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Alzheimer's Congress 2018: Novel therapeutic strategies for alzheimer's disease: Neurotrophy and neurorestoration

Jun Liu

Sun Yat-sen University, China

Alzheimer's Disease (AD) is a neurodegenerative disorder mainly characterized by β-amyloid deposit, τ-hyperphosphorylation and neuron loss with no curative treatments. In recent years, the main efforts of multinational pharmaceutical companies have been focused on reducing the aggregation of Aβ and τ-proteins but with repeated defeats. According to statistics of Adis R&D, between 1998 and 2014, major pharmaceutical companies launched a total of 123 drugs for AD but only three drugs and one combination therapy program have been approved by the FDA. However, without exception, none of these 123 drugs can cure AD and even delay the progression of the disease. So we should shift our focus from alleviating the AD-like pathologies to neuroprotection, which means the preservation of neuronal structure and/or function. As far as we know, there are some therapeutic strategies of neuroprotection for AD, such as the application of NMDA receptor antagonists, Acetylcholinesterase Inhibitors (ACEIs), anti-inflammatory agents, antioxidants, neurotrophins and Chinese medicine and so on. Our research group has found that neurotropin (a non-protein bioactive agent extracted from rabbit inflamed skins inoculated with Vaccinia virus vaccine), GQDG (Graphene Quantum Dot Conjugated with neuroprotective peptide-glycine-proline-glutamate), edaravone, EGb761 (Ginkgo Biloba extract) and β-sitosterol exerted potent neuroprotective effects in AD. In conclusion, a single cure for AD is unlikely to be found and multi-target therapies should be addressed.

Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. The huge variety of neurodegenerative diseases, in terms of pathological characteristics, symptoms, and treatments, makes it very difficult to classify them in general terms. Taking into account the different neurodegenerative diseases, one of the parameters we can considerer is prevalence. According to this, there are two most prevalent neurodegenerative diseases: Alzheimer's disease (AD) and Parkinson's disease (PD). This affirmation is substantiated in the literature. In 2015, there were 46.8 million AD patients worldwide with direct and indirect costs to society of 81,800 million USD, and in 2016 there were 6.1 million individuals with PD worldwide. Dementia is a major symptom of AD, consisting of memory impairment accompanied by dysfunction, which is responsible for the inability to develop daily life activities. Vascular dementia is quite important since it is considered the second most common cause of dementia in the aging population and also is thought to underlie AD. This disorder consists of a decline in cognitive skills caused by blocking or reduction of blood flow to the brain. On the other hand, PD is characterized by motor symptoms such as bradykinesia/akinesia, resting tremor, rigidity, and postural abnormalities, and non-motor symptoms such as dementia, hyposmia, depression, and emotional changes.

Behavioral and psychological symptoms of dementia (BPSD) represent neuropsychiatric symptoms occurring in subjects with dementia. They are clinically relevant as cognitive symptoms as they strongly correlate with the degree of functional and cognitive impairment. BPSD include anxiety, elation, hallucinations, agitation, irritability, abnormal motor behavior, apathy, depression, and sleep or appetite changes.

Although some of these BPSDs could be alleviated by the use of atypical antipsychotics, these compounds have been described to induce clinically significant metabolic adverse events, increasing mortality in patients with dementia.

Despite the high prevalence of these diseases, the treatments available today are not able to significantly modify the progress of the disease, since these treatments only treat the symptoms of it. A substantial part of traditional treatments for neurodegenerative diseases including AD, cerebral amyloid angiopathy, frontotemporal dementia, mild cognitive impairment, and PD are based on immunotherapy, most of them active and passive immunotherapy trials conducted based on amyloid, tau, and α-synuclein targeting.

ome other studies have suggested the use of small molecules for AD treatment, able to cross the BBB, like statins. These include simvastatin, a HMG-CoA reductase inhibitor, approved by FDA for the treatment of hypercholesterolemia and diabetic cardiomyopathy. In that sense retrospective clinical studies directed by Wolozin and colleagues, demonstrated a significant reduction (at least 50%) in the risk incidence of suffering AD and PD after simvastatin administration. Now, research is focusing on finding new disease-modifying therapies to slow disease progression.

Better understanding of the triggering factors involved in the onset and progression of the disorders are crucial for developing novel therapies. The main characteristic of these diseases is the existence of two subtypes: Familial and idiopathic forms. The familial form, which an average of 5% of patients will develop before 65 years of age, is associated with various genetic mutations. The idiopathic form of the disease, which accounts for 95% of cases, is associated with aging and has some other unrevealed risk factors.

In the case of AD, the familial form is caused by mutations of genes coding for amyloid precursor protein (APP), presenilin-1 (PSEN-1), and presenilin-2 (PSEN-2). In familial PD, there is a longer list of related gene mutations, for example, α-synuclein (SNCA), Leucine-rich repeat kinase 2 (LRRK2), PTEN induced kinase 1 (PINK1), ATPase cation transporting 13A2 (ATP13A2), and other genes, like PARK. The importance of identifying and understanding the roles of these genes in the underlining pathological mechanism could reveal new therapeutic approaches.

Foot Note: This work is partly presented at 10th World Congress on Alzheimer's Disease & Dementia, May 30-31, 2018 Osaka, Japan