Editorial: Experimental and Innovative Approaches to Multi-Target Treatment of Parkinson's and Alzheimer's Diseases

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Editorial on the Research Topic

Experimental and Innovative Approaches to Multi-Target Treatment of Parkinson's and Alzheimer's Diseases

Alzheimer's disease (AD) and Parkinson's disease (PD) are incurable and the most common neurodegenerative disorders. Current methods for AD and PD treatment are mostly symptomatic, while a new effective pathogenesis-relevant therapy that would block the disease course and restore all the compromised functions is demanded. AD and PD pathogeneses are largely associated with the accumulation of neurotoxic protein aggregates in the brain, i.e. toxic forms of amyloid-beta (Aβ), alpha-synuclein, and tau protein (Selkoe and Hardy, 2016; Rocha et al., 2018). Hence, enhancing the pathological protein elimination has attracted increasing attention. In June 2021, the FDA approved the drug Aducanumab (brand name-Aduhelm) based on a monoclonal antibody against amyloid. However, the introduction of this drug into widespread clinical practice raises certain skepticism (Knopman and Perlmutter, 2021), mainly due to the uncertain therapeutic effect or clinical benefit. There is also a concern about targeting amyloid or alpha-synuclein directly since Aβ precursor protein and alpha-synuclein are both involved in normal physiological function (Dawkins and Small, 2014; Nellikka et al., 2021) and thus their content should not fall below the critical level. Failure of clinical trials of "Aβ-oriented" drugs may also be related to their use at the late stages of AD, whereas these agents could be effective when pathological aggregation of Aβ just begins preceding the initial signs of cognitive impairment in patients for at least 10–20 years (Frozza et al., 2018). Moreover, neurodegenerative disorders have a multifactorial etiology and involve various pathological processes in addition to neurotoxicity of protein aggregates, such as oxidative stress, neuro-inflammatory response, disturbed neurotrophic function and neurogenesis, synaptic and neurotransmission dysfunction, ion disbalance, etc. that often closely interact and overlap. Therefore, researchers develop multipurpose drug combinations (combination-drugs-multi-targets, CDMT) that do not cause adverse side effects (Sahoo et al., 2018). Multipurpose therapy aimed at various important pathogenetic hubs is a novel trend regarded as a promising strategy for AD and PD therapy.

Currently, a number of research teams work within the CDMT strategy. For example, a recent study from Japan reported on the prevention of neurodegenerative dementia by intranasal rifampicin and resveratrol combination in mice (Umeda et al., 2021). Series of studies revealed that

antibiotic drug ceftriaxone within a strategy of drug reprofiling produces neuroprotective effects both in AD and PD models through suppressing the glutamate-induced excitotoxicity, modulating the expression of genes related to Aβ metabolism, enhancing neurogenesis, attenuating neuro-inflammatory response, and recovery of neuronal density (Ho et al., 2014; Weng et al., 2016; Tikhonova et al., 2017, 2018). Moreover, a combination of ceftriaxone with erythropoietin allowed reducing the dosage of ceftriaxone by 20 times with maintained efficiency in a PD model (Huang et al., 2015). Finally, the promising results of clinical trials of phase III in China of GV−971 for treating people with mild to moderate AD were reported recently (Xiao et al., 2021). GV-971 is an oligosaccharide derived from marine organisms that affects such pathogenetic mechanisms of AD development as inhibition of Aβ fibril formation, neuroinflammation, and recondition of dysbiosis of gut microbiota (Martins et al., 2020; Ettcheto et al., 2021).

The aim of this Research Topic was to provide an updated overview on the approach of multi-targeted therapy for AD and PD and related issues. Several research groups contributed interesting points of view on this subject and elucidated important current aspects of the problem.

The central theme of the Topic is masterly illustrated by Reich and Hölscher who provided an accurate review of acylated ghrelin as a multi-targeted therapy for AD and PD. The review illustrates the wide-ranging neuroprotective properties of the acylated form of the hormone ghrelin and discusses its potential to ameliorate pathologic changes occurring in AD and PD as well as complications of long-term treatment with the drug.

Tikhonova et al. contributed an original work in which multiple neuroprotective effects of antibiotic ceftriaxone against AD-like pathology are discussed, mainly focusing on mechanisms related to Aβ burden and neuro-inflammatory response.

Komleva et al. reviewed the pathological role of inflamm-aging, brain insulin resistance, and their cross-talk in aging and neurodegeneration. The review summarizes current knowledge on immunosenescence, inflamm-aging, and metainflammation and discusses potential mechanisms of calorie restriction as multi-purpose approach that may effectively break the vicious cycle of metainflammation, improve insulin resistance and slow the onset of neurodegeneration.

Studies on PD have mostly focused on processes and targets in the central nervous system. In clinical practice, neuromodulation techniques such as deep brain stimulation (DBS) are applied to control drug-resistant symptoms of PD. In a case report by Chang et al., a method of bilateral globus pallidus interna (GPi) combined with subthalamic nucleus (STN) variable frequency DBS (bSGC-DBS) implantation was introduced. The case of a young-onset PD patient with refractory dyskinesia explores multi-electrode and multi-target stimulation for the treatment of dystonia disorders.

On the other hand, a review by Ma et al. emphasizes the importance of the peripheral nervous system (PNS) in

PD pathology. The paper discusses the use of pathological changes in PNS for clinical diagnosis of PD as well as the application of PNS targets for PD therapy, namely Schwann cell transplantation in the treatment of PD animal models is described. Wichit et al. contributed an original clinical work in which monoamine levels in peripheral body fluids were analyzed in association with clinical profiles in PD patients. The paper points to the involvement of several neurotransmission systems in PD pathology. An original research article by Seo and Yeo focuses on the alterations in muscle proteins that could impair muscle function and add to the bradykinesia and tremor in a pharmacological 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD.

Two groups contributed original research papers on the effects of electroacupuncture in mouse AD models and discussed underlying mechanisms. Xu et al. focused on the regulation of phospho-tau and glucose metabolism associated with the Akt/GSK3β signaling pathway while Xie et al. concentrated on M2 microglia polarization and glia anti-inflammation.

And last but not least, Ahanger et al. reviewed the role of monosodium glutamate in protein aggregation through a biophysical approach and discussed its potential impact on neurodegeneration.

Taken together, the papers collected in this Issue present the most recent knowledge and experimental evidence about the multi-target approach for therapy of neurodegenerative disorders and offer a new perspective and interesting hypotheses on this topic.

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REFERENCES

Dawkins, E., and Small, D. H. (2014). Insights into the physiological function of the beta-amyloid precursor protein: beyond Alzheimer's disease. *J. Neurochem.* 129, 756–769. doi: 10.1111/jnc.12675

Ettcheto, M., Busquets, O., Cano, A., Sanchez-Lopez, E., Manzine, P. R., Espinosa-Jimenez, T., et al. (2021). Pharmacological Strategies to Improve Dendritic Spines in Alzheimer's Disease. *J. Alzheimers Dis.* 82, S91–S107. doi: 10.3233/JAD-201106

Frozza, R. L., Lourenco, M. V., and De Felice, F. G. (2018). Challenges for Alzheimer's disease therapy: insights from novel mechanisms beyond memory defects. *Front. Neurosci.* 12, 37. doi: 10.3389/fnins.2018.00037

Ho, S. C., Hsu, C. C., Pawlak, C. R., Tikhonova, M. A., Lai, T. J., Amstislavskaya, T. G., et al. (2014). Effects of ceftriaxone on the behavioral and neuronal changes in an MPTP-induced Parkinson's disease rat model. *Behav. Brain Res.* 268, 177–184. doi: 10.1016/j.bbr.2014.04.022

Huang, C. K., Chang, Y. T., Amstislavskaya, T. G., Tikhonova, M. A., Lin, C. L., Hung, C. S., et al. (2015). Synergistic effects of ceftriaxone and erythropoietin on neuronal and behavioral deficits in an MPTP-induced animal model of Parkinson's disease dementia. *Behav. Brain Res.* 294, 198–207. doi: 10.1016/j.bbr.2015.08.011

Knopman, D. S., and Perlmutter, J. S. (2021). Prescribing aducanumab in the face of meager efficacy and real risks. *Neurology* 97, 545–547. doi: 10.1212/WNL.0000000000012452

Martins, M., Silva, R., M, M.M. P., and Sousa, E. (2020). Marine natural products, multitarget therapy and repurposed agents in Alzheimer's disease. *Pharmaceuticals.* 13. doi: 10.3390/ph13090242

Nellikka, R. K., Bhaskar, B. R., Sanghrajka, K., Patil, S. S., and Das, D. (2021). alpha-Synuclein kinetically regulates the nascent fusion pore dynamics. *Proc. Natl. Acad. Sci. U S A* 118. doi: 10.1073/pnas.2021742118

Rocha, E. M., De Miranda, B., and Sanders, L. H. (2018). Alpha-synuclein: pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. *Neurobiol. Dis.* 109, 249–257. doi: 10.1016/j.nbd.2017.04.004

Sahoo, A. K., Dandapat, J., Dash, U. C., and Kanhar, S. (2018). Features and outcomes of drugs for combination therapy as multi-targets strategy to combat Alzheimer's disease. *J. Ethnopharmacol.* 215, 42–73. doi: 10.1016/j.jep.2017.12.015

Selkoe, D. J., and Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol. Med.* 8, 595–608. doi: 10.15252/emmm.201606210

Tikhonova, M. A., Amstislavskaya, T. G., Belichenko, V. M., Fedoseeva, L. A., Kovalenko, S. P., Pisareva, E. E., et al. (2018). Modulation of the expression of genes related to the system of amyloid-beta metabolism in the brain as a novel mechanism of ceftriaxone neuroprotective properties. *BMC Neurosci.* 19, 13. doi: 10.1186/s12868-018-0412-5

Tikhonova, M. A., Ho, S. C., Akopyan, A. A., Kolosova, N. G., Weng, J. C., Meng, W. Y., et al. (2017). Neuroprotective effects of ceftriaxone treatment on cognitive and neuronal deficits in a rat model of accelerated senescence. *Behav. Brain Res.* 330, 8–16. doi: 10.1016/j.bbr.2017.05.002

Umeda, T., Sakai, A., Shigemori, K., Yokota, A., Kumagai, T., and Tomiyama, T. (2021). Oligomer-targeting prevention of neurodegenerative dementia by intranasal rifampicin and resveratrol combination - a preclinical study in model mice. *Front. Neurosci.* 15, 763476. doi: 10.3389/fnins.2021.763476

Weng, J. C., Tikhonova, M. A., Chen, J. H., Shen, M. S., Meng, W. Y., Chang, Y. T., et al. (2016). Ceftriaxone prevents the neurodegeneration and decreased neurogenesis seen in a Parkinson's disease rat model: an immunohistochemical and MRI study. *Behav. Brain Res.* 305, 126–139. doi: 10.1016/j.bbr.2016.02.034

Xiao, S., Chan, P., Wang, T., Hong, Z., Wang, S., Kuang, W., et al. (2021). A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia. *Alzheimers Res. Ther.* 13, 62. doi: 10.1186/s13195-021-00795-7