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Review

Huntington's Disease Appears to Increase Diabetes Mellitus Risk

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Abstract

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder, and the onset of HD is mainly in middle and old age. The HD gene is known to be a disease-causing gene. There is highly polymorphic CAG repeated in the first exon, and the amino acid encoded by the CAG sequence is glutamine. This led to the encoding of a macromolecular protein containing the polyglutamine sequence (PolyQ) - Huntingtin. Abnormal amplification of CAG produces a mutated Huntingtin protein (MHTT). In addition to causing motor, cognitive and mental disorders, the disease may also increase the risk of diabetes. The aggregates produced by the MHTT, in addition to the aggregation of neurons, can also accumulate in endocrine cells such as islet cells, thereby producing cytotoxicity. This article attempts to briefly describe the risk that HD may increase diabetes.

Key words: Huntington's disease（HD）; Diabetes Mellitus; Insulin secretion; Pancreatic β cells; Insulin resistance.

Introduction

Neurodegenerative diseases severely affect the quality of human life, such as Alzheimer's disease (AD), Parkinson's disease, and HD for which there are no therapies that meaningfully control or prevent the development of intolerable disability (1). The number of CAG repeats typically ranges from around 10 to 35. However, when the number of repeats reaches 40 and above, the fatal neurodegenerative HD occurs (2). Compared with the normal population, the incidence of diabetes in patients with various neurodegenerative diseases, such as Huntington's disease, AD and Parkinson's disease, is significantly increased (3).

Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia caused by multiple causes, including defects in insulin

secretion and/or action. Diabetes is divided into type I diabetes, type II diabetes, gestational diabetes and other special types of diabetes (4). Type I diabetes is caused by the destruction of islet β-cells, often resulting in an absolute lack of insulin. Type I diabetes usually develops at a young age, with rapid onset, marked symptoms, and moderate to severe clinical symptoms, including weight loss, diuresis, dysuria, multiple drinks, body weight loss, ketonuria and ketoacidosis (5). Type II diabetes is mainly insulin resistance accompanied by progressive deficiency of insulin secretion until insulin deficiency accompanied by insulin resistance. The clinical manifestations of patients with type II diabetes include diuresis, polyphagia, weight loss, fatigue, and visual loss (6). Other genetic syndromes associated with diabetes include Parkinson's disease, AD, and Huntington's disease.

The purpose of a study was to investigate the association between diabetes and risk factors for all types of dementia (ATD), the results showed a 73% increased risk of ATD and a 56% increased risk of AD in diabetes patients (7). Another study reported that about 10% of HD patients had diabetes in the last quarter of the 20th century (8), and by the beginning of the 21st century, several articles reported diabetes in the HD mouse model (9-12). The prevalence of glucose metabolism disorders in HD is significantly higher than in the general population because of the effects on the endocrine system found in certain hereditary nervous system diseases (3,13-14). In 2014, Hu et al. studied the incidence of diabetes in a member of a five-generation Chinese HD family. The results showed that the incidence of diabetes in this family of HD patients was 18 times higher than that in the ordinary Chinese population (15). Here we review the presence of insulin resistance and damage to islet β-cells in HD with diabetes.

1. MHTT reduces insulin secretion

1.1 Insulin secretion vesicles decrease, and insulin secretion is reduced

Insulin is an important and effective means of controlling hyperglycemia. Deficiency of β-cell function plays a key role in the pathogenesis of type II diabetes. Decompensation of β-cells against insulin resistance is the last common mechanism, leading to the onset of type II diabetes. The related research revealed that 12-week-old R6/2 HD transgenic mice reduced insulin release. Further studies have shown that the number of islets β cells in these HD mice is significantly reduced, and the number of insulin secretory vesicles in a single cell is reduced by 96%, resulting in decreased insulin exocytosis and decreased secretion (16). Another study shows that R6/1 mouse had impaired glucose tolerance which could be explained by reduced β-cell mass and abnormal insulin release (17). However, the study in 2013 showed that, although glucose dysregulation has a flat glucose curve and delayed insulin peaks after oral glucose load, the risk of diabetes is not supported in HD patients (18). The study in 2008 showed that pancreatic islets in HD patients appear histologically normal (19). This difference may be due to the small number of HD patients' specimens. Maria Bjo¨rkqvist et al. demonstrated that the R6/2 transgenic mouse model of HD developed diabetes due to insufficient β-cell mass and exocytosis (20). To elucidate the secretory defects observed in vivo, Maria Bjo¨rkqvist et al. detected in vitro islet-secreting mice secreted by islets and found that basal insulin secretion and glucose secretion were significantly reduced.

1.2 Insulin gene expression is reduced

A new analytical method has been used to study the energy regulatory dysfunction that occurs in the Huntington's mouse model, and it has been found that the causes of endocrine function, body weight, energy metabolism, normal blood sugar, appetite function and bowel dysfunction are likely to be significant changes in hypothalamus transcription. In other words, there were statistically significant differences occurred in gene

transcription between HD and wild-type mice (21). It turned out that MHTT could form complexes with certain transcription factors in the nucleus, thereby interfering with the interactions between transcription factors and DNA. Furthermore, DNA microarray assay has shown that there are a large number of gene expression changes in HD neuron and animal models, and abnormal changes in gene regulation have occurred before clinical symptoms appear, indicating that abnormal transcriptional regulation plays an important role in the pathogenesis of Huntington's disease (22). For example, MHTT binds to p53, CREB-binding protein (CBP), specialized protein 1 (SP1) and TATA-binding protein (TBP), affecting its expression in cells. In addition, histone acetyltransferase (HAT) can acetylate histones to initiate gene transcription, while MHTT can reduce histone acetylation levels and affect gene expression (9). mRNA expression in HD transgenic mice decreases with age, and expression of key regulators of insulin gene transcription is also reduced. These regulatory factors include the pancreatic proportion PDX-1, the E2A protein, and the coactivators CBP and p300. Amplification of polyglutamine in the Huntingtin protein disrupts expression of a subset of transcription factors in pancreatic β-cells, thereby selectively impairs insulin gene expression, ultimately leading to insulin deficiency and diabetes (9). MHTT selectively damages insulin transcription factors and decreases insulin mRNA levels.

1.3 MHTT inhibits insulin secretion

Although many studies have confirmed that HD patients or transgenic mice are prone to cause diabetes, there are many controversies. The mutation Htt does not seem to cause the risk of diabetes. Genetically, there are more than 39 CAG repeats. Furthermore, the more repeats, the earlier the onset, the more serious the conditions (2). This indicates that the cytotoxicity of the mutated Huntington is related to the number of CAG repeats. Multiple HD mouse models showed changes in islet cytokine volume and reduced insulin secretion as blood glucose abnormalities, is possibly due to accumulation of MHTT. Bronwen Martin et al. studied the blood glucose of HD mouse model induced by Ex-4 (23). In addition, the decreased insulin sensitivity caused by the mutation of Htt is also related to the higher number of CAG repeats. The more CAG repeats, the lower the insulin sensitivity (24). HD mouse models expressing high glutamine repeats have higher diabetes occurrence, while HD patients expressing fewer glutamine repeats exhibit only pre-diabetes symptoms, such as normal blood sugar, insulin stimulation and insulin sensitivity decreased after glucose stimulation (25). Autophagy is a cellular reaction that leads to non-specific degradation of cytoplasmic components, such as organelles. Autophagosome and lysosome fuse, and lysosomal hydrolytic enzymes degrade the endometrium of autophagosome and cytoplasmic components (26). A recent study identified animal models of AD. HD and many other normal and pathological conditions, including immune diabetes (27). Alise Hyrskyluoto et al. demonstrated that the ubiquitin-proteasome system （UPS） plays a crucial role in the degradation of mtHtt aggregates, while autophagy is minima (28).

In my opinion, by inducing autophagy, proteins can be inhibited from aggregation in islet β-cells, protecting cells from neurotoxin-induced cell death, and MHTT can be inhibited from aggregation in islet β-cells by UPS. It has been shown that the development of central nervous system diseases is associated with changes in autophagy and damage, such as AD and other neurodegenerative diseases (29).

1.4 Unbalanced systemic energy homeostasis due to mitochondrial function impairment

Emerging evidence indicate that mitochondrial dysfunction is associated with disparate diseases, including obesity (30), mitochondrial diseases (31), neurodegenerative diseases (32), aging (33),

diabetes and cancer (34). Because lipid peroxidation produces a large amount of reactive oxygen species (ROS) and degradation products, such as malondialdehyde (MDA), resulting in mitochondrial dysfunction, energy balance disorder, causing cell excitotoxicity and apoptosis (35). In addition, mitochondrial function damage affects the oxidative phosphorylation, nutrient metabolism and apoptosis of β cells, while the secretion of insulin in β cells depends on the opening of ATP-dependent potassium channels, so insulin secretion is closely related to mitochondrial function.

The peroxisome proliferator activator receptor tyanticoactivator (pgc-1) is an important regulator of mitochondrial biosynthesis and respiratory chain and may also be an important factor in the regulation of system energy homeostasis in HD patients, including fatty acid oxidation, insulin sensitivity and carbohydrate metabolism (24). In HD patients, MHTT may inhibit the transcriptional activity of PGC-1α and its target genes in muscle, fat, liver and other tissues, resulting in lipid metabolism and glucose metabolism disorders and decreased insulin sensitivity in surrounding tissues (36). A study using functionalized nanosheets as a non-destructive intracellular glucose measurement technique showed impaired glucose metabolism in rat striatum cells. Impaired glucose metabolism and altered gene expression associated with energy metabolism are among the causes of HD pathogenesis (37). McAninch EA et al. demonstrated that activated deiodozyme (thr92ala-d2) accumulates in Golgi bodies and its presence and/or subsequent oxidative stress disrupt basic cellular functions and increase apoptosis. The findings are reminiscent of disease mechanisms observed in other neurodegenerative diseases, such as HD, and may lead to unresolved neurocognitive symptoms in affected carriers (38). Wright DJ et al. demonstrated that N-acetylcysteine (NAC) can delay the development of motor defects in the HD R6/1 model and may achieve this by improving mitochondrial dysfunction. Therefore, NAC has potential application prospects in HD therapy (39). Recent studies have shown a correlation between mitochondria and autophagy. In this context, it has been reported that cells lacking mtDNA or functional oxidative phosphorylation complexes are impaired in autophagy (40).

2 Insulin resistance

Insulin resistance refers to the phenomenon of insufficient response of cells to normal concentrations of insulin, which is manifested by decreased glucose uptake efficiency and compensatory hyperinsulinemia, most commonly in diabetes. Insulin resistance is one of the important causes of the disease. It can easily pass through the blood-brain barrier to reach the brain, which means that insulin can affect many brain functions.

A study based on 29 untreated non-diabetic HD patients found that, in addition to decreased insulin secretion, decreased insulin sensitivity and elevated levels of insulin resistance often occur in HD patients with normal blood glucose (29). Other studies have shown that insulin resistance is mediated by Huntingtin gene mutations and interactions between glucose metabolism and other metabolic pathways (41). Arora A et al. reported the role of SIRT2 in regulating insulin sensitivity in neuronal cells in vitro and observed that down-regulation of SIRT2 improved AKT activity and insulin-stimulated glucose uptake in insulin-resistant neurons (29). In addition, the higher the repetition rate of CAG, the lower the insulin sensitivity (24).

One hypothesis about the relationship between insulin resistance and neurodegeneration is that insulin resistance represents a metabolic stressor that affects potential neurobiological templates in a way that leads to pathological phenotypes. In a study of 29 patients with HD in HD patients, Robert c. Block et al. demonstrated that HD high levels of insulin resistance and performance for the homeostasis model assessment (HOMA index) and lower insulin sensitivity. Compared with healthy controls, the acute insulin response in patients with

HD was reduced, as was the proinsulin index (the ratio of plasma insulin to plasma glucose). Although there may not be a causal relationship between insulin resistance and neurodegeneration in these studies, the number of CAG repeats in the mutant Huntington gene shows a decrease in acute insulin reactivity. HD was also associated with insulin resistance patterns, characterized by metabolic states that resulting in weight loss and a lower BMI than people without Huntington's disease. Insulin resistance appears to be a metabolic stress source that causes disease progression (42). The mice developed diabetes and glucose intolerance within nine weeks, and more than 70% developed diabetes within fourteen weeks. In the same Huntington's mouse model, in addition to being present in brain tissue, intranuclear inclusions are also present in pancreatic cells and are histopathological markers of HD (11).

Conclusion

HD is mainly characterized by progressive dyskinesia and cognitive decline. HD patients begin to develop mental symptoms and AD in youth or middle age and continue to increase until death (43). There is currently no effective treatment available worldwide. There is a CAG trinucleotide repeat in the first exon of the HD gene, which encodes a poly-glutamine fragment (Poly-Q) at the N-terminus of Htt, and the mutated HD gene is encoded to produce an ultra-long Poly-Q. Mutant HD genes encode MHTT with ultra-long Poly-Q structure. MHTT misfolding is the material basis of HD neuropathological damage, thus reducing its formation or promoting its clearance is of great significance to delay the pathological process of HD (44).

HD places a huge burden on the country, the family and the individual. With the improvement of people's living standards and the formation of many bad habits, the incidence of many diseases related to insulin resistance and insulin secretion reduction represented by diabetes is gradually increasing. This paper reviews that mutation Htt may reduce the number of vesicles secreted by insulin, decrease the expression of insulin gene, inhibit the secretion of insulin and mitochondrial function damage, impairing islet β-cell function and reducing insulin sensitivity. Although many experiments have found that HD is associated with diabetes, its specific mechanism is still unclear and needs further study.

Declarations

1) **Consent to publication**
   We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2) **Ethical approval and consent to participants**
   Not applicable.
3) **Disclosure of conflict of interests**
   We declare that no conflict of interest exists.
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5) **Availability of data and material**
   We declare that the data supporting the results reported in the article are available in the published article.
6) **Authors' Contributions**
   Authors contributed to this paper with the design (Lulu Zhao and Gang Li), literature search (Lulu Zhao and Gang Li), revision (Lulu Zhao, Gang Li, XiaoFei Zhang, Xin Miao, Haiyan Xing and Shengnan Wang), editing (Lulu Zhao, Gang Li, XiaoFei Zhang, Xin Miao, Haiyan Xing and Shengnan Wang) and final approval (Lulu Zhao).
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8) **Authors' biography**
   None

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