Neuroinflammation in parkinson’s disease: literature reviews examples

Science, Genetics

Its role in Microglia causing dopamine cell death

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Introduction

The list of prominent neurodegenerative disorders has Alzheimer’s at the topmost level and closely following it is the Parkinson’s disease. The latest researches pertaining to the Parkinson’s pathogenesis have narrowed down to the crucial relevance of Neuroinflammation and establishment of microglia. Thus there has to be a concrete substantiation to prove that Neuroinflammation has a significant contribution in causing Parkinson’s disease and other neurodegenerative diseases. Another approach to ratify the same can be done by proposing that genetic deficiency is not the sole cause for reduction of neural protective factors, thereby keeping a check over the microglia or controlling the sensitivity of the Dopamine neurons. However, if persistent inflammation is accounted for reducing the general levels of neuroprotective factors, it can be further deduced that the genetic insufficiency of neural defensive factors such as RGS10 can also be an aftereffect of only environmental cause like aging, persistent systemic disease, etc.

Thus even the environmental triggers can result in raising the susceptibility to the dopamine neuron death and they also affect the patient’s medical stature towards developing the Parkinson’s disease. However, the latest studies in field of Parkinson’s disease have testified epidemiology related facts over possible use of anti-inflammatory and immune-modulating drugs which are rather used as neuroprotective agents for evading nigrostriatal

deterioration and consequently leading to the motor functioning issues in Parkinson’s disease.

Literature review

A wide range of neurally deteriorating diseases , when coupled along with the aging phenomena, are often found connected with persistent inflammation. This list of diseases include the Alzheimer’s disease , Amyotrophic Sclerosis , Parkinson’s disease, amyotrophic sclerosis, and age oriented muscular deterioration (Block and Hong, pp. 58). The Parkinson’s ailment is among the most prominent neuro-degenerative ailments (Schepira, pp. 56). As it is age oriented sickness, often witnessed by emergent shivering, delayed motor motions, positional unsteadiness and clogged muscles (Gelb et al., pp. 36). The movement lag indications are medically curable with use of dopamine affecting medicines, on the other hand, the movement efficiency gradually diminishes along with rising clinical symptoms, owing to evolution of the primary neurodegeneration (Schapira, pp. 45). Further studies have worked in field of analyzing the factors that cause drastic loss in dopamine neurons . The majority of above stated clinical aspects are the cause for rigorous fall in dopamine neurons at the Substantia Nigra region and cause occurrence of proteinaceous substance termed as the Lewy molecules (mainly made up of fibre α-synucleine) and the generic proteins inside a few residual nigral neurons (Lees et al., pp. 2056). However, there is still a dispute regarding the Lewy bodies’s direct involvement into dopamine neuronal death or in possibly seizing tiny neurotoxic protein clusters to protect the neural feasibility (Goldberg and

Lansbury, pp. 115). The recent studies have acknowledged the transfromation in genes associated with the most uncommon innate forms of Parkinson’s. These studies have further led to assumption that such mutations endorse additional arrangement of generalised protein system and cause the failure of nigral structures . The above deductions are successfully retrieved even though the precise molecule oriented mechanisms are indistinct and the clinical testing in case of human models enduring these mutations is extremely changeable (Bonifati, Lim and Ng, pp. 1707). The survival of continuing inflammatory mechanisms that can add to development of Parkinson’s Disease, is based on substantiation of developing microglia, gathering of cytokines, initiation of the nuclear factor pathway , and oxidative harm to proteins in the brains of Parkinson’s patients, which can also be apparent in post-mortem Parkinson’s Disease brains at autopsy (McGeer et al., pp. 222) and even in most of the experimental models of diagnosis of Parkinson’s Disease (Czlonkowska , Kohutnicka , Kurkoswa , pp . 142).

Summary

The studies in field of Parkinson’s causes and role of chronic neural inflammation in case of mocroglia development in dopamine cell death have drawn a gamut of definite and still explicable set of conclusions. Even though the main molecular and cellular process which cause the evolution of these neurodegenerative diseases are obviously differing, there has to be a common determinant to track these molecular or cellular process, like those of neural transformation, oxidation, truncation, or protinaceous aggregation.

Hence all of above factors cumulatively cause the death of neurons via development of inhabitant microglial growths in definite brain segments. If the preliminary trigger that initiated microglia development is not sorted and cured, similar to that of a genetic alteration or a protracted environmental exposure with immunological slur. Consequently, a self- supported chain of neuroinflammation can result in such a chronic inflammatory environment, which can incite neuronal dysfunction and ultimate death of susceptible dopamine cellular populations.

As a result, well-timed liberation of anti-inflammatory routine in patients, who are recognized to be prone to genetic mutations vulnerability, may result in safeguarding the neuroprotective effects. Hence we can summarize that, the studies conducted by Human clinical imaging; postmortem investigations and detailed epidemiological studies have lately tinted the role of neuroinflammation in causing the Parkinson’s disease and elevating the scope of diagnosing regular inflammation acting as an environmental instigator to endorse gradual degeneration of dopaminergic neurons.

Detrimental impacts of Neuroinflammation over dopamine cell survival

Over the last few years of rigorous research, a definite pool of concrete evidence has been attained to imply that inflammation resulted oxidative stress and cytokine reliant toxicity, together can put in towards nigrostriatal trail degeneration, and further accelerate the expansion of this ailment in case of people suffering from idiopathic Parkinson’s Disease. The segment of substantia nigra (SNL) deteriorates prior to and more sternly in case if Parkinson’s Disease than the other nigral component. Still the reason of this

brain’s provincial proneness to deterioration in case of Parkinson’s disease has remained indistinct.

A multiplechip study of Parkinson’s disease regulated brain (in context with the rendering of inflammation-derived oxidative stress and mitochondrial dysfunction) has demonstrated amplified coding of genes scheduling inflammation favoring cytokines and parts of the mitochondria linked electron movement links (Duke et al., pp. 88). In specific cases, in spite of being inflicted for a large time , patients suffering from idiopathic Parkinson’s are found to have raised neuroinflammation infected basal ganglia, and over the front and cortical region, when evaluated in comparison to those of same aged healthy brain controls (Gerhard et al., pp. 408).

The above remarkable results suggest that alteration in microglia commencement along the infected nigrostriatal trail, are expected to occur earlier in the Parkinson’s disease and occur concurrently with the loss of dopaminergic terminals. Aggrandizing the output and deductions, these studies sturdily suggest that brain’s microglia development may commence prior to the actual disease process and stay prepared, which gives them enough stability to sternly react and unusually offer response to ensuing stimuli, thereby augmenting to inflammation-induced oxidative stress over susceptible neuronal populations.

Causal for dopamine cell death

A crucial aspect of the oxidative stress theory in case of Parkinson’s Disease, is that chance of temporary initiation factor like toxins, bacterial inclusions, viral infections, exposure to pesticides, etc, may activate an dynamic and

self-sustaining series of constant neuroinflammation (via amplified generation of chemokines, cytokines, ROS/RNS and microglial molecules sticking together) . This process can further serve to endorse accumulation of microglia commencing around dopamine cells (McGeer et al., pp. 224) and will add to permanent neuronal malfunction leading to ultimate cell death. Researched Data ratifying this notion comprise of studies which conclude that cell death is not mandated to begin microglia commencement. Although, the microglia development is potent enough of instigating cell death, provided the microglia development turns to be self-sustaining. This was evident as, the intranigral management of Prostaglandin J2 , was just exposed to instigate microglia commencement, discerning nigral deterioration of Dopamine neurons, array of ubiquitin- and α-synuclein-immunoractive accumulation in the secured Dopamine neurons, and consequent motor function deficit (Pierre et al., pp. 18). One more research favoring this notion is in case of concerned mice depicting raised levels of human α-synuclein gene (also expected in case of individuals who have triplication of t α-synuclein) , which showed enlarged microglial load and superior levels of generated cytokines , which foreran the loss of dopaminergic neurons (Theodore et al., pp. 1152).

The genetic and environmental factors linked to Neuroinflammation causing Parkinson’s

The Neuroinflammation can also be propelled by immunological situations (like bacterial and viral contagions), neuronal injury for example brain trauma, and determinants leading to persistent inflammatory syndromes like , rheumatoid arthritis, diabetes- 2 type, and manifold sclerosis and

environmental toxins like pesticides (Aloisi, pp. 124)Most of these mechanisms can augment the percolation levels of the blood brain barrier, which further regulates infiltration of lymphocytes, macrophages and possibly other environmental toxins hooked on with the brain parenchyma. Many environmental triggers are researched to encourage Neuroinflammatory responses and therefore, concerned with the idiopathic Parkinson’s disease. The aftereffects include disturbing head injuries, virally induced inflammation, when revealed to grave metals, organophosphate compounds, neurotoxins, and pesticides like paraquat and rotenone (Casals, Elizan and Yahr, pp. 673).

Substantiation ratifying the above mentioned deductions are from a latest study conducted, for mice possessing alterations in the Parkin gene, which is supposedly associated with the hereditary parkinsonism. The study used small-dose unceasing systemic direction of the bacterial endotoxin lipopolysaccharide (LPS) , which resulted in noteworthy failure of nigral dopamine neurons in already Parkin lacking mice , but this observation was not same in case of wild-type mice , in spite of the fact that both groups testified similar rise in traces of neuroinflammation (Frank-Cannon et al., 2008)

Gaps in the research conducted till date

The studies conducted so far have given fair indication of probable contribution of chronic inflammatory mechanisms and interdependence of the environmental and genetic factors, to deduce a cause effect relationship with respect to Parkinson’s. However, in addition to earlier gained

information, it is also imperative to classify other hopeful aspects as well as small molecules, to cross the blood-brain barrier and to create safe and soundly proficient modes of deliverance for those unable to across this barrier. Hence, we analyze the possible gaps in currently pursued studies, solving through which, a flourishing result may certainly amend the route of Parkinson’s pathogenesis and include therapeutic benefit in case of Parkinson’s disease patients.

The main unreciprocated questions till now include a direct imposition of the fact whether protein aggregates have a significant role as a cause to discerning loss of dopaminergic neurons over substantia nigra. This study may also lay stress over the clinical symptoms to analyze whether neuroinflammation is an effect of or a cause for nigral cell loss.

The association between inflammation, consequent oxidative stress and Parkinson’s disease has eventually grown to be less disputable due to many studies based on proof-of-principle format. These studies have effectively associated inflammatory processes with the consequent progressive loss of nigral dopamine neurons. On the other hand, in spite of the hopeful data budding from various animal researches executed on neuroprotective effects of drugs used for their anti-inflammatory properties, it still stays a query to discern whether anti-inflammatory cure in humans can also prove beneficial in slowing down the Parkison’s progression in aged patients.

Supplementary studies for gene-environment interaction research will be compulsory to launch causality relationship and stretch ahead of simple involvement among these factors and consequent enlargement of idiopathic Parkinson’s disease. So it has to be still concretized that environmental

factors are potent enough to manipulate disease etiology or sequence of Parkinson’s , to bring out clearly that genetic mutations can increase the susceptibility of dopaminergic neurons to get impacted under the influence of environmental stimuli.

Probable cause for the malfunction of earlier conducted clinical experiments over anti-inflammatory drugs may consist of the sophisticated state of the patients, who can participate in the research, have the dosage routine elected for the experiments, and study the impact of wrong anti-inflammatory compound. Hence additional clinical exploration is necessary prior to negating the likelihood of possible long-term impacts of the anti-inflammatory drugs.

Future prospects

Adding on to the studies conducted in this field so far, it is a remarkable fact that most of the currently applied drugs, in curing the chronic inflammation, like NSAIDs, are not practically effective is reducing the inflammations, as they are not capable of generating the efficient anti-inflammation triggering response. In fact, these are found to seize the inflammation favoring response garnered and exposed to the patients. It is also known that the prolonged hereditary inflammation inducing response opens a scope of benefit (Wyss-Coray, pp. 1002), over long-term global reserve of inflammation favoring stimuli. Hence, it may not be the best approach to treat the inflammatory situation linked with neurodegenerative diseases by using the anti-inflammatory drugs. (Wyss-Coray and Mucke, pp. 432). Hence,

the future prospects lie in exploring a possible solution to this scope of directly curing the inflammation condition.

Conclusion

The Parkinson's disease impacts the motor functioning of the aged patients, causing a sluggish and progressive deterioration of dopaminergic neurons in the region of substantia nigra. Regardless of exhaustive research in this field, still the root of the neuronal loss in Parkinson's disease is inadequately explicated. The Neuroinflammatory mechanisms can put in to the fall of neural events, which ultimately lead to neuronal degeneration. In this report, we tried to garner various evidences to see the impact of chronic inflammation in worsening the Parkinson’s disease effect. We have also identified the various component cellular and molecular events, linked with neuroinflammation, which finally cumulate towards the degeneration of dopaminergic neurons, evident in studies conducted over animal models of the disease.

On the whole, currently obtainable data indicate the significance of anti-inflammatory studies in pathological mechanisms, over the Parkinson's disease, which are frequently intervened by the consequent activities in neural regions. This dopaminergic cellular reply to neurodegeneration triggers harmful mechanism like those of oxidative stress and cytokine apoptosis. Finally, we have also garnered various therapeutic strategies (counting anti inflammatory drugs and therapeutic immunization) expected at mitigating the inflammatory processes that can prove to be significant in slowing down the development of Parkinson's disease.

Biliography

Aloisi F 1999, The role of microglia and astrocytes in CNS immune surveillance and immunopathology, Adv Exp Med Biol; 468: pp. 123–133. [PubMed]

Block ML, Hong JS. 2005, Microglia and inflammation-mediated neurodegeneration: multiple triggers with a common mechanism, Prog Neurobiol; 76: pp. 77–98. [PubMed]

Block ML, Zecca L, Hong JS. 2007, Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci ; 8: pp. 57–69. [PubMed]

Bonifati V 2007, LRRK2 low-penetrance mutations (Gly2019Ser) and risk alleles (Gly2385Arg)-linking familial and sporadic Parkinson’s disease, Neurochem Res ; 32: pp. 1700–1708. [PubMed]

Casals J, Elizan TS, Yahr MD 1998, Postencephalitic parkinsonism--a review, J Neural Transm.; 105: pp. 645–676. [PubMed]

Czlonkowska A, Kohutnicka M, Kurkowska-Jastrzebska I, Czlonkowski A 1996, Microglial reaction in MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) induced Parkinson’s disease mice model, Neurodegeneration; 5: pp. 137–143. [PubMed]

Duke DC, Moran LB, Pearce RK, Graeber MB 2007, The medial and lateral substantia nigra in Parkinson’s disease: mRNA profiles associated with higher brain tissue vulnerability, Neurogenetics; 8: pp. 83–94. [PubMed]

Gelb DJ, Oliver E, Gilman S 1999. Diagnostic criteria for Parkinson disease, Arch Neurol; 56: pp. 33–39. [PubMed]

Gerhard. A, Oertel W, Banati R, Hotton. G, Turkheimer. F, Hammers. A,

Eggert. K , Brooks D 2006, In vivo imaging of microglial activation with PK11195 PET in idiopathic Parkinson’s disease. Neurobiological Disesase; 21: pp. 404–412. [PubMed]

Goldberg MS, Lansbury PT, Jr. 2000, Is there a cause-and-effect relationship between alpha-synuclein fibrillization and Parkinson’s disease? Nat Cell Biol; 2: pp. E115–119. [PubMed]

Lees AJ, Hardy J, Revesz T 2009, Parkinson’s disease, Lancet, 373: pp. 2055–2066. [PubMed]

McGeer EG, Klegeris A, McGeer PL 2005, Inflammation, the complement system and the diseases of aging. Neurobiol Aging; 26(Suppl 1): pp. 94–97. [PubMed]

McGuire SO, Ling ZD, Lipton JW, Sortwell CE, Collier TJ, Carvey PM 2001, Tumor necrosis factor alpha is toxic to embryonic mesencephalic dopamine neurons. Exp Neurol; 169: pp. 219–230. [PubMed]

Pierre SR, Lemmens MA, Figueiredo-Pereira ME 2009, Subchronic infusion of the product of inflammation prostaglandin J2 models sporadic Parkinson’s disease in mice. J Neuroinflammation; pp. 6: 18. [PMC free article] [PubMed]

Schapira AH. Neurobiology and treatment of Parkinson’s disease 2009a, Trends Pharmacol Sci.; 30: pp. 41–47. [PubMed]

Schapira AH 2009b , Molecular and clinical pathways to neuroprotection of dopaminergic drugs in Parkinson disease. Neurology; 72: pp. 44–50. [PubMed]

Theodore S, Cao S, McLean PJ, Standaert DG 2008, Targeted overexpression of human alpha-synuclein triggers microglial activation and an adaptive immune response in a mouse model of Parkinson disease. J Neuropathol Exp

Neurol; 67: pp. 1149–1158. [PMC free article] [PubMed]

Wyss-Coray T 2006, Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med; 12: pp. 1005–1015. [PubMed]

Wyss-Coray T, Mucke L 2002 , Inflammation in neurodegenerative disease--a double-edged sword. Neuron; 35: pp. 419–432. [PubMed]