dementia is to use a multi-target therapy. This particular approach is based on the use of multifunctional molecules designed to act simultaneously on at least two disease targets (and for this reason known as "multi-target directed ligands"), with the aim to achieve synergistic actions and, in this way, better therapeutic efficacy (Santos et al., 2016; Chaves et al., 2017). On the basis of past studies and considering the drugs already used in therapy, the most investigated targets are inhibition of acetylcholinesterase, chelation of copper, iron and/or zinc cations, antioxidant activity, inhibition of Abeta amyloid plaques aggregation, monoaminoxidase (MAO) enzymes inhibition, and NMDA receptor antagonism (Santos et al., 2016).

Recently, several studies have proved that the modulation of particular molecular pathways may also be a winning approach against the neurodegenerative disorders in general. In particular, the reduction of chronic inflammation by peroxisome proliferator-activated receptor (PPAR) agonists may represent a strategy to protect neuronal cells that are compromised in these diseases. In addition, the metabolic properties of PPARs are well known in many physiological situations including those related to the central nervous system. In fact, these receptors are able to reduce the Abeta induced neurotoxicity and regulate the normal function of blood-brain barrier, acting, under several pathological conditions typical of AD, in order to restore its impaired functions. The PPAR-gamma receptor subtype is also able to balance the energy status in the brain of AD patients by the maintenance of the content of lipids and carbohydrates in neuronal cells (Agarwal et al., 2017).

The classical drugs that act through PPAR activation are fibrates (PPARα agonists) and glitazones (PPARγ agonists) and are used in the therapies of atherosclerosis and diabetes, respectively. In the last ten years, in order to identify new structures with improved therapeutic activity and less side-effects, many studies have been addressed to the preparation and characterization of new synthetic molecules able to activate more PPAR subtypes (PPAR dual agonists and/or pan-agonists) and to selectively modulate them (SPPARMs), and innovative and low-cost techniques for fast high throughput preliminary screenings have been developed with very interesting results (Fracchiolla et al., 2012; Temporini et al., 2013; Laghezza et al., 2015; Piemontese et al., 2015). The further optimization of these ligands can lead to the introduction of innovative therapeutic protocols in which only one drug instead of the classical cocktail of molecules will be administered for the treatment of hyperglycaemia, dyslipidaemia and related inflammatory diseases. This novelty surely will meet the compliance of millions of patients (Fracchiolla et al., 2012; Laghezza et al., 2015; Piemontese et al., 2015).

The fascinating possibility to introduce PPAR ligands in the therapies for the treatment of neurodegenerative disease also will encourage the researchers to design and synthesize new potential drugs. However, these new molecules need to be designed in order to be able to pass the blood-brain barrier (*i.e.*, molecular weight < 500 Da and low polarity) and have pharmacological activity in the central nervous system.

Recently, resveratrol and other polyphenols were also demonstrated to interact with PPAR receptors modulating their activities (Piemontese, 2017). Therefore, it is conceivable that in the next years, the possibility of the use of natural molecules that combine PPARs agonism with neuronal cell protection activity will appear more and more attractive. In fact, polyphenols derived from plants (but also several molecules with similar chemical properties can be products of the metabolism of fungi) may also prevent the damage of the neuronal cells in an indirect way: in particular, some natural derivatives present a metal chelating action and could be able to significantly reduce the aggregation of Abeta amyloid plaques and, consequently, the formation of reactive oxygen species (ROS), that are typical, for instance, of the first stages of AD. The mechanism by which this goal is achieved could be explained by the removal and/or redistribution of metal ions (copper, zinc, and iron cations) at the level of the nervous system operated by che-

lators (Habtemariam, 2016). Other molecules, in turn, could simply act as antioxidant and counteract in this way the action of ROS. In the future, these natural compounds could be extracted and used as food supplement to support traditional therapies for neurodegenerative diseases (Piemontese, 2017).

However, improving the diet with consuming healthy food that contain bioactive substances, such as polyphenols, is in itself a good habit that should be encouraged. So, patients, families, physicians, institutions have to work in next years in order to promote a better way to choose the food that people eat. This virtuous circle will involve food industry as well. The growing interest in emphasizing the quality and the effectiveness of antioxidant products needs, however, be joined to a strict monitoring of these foods as they may contain natural or synthetic contaminants, such as mycotoxins, pesticides, and heavy metals (Solfrizzo et al., 2015; Zivoli et al., 2016; Piemontese et al., 2017). In the last years, many researches have been performed in order to discover new and safer analytical methods with the aim to control both raw materials and final products. Many studies about the exposure of people to food contaminants have been reported as well (Solfrizzo et al., 2015; Zivoli et al., 2016; Piemontese, 2017; Piemontese et al., 2017). We are on the way, but it is important stay on the guard.

Natural molecules can also be an inspiration, as common in the history of pharmaceutical chemistry, for the design of new drugs. Or they can be used as precious starting material for the preparation of new, promising molecules. This semi-synthetic approach, joined to the above described multi-target strategy can prove to be the key to improving the results achieved to date. Too many years have passed since the approval of the last active drug in the treatment of AD. And people cannot wait longer.

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