BIBLIOGRAPHIC INFORMATION SYSTEM

Journal Full Title: Journal of Biomedical Research & Environmental Sciences

Journal NLM Abbreviation: J Biomed Res Environ Sci

Journal Website Link: https://www.jelsciences.com

Journal ISSN: 2766-2276

Category: Multidisciplinary

Subject Areas: Medicine Group, Biology Group, General, Environmental Sciences

Topics Summation: 128

Issue Regularity: Monthly

Review Process: Double Blind

Time to Publication: 21 Days

Indexing catalog: Visit here

Publication fee catalog: Visit here

DOI: 10.37871 (CrossRef)

Plagiarism detection software: iThenticate

Managing entity: USA

Language: English

Research work collecting capability: Worldwide

Organized by: SciRes Literature LLC

IndexCopernicus ICV 2020: 53.77

Manuscript should be submitted in Word Document (.doc or .docx) through

Online Submission

form or can be mailed to support@jelsciences.com

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JOURNAL OF BIOMEDICAL RESEARCH & ENVIRONMENTAL SCIENCES
issn: 2766-2276
SUBJECT AREA(S): PARKINSONS DISEASE | BRAIN DISORDERS | NEUROLOGICAL DISORDERS | NEUROLOGY
DOI: 10.37871

REVIEW ARTICLE

Parkinson's Disease-Like Neuropathology and Phenotype Following Induction of Oxidative Stress and Inflammation in the Brain

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ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative disorder characterized by motor deficits caused by the loss of dopaminergic neurons in the Substantia Nigra (SN) and Ventral Tegmental Area (VTA). However, clinical data revealed that not only the dopaminergic system is affected in PD. Pharmacological models support the concept that modification of noradrenergic transmission can influence the PD-like phenotype induced by neurotoxins. Exposure to ambient pollutants such as air pollutants also can be adversely impacted the Central Nervous System (CNS) by the activation of proinflammatory pathways and reactive oxygen species. Thus, targeting neuroinflammation and oxidative stress can be a useful strategy to eliminate the obvious symptoms of neurodegeneration. Overall, in the current mini-review, we examined the neuroprotective role of noradrenaline in the model of oxidative stress and neuroinflammation.

INTRODUCTION

Air pollution and other ambient pollutants exposure can be adversely impacted the Central Nervous System (CNS) by the activation of proinflammatory pathways and reactive oxygen species. It is estimated that 20-70 % of urban air pollutants are resulting from traffic combustion [1-3] and 85% of Particulate Matter (PM) in urban areas is related to traffic [4]. New evidence suggests that air pollution exposure has been known as one of the main sources of neuroinflammation and oxidative stress, causing CNS and neuropathology disease [5-7]. Activation of ROS and pro-inflammatory pathways by PM is thought to elicit maladaptive responses that can in turn adversely impact organ function and the CNS also isn't immune to air pollution impact [5,8,9]. There are several pathways via which can be transmitted inflammatory signals from environment to brain [6], so in people exposed to urban air pollutants, activation of the peripheral immune system may lead to neuroinflammation [10]. Neuroinflammatory reactions are triggered by oxidative stress, cytokines, and chemokines and can lead to impaired neurotransmitter and neurotrophin signaling disorders, abnormal protein accumulation, neurodegeneration, and neuronal remodeling [11]. Prolonged exposure to these pollutants may lead to an increase in the inflammatory markers upregulation and exacerbate previous neurodegenerative disorders [12-15]. In addition, new findings support the involvement of neuroinflammation in the pathogenesis of emotional and cognitive disorders [16,17]. Neurodegenerative Diseases (NDs) pose a greater risk to humans, more precisely to the elderly population [18], and according to

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DOI: 10.37871/jbres1408

Submitted: 24 January 2022

Accepted: 29 January 2022

Published: 31 January 2022

Keywords

- Parkinson's disease
- Neurotoxins
- Neurodegeneration
- Neuroinflammation
- Noradrenergic system

MEDICINE GROUP

PARKINSONS DISEASE | BRAIN DISORDERS | NEUROLOGICAL DISORDERS | NEUROLOGY

VOLUME: 3 ISSUE: 1 - JANUARY, 2022

How to cite this article: Ehsanifar M, Montazeri Z. Parkinson's Disease-Like Neuropathology and Phenotype Following Induction of Oxidative Stress and Inflammation in the Brain. J Biomed Res Environ Sci. 2022 Jan 31; 3(1): 105-110. doi: 10.37871/jbres1408, Article ID: JBRES1408, Available at: https://www.jelsciences.com/articles/jbres1408.pdf

the WHO, it will overtake cancer in the next 20 years [19]. These diseases include a number of neurological disorders characterized by a diverse array of pathophysiology and are associated with cognitive impairment and/or mobility impairment [20]. It includes a wide range of disorders, the two most common of which are Parkinson's Disease (PD) and Alzheimer's Sisease (AD) [21,22]. Neurodegenerative diseases are common to many of the major processes associated with dysfunction and neuronal death, including oxidative stress and the formation of free radicals, neuroinflammation, protein folding and malformation, bioenergy disorders, and mitochondrial dysfunction [23]. PD, the second most common neurodegenerative disorder, is characterized by increased production of oxygen free radicals leading to alterations of the cellular constituents and subsequent loss of dopamine and dopaminergic neurons, which are directly responsible for the disease symptomatology (bradykinesia, tremor, rigidity, impaired posture and balance) [24]. Most cases (up to 90%) have a sporadic occurrence, and even for cases in which genetic factors have been identified, distinct molecular pathways leading to eventual and inevitable cell death are unclear. As a result, existing therapies are currently based on the symptoms of the disease, and although they do reduce the usual symptoms to some extent, they do not restore neuronal function or prevent neuronal loss. An important factor that significantly reduces therapeutic efforts is that dopaminergic neuron degradation begins long before the first clinical signs appear, and even rapid diagnosis at this stage does not allow effective treatment, because most cells have already disappeared [25]. Although historically the hallmarks of PD have been related to the degeneration of the Substantia Nigra (SN) and Ventral Tegmental Area (VTA), it has recently become widely accepted that damage to other brain areas precedes the cell loss of SN/VTA neurons, making PD-related neurodegeneration a multi-stage process [26,27]. The extranigral structures involved in PD also include the noradrenergic system [28].

Noradrenaline role in parkinson's disease

Noradrenaline is one of the most important neurotransmitters in the central nervous system, and predictions of noradrenergic neurons originating from the Locus Coeruleus (LC) permeate almost all brain structures. In addition, degeneration of noradrenergic neurons in the LC region is more pronounced in patients with PD and exacerbates the loss of dopaminergic neurons in the SN [29,30]. These findings were underscored in a recent study, which suggested that PD could not be considered a mere dopaminergic neuronal disease [31]. In addition, LC integration is a useful indicator in PD clinical trials to classify patients for clinical trials due to their noradrenergic dysfunction [32]. In fact, PD patients are characterized by the following: reduction of LC MRI contrast limited to the middle and caudal region of this structure, downregulation of Norepinephrine Transporter (NET) density, and loss of the noradrenergic terminal [33]. Studies on animal models are scarce, but support the statement that modification of noradrenergic transmission could affect the basic PD-like phenotype observed in models of pharmacological PD rodents. For example, loss of noradrenaline can worsen the degradation of nigrostriatal dopamine induced by 6-Hydroxy Dopamine (6-OHDA). Conversely, an enhanced level of noradrenaline may have a neuroprotective effect in mice subjected to 1- Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) [34,35]. These results prompt the hypothesis that noradrenergic degradation may be thought of as a prodromal phase of PD that progresses in six neuropathological stages and eventually reaches a threshold responsible for symptoms directly related to profound loss of SN / VTA dopaminergic cells [26]. Recently, it has also been suggested in non-human primates that severe degeneration of ascending noradrenergic protrusions may contribute to dysfunction of the dopaminergic cell groups of the ventral midbrain and subthalamic nuclei neurons observed in PD [36]. Although there is widespread evidence for the effects of noradrenaline on different populations of dopamine neurons in the midbrain, these interactions have not been fully elucidated and this topic has not been studied in PD-related research that focuses primarily on dopamine and dopaminergic systems. As our previous results demonstrated the beneficial effects of noradrenergic system stimulation in a conditional model of progressive Parkinsonism [37], we investigated whether decreased noradrenaline levels lead to early signs of dopaminergic neuron degeneration in SN / VTA. Following that hypothesis, we suggest that an approach focused on studying the long-term effects of noradrenergic degeneration may help elucidate the pathophysiological changes that occur in the pre-symptomatic phase of PD.

Noradrenergic and dopaminergic systems

Although the noradrenergic and dopaminergic systems of the CNS have different characteristics, they are physiologically and functionally having close relationships that can overlap and complement each other. Therefore, abnormalities in these systems can also be closely related to the pathogenesis of many neurodegenerative diseases. Noradrenaline was suggested as a compensatory mechanism in dopaminergic neuronal degradation of PD [28]. Accordingly, a genetic model of PD mice showed that noradrenaline levels were directly related to the loss of dopaminergic cells [38]. Similarly, in a pharmacological PD model, the interrelationships between the two systems were confirmed in a recent study that described the degeneration of LC neurons mediated through NLPR3 inflammation-dependent microglial activation [39]. Understanding the noradrenergic/dopaminergic interaction, especially the modulatory effects of LC-controlled noradrenergic neurotransmission on dopaminergic neurons, may benefit the early diagnosis of the prodromal phase of PD and potential preventive treatment. Neuroinflammation associated with microglial activation and increased reactive gliosis is typical

of neurodegenerative disorders including PD [40]. Human tissues after death from patients suffering from PD but also Huntington's Disease (HD), Alzheimer's Disease (AD), and amyotrophic lateral sclerosis showed reactive astrocytes accompanied by reactive microglia in vulnerable areas [41]. The imbalance between the noradrenergic and dopaminergic systems can directly trigger neuroinflammation and early signs of neurodegeneration. Noradrenergic neurons may affect the wellbeing of dopaminergic neurons, by the induction of inflammatory processes.

Glial activation and neuroinflammation

Glial activation, the release of proinflammatory cytokines, and astrocytic dysfunction have been suggested at the source of the neuroinflammatory process [42,43]. Although inflammation may be the result of persistent neuronal cell death in PD, α-Synuclein may misfold cause glial activation [44]. One of the potential physiological roles of noradrenaline is to protect neurons by inhibiting glial activation and subsequent release of pro-inflammatory factors [45]. This is partly due to the nature of about half of the LC axon terminals that do not form the classical synapses: noradrenaline escapes to the synaptic cleft and reaches adrenergic receptors on glial cells [46], which express all functional adrenergic receptors (α1-, α2-, β1- and β2-ARs) [47]. In addition, laboratory studies have shown that noradrenaline protection measures, at least in part, are due to their ability to weaken the activation of microglia [48] and astrocytes [49]. Noradrenaline deficiency and its modulatory functions may exacerbate glial functions loss. Inflammation was also observed in previous models based on the induction of nuclear stress in other neural populations [50]. Failure to induction of inflammatory cytokines (such as IL-6, IL-1β, or TNFα) may indicate that degeneration of noradrenergic neurons results in a weak inflammatory state, which activates also neuroprotective events such as increased IL-10 expression, probably leads to reduce IL-6 levels. IL-10 is a highly potent anti-inflammatory cytokine that plays an important role in the prevention of inflammatory and autoimmune pathologies [51], and a recent study noted its specific role in PD [52]. That is, heterozygous M83$^{+/-}$ transgenic mice expressing the mutant human A53T α-synuclein under the control of the mouse prion protein promoter, primed with IL-10 and next seeded with preformed α-synuclein fibrils had shorter lifespan or presented exaggerated αSyn pathology [52]. The opposite results were obtained by preconditioning IL-6, which improved the outcome of induced synucleinopathy in mice [53]. Both metalloproteinases have been reported to be neuroprotective in AD or multiple sclerosis [54]. The MMP-3, MMP1 or MMP-9 metalloproteinases, which are prone to inhibition by TIMP1/2, appear to be involved in the pathogenesis of PD as shown in vitro studies on neurotoxic animal models of PD or postmortem tissue of PD patients [55,56]. Also, increasing IL-13 levels can contribute to the death of dopaminergic neurons because activation of the IL-13Rα1 receptor increases their vulnerability to oxidative damage [57,58]. The role of obvious apoptosis-related transcripts like Casp9 (caspase 9) in neurodegeneration is well documented [59]. Enhanced transcription of Sgk1 (Serum/Glucocorticoid Related Kinase 1) is upregulated in the brains of PD patients [60]. Another upregulated transcript is Sparc (Secreted Protein Acidic and Cysteine-Rich) which has been reported to be expressed differently in Parkinson's LRRK2-derived astrocytes from iPSC [61]. An interesting example is the Eukaryotic Initiation Factor 3 (Eif3), one of the most complex factors in translation initiation, which is crucial in ribosomal turnover in translational processes [62]. In addition to reboxetine [37], mirtazapine, a noradrenergic and serotonergic antidepressant drug, was shown to have therapeutic potency in classic pharmacological models of PD: MPTP-treated mice [63] and 6-OHDA- injected mice [64]. Atomoxetine, a noradrenaline transporter blocker, reduces dopaminergic neuronal damage, reduces microglial activation in SN / VTA, and promotes functional improvement of motor defects in the PD model of inflammatory lipopolysaccharide mice [65]. In addition to β2-AR mediating mechanisms, noradrenaline can affect inflammation by suppressing superoxide produced by NADPH oxidase [45]. In contrast, reduction of noradrenaline through pharmacological lesions degenerates dopaminergic neurons in the midbrain by promoting inflammation, reducing neurotrophic factor release, and promoting oxidation in the SN [66,67]. On the other hand, it has also been confirmed that combined noradrenergic and dopaminergic pharmacological lesions lead to more severe motor and non-motor behavioral impairments by increasing neuroinflammation and promoting neuronal death [68].

Disruption of the nucleolar structure and function impair ribosome biogenesis and triggers the so-called nucleolar stress response [69,70], which induces cell death [71]. Nucleolar stress is common in neurodegenerative diseases [72,73]. Dopaminergic neurons in PD patients show impaired nuclear integrity [74]. The notion that nuclear stress may monitor the early stages of the disease is supported by the similar redistribution of B23 (NPM1) found in the progressive HD model of mice and in skeletal muscle sampling of early HD patients [75].

CONCLUSION

Neuronal damage following genetic disorders as well as exposure to chemicals and drugs or environmental contaminants activates proinflammatory cytokines, mainly associated with oxidative stress, and can affect the Central Nervous System (CNS) by activating pro-inflammatory and reactive oxygen species pathways are negatively affected. Glial activation and the effects of oxidative stress on SN / VTA neurons stem directly from the state of gradually dying noradrenergic cells and their loss of function, including the secretory function of noradrenaline. Mechanisms observed before degeneration of the dopamine system may have the potential for early detection of PD. Limiting

mutations to central noradrenergic neurons allows focusing on the description of long-term functional changes in the dopaminergic system, which should be considered. In addition, such a model should allow the testing of potential neuroprotective drugs, which reverse the onset of dopaminergic neuronal degradation. Extensive results may provide an opportunity to anticipate new strategies for drug development. Overall, new evidence that the noradrenergic system controls the function of dopaminergic neurons and homeostasis may open up new avenues for research into the causes of early PD onset.

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How to cite this article: Ehsanifar M, Montazeri Z. Parkinson's Disease-Like Neuropathology and Phenotype Following Induction of Oxidative Stress and Inflammation in the Brain. J Biomed Res Environ Sci. 2022 Jan 31; 3(1): 105-110. doi: 10.37871/jbres1408, Article ID: JBRES1408, Available at: https://www.jelsciences.com/articles/jbres1408.pdf