EDITORIAL

Pharmacological Approaches Targeting Brain Cell Survival in the Context of Neurodegeneration and Potential Treatment Strategies

The decline in both antioxidants defense and aging per se is associated with an increased risk of cognitive impairment, chronic brain damages, that outcome of which manifests as a neurodegeneration. Based on the recent reports neurodegenerative diseases affect more than 100 million worldwide and cause significant economical and personal stress, and require long-term cost effective care. The main motives and key driving horse in the field of neurodegenerative research fields, is the desire for solutions to the ravages of CNS diseases especially Alzheimer's, Parkinson's (respectively AD and PD), and others. An importance topic to address is the use of neuropharmacological-driven approaches that could attenuate neuroinflammatory processes in the diseased brain, and improve the outcome. In this special issue for *Current Neuropharmacology*, contributors discuss a variety of experimental and clinical approaches including the development and delivery of the novel central nervous system agents, gene therapies, and drug- and cell-based strategies, as well as micro RNA therapeutics. All of the treatments target CNS cellular compartment mechanisms and/or the mediators leading to neurodegenerative diseases *in vivo* and/or cytotoxicity *in vitro* as well. These downstream mechanisms include activation of pro and/or anti-inflammatory signaling cascades, production of oxygen, nitric oxide (including nitric oxide oxidation products such as nitrite and nitrate contain reactive species), excitatory mediators and amino acids, and downregulation of growth factors that may lead to the development of neuronal injuries. Thus, this special issue focuses on up-to-date research targeting these pathways and mediators upon CNS damage and potential drug targets.

Pouran Makhdomi and coworkers reported the molecular mechanism of aniline induced spleen and neuronal toxicity in experimental rat exposure. It has been reported that the aniline exposure leads to neuron and spleen toxicity specifically and makes diverse neurological effects and sarcoma that is defined by splenomegaly, hyperplasia, and fibrosis and tumors formation at the end. However, the molecular mechanism(s) of aniline-induced spleen toxicity is not fully understood, and previous studies have represented that aniline exposure results in iron overload and initiation of oxidative/nitrosative disorder stress and oxidative damage to proteins, lipids and DNA subsequently, in the spleen. Elevated expression of cyclins, cyclin-dependent kinases (CDKs) and phosphorylation of pRB protein along with increases in A, B and CDK1 as cell cycle regulatory proteins cyclins, and reduction in CDK inhibitors (p21 and p27) could be critical in cell cycle regulation, which contribute to tumorigenic response after aniline exposure. Critical analysis of the literature showed that the aniline-induced splenic toxicity is correlated to oxidative DNA damage and initiation of DNA glycosylases expression (OGG1, NEIL1/2, NTH1, APE1 and PNK) for removal of oxidative DNA lesions in rat. Oxidative stress causes transcriptional up-regulation of fibrogenic/inflammatory factors (cytokines, IL-1, IL-6 and TNF- α) via induction of nuclear factor-kappa B, AP-1 and redox-sensitive transcription factors, in aniline treated-rats. The upstream signaling events as phosphorylation of I κ B kinases (IKK α and IKK β) and mitogen-activated protein kinases (MAPKs) could potentially be the causes of activation of NF- κ B and AP-1. All of these events could initiate a fibrogenic and/or tumorigenic response in the spleen. Based on the authors' interpretation, most likely the spleen toxicity of aniline is studied more and the different mechanisms are suggested. This review summarizes those events following aniline exposure that induces spleen toxicity and neurotoxicity.

Muneeb U Rehman and coworkers reported recent literature evidence regarding implication of natural products as neuro-protective strategies for neurological disorders. It has been well documented and reported that the natural products have a significant role in the prevention of disease and boosting of health in humans and animals. These natural products have been experimentally documented to possess various biological properties such as antioxidant, anti-inflammatory and anti-apoptotic activities. *In vitro* and *in vivo* studies have further established the usefulness of natural products in various preclinical models of neurodegenerative disorders. Natural products include phytoconstituents, like polyphenolic antioxidants, found in herbs, fruits, nuts, vegetables and also in marine and fresh water flora. These phytoconstituents may potentially suppress neurodegeneration and improve memory as well as cognitive functions of the brain. Also, they are known to play a pivotal role in the prevention and cure of different neurodegenerative diseases, such as AD, epilepsy, PD and other. The large scale neuro-pharmacological activities of natural products have been documented which are due to be the result of either inhibition of inflammatory processes, and/or the up-regulation of various cell survival proteins and/or combination of both. Due to the scarcity of human studies on neuroprotective effects of natural products, this review focuses on the various established activities of natural products in *in vitro* and *in vivo* preclinical models, and their potential neurotherapeutic applications using the available knowledge in the literature.

Studies by Faheem Hyder Pottoo and coworkers discussed the mechanism of the estrogen and serotonin: complexity of interactions and potential implications for epileptic seizures and epileptogenesis. Based on this report, burgeoning literature documents, the confluence of ovarian steroids and central serotonergic systems in the injunction of epileptic seizures and epileptogenesis. In addition, estrogen administration in animals reduces neuronal death from seizures by up regulation of the pro-survival molecule *i.e.* Bcl-2, anti-oxidant potential and protection of NPY interneurons. Serotonin modulates epileptiform activity in either direction *i.e.* administration of 5-HT agonists or reuptake of inhibitors leads to the activation of 5-HT₃ and 5-HT_{1A} receptors tending to impede focal and generalized seizures, while depletion of brain 5-HT along with the destruction of serotonergic terminals leads to expanded neuronal excitability hence abatement of seizure threshold in experimental animal models. Serotonergic neurotransmission is influenced by the organizational activity of steroid hormones in the growing brain and the actuation effects of steroids which come in adulthood. It is further established that ovarian steroids bring induction of dendritic spine proliferation on serotonin neurons thus thawing a profound effect on serotonergic transmission. This review features 5-HT_{1A} and 5-HT₃ receptors as potential targets for ameliorating seizure induced neurodegeneration and recurrent hypersynchronous neuronal activity. Indeed 5-HT₃ receptors mediate cross talk between estrogenic and serotonergic pathways, and could well be exploited for combinatorial drug therapy against epileptogenesis.

Ylia A. Sidorova and coworkers reported the pathophysiology of potential implication of small molecules as a new treatment option for PD. PD is the second most common neurodegenerative disorder worldwide, the lifetime risk of developing this disease is 1.5%. Motor diagnostic symptoms of PD are caused by degeneration of nigrostriatal dopamine neurons. Unfortunately there is no effective treatment for PD and current therapy is limited to supportive care that partially alleviates disease signs and symptoms. As diagnostic symptoms of PD result from progressive degeneration of dopaminergic neurons, drugs restoring these neurons may significantly improve the treatment of PD. A literature search performed by Ylia A. Sidorova *et al.*, using the PubMed, Web of Science and Scopus databases discussed the progress achieved in the development of neurodegenerative agents for PD. Papers published before early 2018 were taken into account. Based on this study, there are several groups of potential agents capable of protecting and restoring dopamine neurons *in vitro* cell cultures as well as animal models that mimic PD including neurotrophic factors and small molecular weight compounds. Based on this very careful analysis, authors' conclusion is that in the promising results of *in vitro* and *in vivo* experiments, none of the found agents have yet shown conclusive neurorestorative properties in PD patients. Meanwhile, a few promising biological and small molecules have been identified. Their further clinical development can eventually give rise to disease-modifying drugs for PD.

Dr. Iván Carrera and Professor Ramon Cacabelos report demonstrates the current drugs and potential future neuroprotective compounds in the context of PD. Unfortunately, the progress made so far in understanding the etiology and pathogenesis of PD has only achieved the development of some clinical approaches intended to treat cognitive and behavioral symptoms such as memory and perception disorders. Despite the major advances in different genetic causes and risk factors for PD, which share common pathways to cell dysfunction and death, there is not yet a complete model of PD that can be used to accurately predict the effect of drugs on disease progression. In addition, clinical trials are also important to test any novel neuroprotective agent, and recently there have been great advances in the use of anti-inflammatory drugs and plant flavonoid antioxidants to protect against specific neuronal degeneration and its interference with lipid and cholesterol metabolism. The increasing knowledge of the molecular events underlying the degenerative process of PD has stimulated research to identify natural compounds capable of halting or slowing the progress of neural deterioration. Polyphenols and flavonoids, which play a neuroprotective role in a wide array of *in vitro* and *in vivo* models of neurological disorders, emerged from the multi-target bio-agents found mainly in plants and microorganisms. This review presents a detailed overview of the multimodal activities of neuroprotective bio-agents tested so far, emphasizing their neurorescue/neuroregenerative activity. The brain-penetrating property of bio-agents may make these compounds an important class of natural drugs for the treatment of neurodegenerative diseases. Although there are numerous studies demonstrating beneficial effects in the laboratory by identifying critical molecular targets, the clinical efficacy of these neuroprotective treatments remains to be proven accurately.

Mahmood Ahmad Khan and coauthors analyzed the current progress on peroxisome proliferator-activated receptor gamma agonist as an emerging therapeutic approach for the treatment of AD. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors known to play an important role in the regulation of glucose absorption, homeostasis of lipid metabolism and further involved in repressing the expression of genes related to inflammation. Thus, agonists of this receptor represent an attractive therapeutic target for AD. In recent, both clinical and preclinical studies show that in use of Peroxisome proliferator-activated receptor gamma (PPAR γ) agonist improves both learning and memory along with other AD related pathology. Thus, PPAR γ signifies a significant new therapeutic target in treating AD. This review has shed

some light on the recent progress of how, PPAR γ agonist selectively modulates different cellular targets in AD and its potential in the future treatment of AD.

Professor Gjumrakch Aliev research team first time critically analyzed potential implication of dendrimers based therapy for AD. AD is characterized by the loss of neurons in different brain regions. It is the most common cause of dementia in the elderly population accompanied by pathological degeneration of the neurons and formation of neurofibrillary tangles (NFT). Senile plaques are formed with amyloid-beta ($A\beta$), hyperphosphorylated tau protein, apolipoprotein E and presenilin associated with protease activity [$A\beta$, gamma-secretase (γS)]. The molecular mechanisms of neurodegeneration most likely include but not limited to apoptosis, oxidative stress (free radical generation that follows the cellular and subcellular damage), inflammation, immune activation, and others. The lack of effective treatments for AD stems mainly from the incomplete understanding of causes of AD. Currently, there are several hypotheses explaining the early mechanisms of AD pathogenesis. Recent years witnessed an unprecedented research growth in the area of nanotechnology, which uses atomic, molecular and macromolecular methods to create products in microscale (nanoscale) dimensions. This review articles has discussed the role of nanotechnology in the development and improvement of techniques for early diagnosis and effective treatment of AD. Moreover, since AD pathology is practically irreversible, applications of disease-modifying treatments could be successful only if early diagnosis of AD is available. This review first time highlights various possibilities for the early diagnosis and therapy of AD, and investigates potential adaptation of nanoparticles-dendrimers, a class of well-defined branched polymers, chemically synthesized with a well-defined shape, size and nanoscopic physicochemical properties reminiscent of the proteins for the treatment of neurodegenerative diseases including AD, PD and many others.

I am confident that review articles which are included in this special issue provide not only new knowledge that also to the pathophysiological hallmarks of the different cellular compartment of the brain in the course of neurodegeneration, but eventually also provide new research direction regarding the treatment of CNS disorders in general.

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