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Neurodegeneration and Huntington's disease

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ABSTRACT
Neurodegeneration is related to many kinds of age-related neuron diseases. Taking Huntington's disease(HD) as an example, it is a fatal hereditary neurodegenerative disorder caused by expanded CAG repeats in specific genes. There is no fundamental treatment for HD, and the mechanism of its occurrence and development is unclear. Currently, there are only drugs that improve individual symptoms, and lose effectiveness after a certain period of time due to resistance. In order to better understand the pathogenesis of this kind of disease and explore more feasible treatment methods, the author briefly reviews the research of basic pathology of this kind of disease, and selecting HD to discuss deeply for its possible treatment means. The result shows that the gene-related brain structural changes is closely related to the occurrence of disease, and it is a genetic disease. Since disease treatments and drugs must be screened and validated in animal models, it is very important to establish cell and animal models that can accurately simulate disease phenotypes and pathology to develop effective disease treatments.

Keywords: *Huntington's disease, neurodegenerative disorder, treatment, chromosome, newborn cells*

1. INTRODUCTION

Huntington chorea (HD), also known as chronic progressive chorea, is a slow-onset inherited neurodegenerative disease that affects about 1 in 10,000 people. At present, chorea is an incurable disease in medical field at home and abroad. It is well known that as an autosomal dominant neurodegenerative disease ,it occurs in all races and the main cause of HD is a mutation in the Huntingtin (HTT) gene on chromosome 4 that produces a mutated Huntingtin protein (Hit). HTT is widely expressed in neurons, and it has been found that HTT is an anti-apoptotic protein in striatum cells and can prevent cystatin activation. So far, no specific drugs can stop the pathological process of HD, mainly because the pathological mechanism of the disease is not clear enough. The structural basis of cytotoxicity caused by excessive poly Q in soluble HTT is a key question to answer the molecular mechanism of HD origin, but there is still a lack of directly explicating structural biological data on the conformational basis of cytotoxicity caused by excessive poly Q.

In current years, there has been an explosion of researches attempting to elucidate the mechanisms of neurodegeneration in HD. In order to have a clear understanding of this kind of research as a whole, this paper takes the relationship between newborn cells and neurodegenerative diseases as a starting point, and the current research progress on the pathogenesis, diagnosis and intervention methods of Huntington's disease are reviewed and summarized. Meanwhile, the possible more effective treatment and social support for huntington's disease in the future are predicted and prospected. Furthermore, the social intervention in addition to drug therapy was further discussed. This paper can provide a better theoretical basis for the in-depth study of this kind of disease in the future.

2. NEW NEURONS' GREAT EFFECT ON NEURODEGENERATIVE DISEASES

Throughout the development of human life, from embryo to adult, the brain, like other parts of our body, works, develops and matures — a series of changes are inseparable from the production and death of new cells. Once it is abnormal, diseases will follow one after another. Neurodegenerative diseases are more common in older people, and studies have found that changes in the cells involved are also closely linked to "geriatric diseases".

2.1 Brain structural changes in relation to related genes and neurodegenerative diseases

On the surface, newborn neurons seem a little contradictory when studying age-related diseases such as

Alzheimer's disease, but in fact, the development and damage of the nervous system are related to the elimination of axons, dendrites and synapses. The generation and death of cells can also be observed in neurodegenerative diseases. At the genetic level, certain genes such as alpha-membrane proteins and PSEN also play a key role in neurodegenerative diseases because they physiologically regulate brain plasticity, especially as membrane proteins concentrated in synapses. For example, in Parkinson's, misfolded aggregates of alpha-synuclein develop in brain neurons, including the hippocampus, an area that plays a crucial role in memory formation.

In Parkinson's disease and Huntington's disease, changes in the dentate gyrus (DG), subventricular region (SVZ), and olfactory bulb system (OB) occur in parallel with early symptoms of neurodegenerative diseases such as depression, anxiety, or olfactory dysfunction. Therefore, the pathogenesis of neurodegenerative diseases is closely related to the problem of brain plasticity. Brain plasticity is initially thought of as changes in synaptic transmission, synaptic contact, and gene expression levels, but the concept of brain plasticity has become more complex as new nerve generation in the brain has been studied.

2.2 The mechanism of new neurons linked to brain changes

Recent studies have identified the generation of new neurons in the subventricular region of the dentate gyrus of the hippocampus and the olfactory bulb system in adults. These newly generated neurons have the electrophysiological properties of functional neurons, connect to neighboring cells, and are integrated into existing neuron circuits [1]. These findings overturn the long-held belief that the mammalian brain is a post-mitotic, highly differentiated structure that cannot produce new neurons. Adult neurogenesis involves several key steps, including asymmetric cell division of stem cells, producing a daughter stem cell and a daughter stem cell that has the potential to develop into a neuron. Many regulatory and regulatory layers of adult neurogenesis have been identified, including various transcriptional and epigenetic regulatory and signaling pathways, as well as environmental factors, age, and diseases such as neurodegenerative diseases; Hippocampus — or OB — dependent functions in the formation of new memories, acquisition of new skills, and olfactory learning are also partly attributed to different stages of adult neurogenesis.

2.3 Pathomechanism of adult neurogenesis for the study of neurodegenerative diseases

Whether impaired neurogenesis in adults is related to the deficits observed in neurodegenerative diseases is unclear. However, impaired smell and hippocampal related cognitive and emotional impairments are common in many different neurodegenerative diseases. Analysis of adult neurogenesis provides a unique opportunity to analyze the biology of neural stem cells in the pathological adult environment. Understanding how and at what level of development neural stem cell production is affected in brain diseases involving neurodegeneration will lead to a better understanding of these disease conditions at the cellular level. Understanding neurogenesis in neurodegenerative diseases will lead to disease-related signaling pathways and compounds that recognize disease modifications. Another goal may be to use endogenous neural stem cell stimulation as a means of inducing nerve regeneration. Neurodegenerative diseases include a range of diseases with a common feature of progressive loss of structure or function of neurons and glial cells in the brain and spinal cord. Many neurodegenerative diseases are the result of loss of neurons and also involve glial cells. While neuronal degeneration primarily affects or begins with specific neurons, there are many similarities between different neurodegenerative diseases, and in the late stages of the disease, abnormal protein aggregates are no longer confined to specific areas of the brain.

Some acute pathological stimuli can promote neurogenesis in adults, including stroke, epilepsy, and acute trauma; Neurodegenerative diseases are characterized by chronic and slow progression [2]. Neurons in neurodegenerative diseases are affected by neuronal dysfunction at the levels of synaptic transmission, synaptic contact, axon, and dendritic mutation. In different neurodegenerative diseases, neurite degeneration and neuronal cell loss are present in specific populations of neurotransmitters. In addition, the number of functional neurons in the neuronal region and adult neurogenesis were altered or decreased. Brain regions differ in their vulnerability to aging. Some of the areas that are very sensitive to age-related neurodegenerative changes are DG and OB in the hippocampus, hypothalamus.

3. CURRENT RESEARCH

3.1 Current outcome measures

HD is a widely known neurodegenerative disease which lacks efficient treatment. Before discussing treatments of HD, its diagnose and measurement matter a lot. The UHDRS is a collection of scales, tests, and questionnaires designed to rate the severity of HD comprehensively. It was designed to diagnose and track the degenerative progression of the disease after motor symptoms were manifest; it was not designed to assess earlier stages of the disease or to be sensitive to clinical improvement. However, because this scale is used regularly in clinical practice, it is recommended that it

continue to be included in clinical trials for manifest HD patients until it can be replaced by an improved scale. The UHDRS includes medical and psychiatric history, current medications, HD history, and assessments of motor, cognitive, behavior, and functional status. This assessment tool provides clinicians with a diagnostic confidence score (DSC) that is currently the gold standard for distinguishing manifest HD from premanifest HD. The Shoulson and Fahn Total Functional Capacity Scale (TFC) is a component of the UHDRS and is the most widely accepted tool for assessing disease stage ranging from stages 1 to 4 [3].

Although these tools do include many relevant aspects of the disease, such as motor, cognition, behavior, and functional status, their utility is limited to a narrow window of time within the course of the disease because of floor and ceiling effects at earlier and later stages. Further, these tools are developed to guide clinicians in making the initial diagnosis of HD and monitoring disease progression, rather than as tools to assess therapeutic effectiveness. Thus, it remains to be demonstrated how sensitive they will be to treatment-induced improvements. For example, one of the questions in the TFC assesses how well and how independently HD patients manage their finances. Although this is a useful tool for gauging functional decline, it is less likely to detect improvement because after a person demonstrates difficulty managing the household finances, that role likely gets transferred to his or her partner. If a treatment effectively enabled that person to have the capacity to once again manage his or her own finances, it would be likely to go unnoticed because the opportunity to assess this no longer exists. In other words, it is difficult to assess a person's ability in the absence of opportunity.

There is a reciprocal relationship between cognitive performance and both mood and motor functioning, all of which are impaired in HD. In other words, cognitive performance can both affect and be affected by mood and motor functioning. There are two direct implications of this. First, a treatment that is thought to directly affect one domain, such as cognition, might secondarily have an effect on motor performance. Thus, even a domain-focused trial should measure a broad spectrum of outcomes. Second, although it is important to have tools that can assess cognition, motor function, and mood individually, there is also merit in designing tools that measure functional performance that is dependent on more than one modality.

3.2 Chronic neurodegeneration

Chronic neurodegeneration has different effects on stem cell maintenance, proliferation, survival and functional integration. Huntington's disease is a destructive autosomal dominant neurodegenerative disease caused by repeated amplification of CAG trinucleotide within the Huntington's disease gene. Clinical symptoms include progressive involuntary dance movements, motor retardation, cognitive decline and mental syndrome. Olfactory function was impaired in patients and presymptomatic gene carriers. The aggregation of the mutant protein leads to the damage of neurons in the neostriatum and other neurons in the cortex, and in some theories, the presence of toxic oligomers is suspected to be responsible for this harmful effect.

The abnormal Huntington's protein first affects the basal ganglia of the brain, making it unable to modify or inhibit the brain's commands. As a result, muscles throughout the body move uncontrollably, in dance-like movements. In the advanced stages of the disease, even the surface of the brain, which is responsible for giving instructions, gradually dies, and patients may lose all mobility, leading to cognitive decline and even dementia. The main pathological changes of Huntington's disease were basal ganglia atrophy, especially caudate nucleus, putamen and globus pallidus atrophy. The loss of neurons in the caudate nucleus and putamen is associated with dance-like movements, and the loss of cortical neurons may be associated with dementia [4].

3.3 Adult neurogenesis in a transgenic animal model of Huntington's disease

In most previous studies, the conclusion was that neuronal differentiation was not affected by HD. However, by studying mouse and rat HD models, we found that the proliferation rate of progenitor cells in the TWO HD mouse models in DG decreased, and the number of new neurons in HD mice decreased. The researchers tested different stimuli that promote neurogenesis in adults. Physical activity and environmental enrichment have positive effects on survival, cognitive performance, striatal BDNF levels and reduced intraconuclear inclusion body load. In these models, conditions such as seizures could not reverse the reduction of adult neurogenesis, and only environmental enrichment could increase the level of hippocampal neurogenesis to a certain extent. Important molecular clues have been found in transgenic rat models of HD, and age-related studies are possible due to the long lifespan of these groups of animals [5].

Compared with decreased neuron proliferation in DG, SVZ proliferation did not change in mice. And there were also fewer new neurons in OB. The researchers reported increased cell proliferation in human SVZ. Neuroblast migration to the striatum has also been reported in mice. However, these adult nerve cells do not survive in the striatum and form mature, functional neurons, suggesting that the striatum microenvironment stimulates abnormal migration of new cells but does not allow functional integration [6]. The phenomenon of ectopic migration of SVZ as microenvironment changes has some similarities to the phenomenon observed after stroke.

4. DISCUSSION

Understanding the specific etiology of neurodegenerative diseases is very helpful to explore and try new treatments. Taking HD as an example, like most neurodegenerative diseases, there is no specific treatment for Huntington's disease. Although there is no effective drug to delay the progress of Huntington's disease, common symptoms such as dance movements and mental disorders can be improved to varying degrees by reasonable drug treatment, and the quality of life of patients can be improved and complications can be prevented. Patients and potential sufferers should be given confidence, and appropriate social support should be given to help them persevere.

Among the limited number of HD patients who are willing to participate in clinical research and who learn about a given trial, it is then necessary to find those particular individuals suitable for the specific study planned. If there is a drug that may potentially improve apathy, only patients who have suffered from this problem for a sufficient amount of time and in whom apathy is sufficiently severe to produce important disability should be enrolled in the trial. If this is not done, there may be no window for the drug to exert its potential benefit, and it might be discarded wrongly, in what is known as a false-negative trial. To find HD patients with the characteristics that make them good candidates for a particular trial, in a reasonable time frame, requires very substantial coordination between the medical community and patients' organizations. Although health services collect and organize medical data, it is beyond their reach to do this for the benefit of clinical research in each given field of medicine. Furthermore, the collection and curation of private medical data in conditions that safeguard the privacy in accordance with the current status of law is extremely expensive. Two parallel efforts have been undertaken to increase the efficiency of clinical research and clinical trials.

In HD, experimental therapeutics and large clinical trials have merged into a single discipline because of the lack of adequate tools that would make the small, short-term, explanatory studies that are characteristic of experimental therapeutics truly possible. But the researcher still have space to work for treatment. For instance, inducing revere differentiation of autologous olfactory bulb stem cells can be a hopeful way to slow down and treat the disease. The olfactory bulb is one of the few systems in the nervous system that can continue to self-proliferate. By extracting the neurons from the patient in this region, inducing them, and then re-cultivating and transplanting stem cells, the irreversible brain structural damage can be repaired to some extent.

5. CONCLUSION

Huntington's disease is a genetic disorder, with heredity as the sole cause. Huntington's sufferers tend to be dismissed as "weirdos" who make people "take a detour". This paper tries to understand its pathogenesis from a new perspective, that is, the production of new neurons related to the structural changes of the brain. And the cognition of it needs to be further studied. There is a signal that with the progress of science and technology, the research and development of new drugs, nursing and rehabilitation work, and psychological counseling, the "dance" of Huntington's disease patients will gradually slow down and stop. So far, there is no special and efficient drug treatment, but the existing drugs can alleviate some symptoms of HD to a certain extent. The future treatment direction can explore the feasibility of experimental treatment and establish corresponding animal models for verification and exploration. In addition, their mental health needs to be paid more attention too. Huntington's disease patients themselves prone to anxiety, depression, coupled with their own onset of the lack of effective treatment means, seriously affect the daily work and life. "Motor and cognitive rehabilitation for Huntington's disease should be started as early as possible, as well as psychological counseling for emotional and emotional problems".

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