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MINI REVIEW

Metabolic Syndrome and Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases are progressive disorders that affect central nervous system and gradually worsen over time. Despite many experimental and clinical studies being performed, no effective cure has been found yet. Protein aggregation, excitotoxicity, neuronal death, inflammation, mitochondrial dysfunction, oxidative stress and metabolic syndrome are among the major role players in neurodegeneration. Increasing evidence demonstrates that metabolic syndrome is interrelated with many neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's Diseases.

Keywords

Parkinson's disease, Alzheimer's disease, Huntington's disease, Glucose tolerance, Metabolic syndrome, Neurodegeneration

Introduction

Metabolic syndrome is a series of conditions such as high blood pressure, high blood sugar, increased body fat, and abnormal cholesterol or triglyceride levels that increase the risk of heart disease, stroke and diabetes. Metabolic syndrome is generally known to be caused by insulin resistance, abnormal adipose function and associated with obesity, high blood pressure, high blood sugar, high serum triglycerides, low high-density lipoprotein (HDL) levels and high low-density lipoprotein (LDL) levels. Dysfunctional metabolism generally means disturbed glucose metabolism and elevated insulin resistance, which occurs close to middle age in majority of the population. Metabolic syndrome increases the risk of developing heart disease and type II diabetes [1,2]. The most important factors causing metabolic syndrome are diet [1] genetics [2], aging, low physical activity [3,4] and mood disorders [5].

Metabolic syndrome and neurodegenerative diseases both majorly affect middle-aged or elderly people. Age-related neurodegenerative disorders display progressive and severe cognitive and/or motor symptoms that lead to reduced quality of life resulting in death. Metabolic dysfunction and neurodegeneration are closely related. Abnormal glucose tolerance or insulin resistance are mostly observed in neurodegenerative diseases [6,7].

It is not exactly known whether dysfunctional metabolism is etiologically related to Alzheimer's, Parkinson's or Huntington's Diseases. It is not clear whether metabolic syndrome is the cause or the consequence of the disease. Many experimental and clinical studies targeting central nervous system failed as therapeutics and urgent cure is needed for these diseases. Recent studies showed that therapeutics developed to prevent metabolic dysfunction may improve cognitive and motor symptoms in neurodegeneration [8,9].

Metabolic Syndrome in Alzheimer's Disease

Alzheimer's Disease is a chronic, progressive neurodegenerative disorder resulting in dementia in most of the cases. The disease is associated with amyloid plaques and tau tangles in the brain. As with many complex diseases, five to ten percent of the cases turn out to be genetic and the rest is found to be sporadic [7,10].

Various studies demonstrated that excess body weight during middle age is closely related to the risk of Alzheimer's Disease (AD). Obesity (Body Mass Index (BMI) greater than 30) at 40-45 years of age is associated with a 3-fold increase and being overweight (BMI 25-30) is associated with a 2-fold increase in Alzheimer's Disease risk when compared to individuals having normal BMI [7]. However, another study showed that a

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BMI with a higher baseline and a BMI with a slower rate of decline were protective against Alzheimer's Disease [10].

Abnormalities and dysfunction in glucose homeostasis is associated with cognitive dysfunction. It is observed that patients with either type 1 or type 2 Diabetes Mellitus demonstrate memory impairment and attention deficits on cognitive tests when compared to control subjects [11]. It is not known whether neuronal damage is irreversible in these cases. Many studies showed that hyperglycemia might be linked to the Alzhemier's Disease pathophysiology. When mice are administered high amounts of glucose, there is an increase in tau cleavage and apoptosis resulting in neuronal death in mice brain. *db/db* mice are experimental models commonly used for Diabetes Mellitus. These mice display an elevated level of tau phosphorylation in their brains compared to control mice [12].

Recent findings suggest that insulin might contribute to cognitive function. Therefore, insulin abnormalities may exacerbate cognitive impairments. Insulin may also play a role in trafficking the amyloid precursor protein and interfere with its degradation [13]. High blood pressure was shown to be connected with Alzheimer's disease although the underlying molecular mechanisms are not clearly known [14]. Recent studies also found that white matter hyperintensities (WMH) are more highly associated with preclinical Alzheimer's disease compared to imaging and other cognitive markers [15]. However, the association between WMH and cognition was not found to be consistent throughout the literature [16].

In summary, various studies show that metabolic syndrome is related to neurodegeneration in Alzheimer's Disease. However, the underlying molecular mechanisms are not clearly known.

Metabolic Syndrome in Parkinson's Disease

Parkinson's disease (PD) is a second major neurodegenerative disease after Alzheimer's Disease and affects people generally around 50-60 years of age [17]. Classical disease symptoms are bradykinesia, resting tremor and rigidity. Neuronal loss is observed in the pars-compacta of the substantia nigra in brain. Protein aggregates, which are composed of protein α-synuclein called Lewy bodies and Lewy neurites, accumulate in human brain.

Parkinson's Disease patients generally lose weight after their diagnosis and continue losing weight afterwards. In contrast to Alzheimer's Disease, obesity is not considered to be a risk factor for Parkinson's Disease [18]. However, recent studies have found a link between dysfunctional glucose homeostasis and Parkinson's Disease [19]. Large epidemiological studies did not find any specific association between Diabetes Mellitus and Parkinson's Disease [20]. On the other hand, there are still findings of abnormal insulin signaling in Parkinson's Disease patients [21]. Insulin is known to influence several processes in the brain including neuronal survival and growth, and dopaminergic transmission. Therefore, it is thought that a process analogous to peripheral insulin resistance might occur in the brains of Parkinson's disease patients, even without diabetes [22].

Metabolic Syndrome in Huntington's Disease

Huntington's Disease (HD) is a third major neurodegenerative disease that is autosomal dominant genetically. Huntington's Disease is seen much earlier in life compared to Parkinson's and Alzheimer's diseases, generally in the fourth to fifth decade. Disease symptoms are tremor, dystonia, chorea, cognitive dysfunction and abnormal behavior. There is severe neuronal death in striatum, caudate and putamen [23]. The genetic defect that causes the disease involves a protein called Huntingtin. Due to the expanded trinucleotide CAG repeats in exon 1 of the HD gene, mutant Huntingtin protein forms. This mutant protein accumulates as protein aggregates in Huntington Disease brains of patients [24]. The number of CAG repeats is in direct proportion to the severity of disease.

Weight loss is commonly observed in Huntington's Disease patients. HD patients generally have a lower BMI than control subjects [25,26]. Obviously, energy balance system is defected due to the effects of mutant Huntingtin on peripheral tissues. Some studies have found a link between the risk of developing Diabetes Mellitus and Huntington's Disease [27]. Some studies indicate that Huntington's Disease patients might have an abnormal glucose tolerance test results or elevated insulin resistance [28,29]. Some experimental studies including mice also exhibit similar results showing an association between glucose metabolism and Huntington's Disease. Targeting metabolic syndrome in Huntington's Disease might be beneficial for treating this disease. Solutions not only affecting central nervous system, but the entire body will be more effective.

Conclusion

Alzheimer's, Parkinson's and Huntington's Diseases are progressive age-related disorders eventually resulting in death. Neurodegeneration is defined by different hallmarks that are common among neurodegenerative diseases. These are protein aggregation, mitochondrial dysfunction, neuronal loss via apoptosis or necrosis, lysosomal dysfunction, excitotoxicity and metabolic syndrome. All these hallmarks are made up of various cellular pathways. Targeting any of these pathways will be important in developing therapeutics for these complex diseases. Metabolic syndrome is a heavily age-dependent condition. Although some results are inconsistent or not replicable in literature, targeting metabolic syndrome is still critical since dysfunctional metabolism is associated with all neurodegenerative diseases. Finally, enlighten-

ing the link between neurodegeneration and metabolic syndrome will pave the way for new and effective cure against age-related neurodegenerative diseases.

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