

ALZHEIMER'S AND HUNTINGTON AS NEURODEGENERATIVE DISEASES

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Abstract – Neurodegenerative diseases (NDD) are a group of diseases characterized by progressive loss of neuron function and structural deterioration. This may be due to damage at birth, as well as by the effect of genetic factors and aging, or as a combination of these. Of these diseases, the more common Alzheimer's disease (AD) generally presents at an advanced age, while Huntington disease (HD) tends to occur at an early age. AD is the most common cause of dementia in the elderly. AD is the most common cause of dementia in the elderly, is a progressive neurodegenerative disease that causes loss of cognitive function and ultimately death. The pathology of AD is mainly composed of senile plaques and neurofibrillary tangles (NFT). HD, one of the neurodegenerative diseases of the central nervous system, is a trinucleotide repeat disorder. HD is characterized by involuntary movements called Korea, memory loss, impaired motor coordination, and accompanying psychiatric symptoms.

In this study, the most common neurodegenerative disease (Alzheimer's and Huntington disease) will be discussed and experimental models designed to investigate the pathogenesis, diagnosis and treatment options of neurodegenerative diseases will be discussed.

Keywords – Neurodegenerative diseases, Alzheimer's, Huntington, experimental models

I. INTRODUCTION

DEFINITION AND CLASSIFICATION OF NEURODEGENERATIVE DISEASES

Neurodegeneration can be defined as progressive loss of neurons structurally or functionally [1]. This can be caused due to damage during birth or due to genetic factors and aging. The rare occurrence of Alzheimer's and Parkinson's disease under 40 years of age indicates that aging is an important risk factor for these diseases. On the other hand, amyotrophic lateral sclerosis and Huntington's disease are neurodegenerative diseases occurring at early ages [2].

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common cause of dementia and a progressive neurodegenerative disease which can be characterized by cognitive impairment, neuropsychiatric symptoms, and functional loss followed by insidious onset memory impairment [3]. Alzheimer's is diagnosed by histopathological diagnosis with the presence of amyloid plaque and intraneuronal neurofibrillary tang formation around neurons accompanied by amyloid angiopathy, granulovacuolar degeneration and Hirano bodies in brain tissue which are found by autopsy of patients with typical clinical features [3-5]. The main component of senile plaques is the b-amyloid peptide, which is part of the amyloid

precursor protein (APP). Neurofibrillary tangles occur as a result of polymerization of phosphorylated tau protein [2]. Animal models designed for Alzheimer's disease are based on creating neurotransmitter deficiency with substances that lead to developing structure related neuronal death or local damage [6].

Non-transgenic Alzheimer's models

Mainly obtained by intracerebroventricular or intrahippocampal injection of b-amyloid or tau protein directly into the brain. Researchers can use these models if they do not have the means to produce a transgenic mouse colony or if they do not prefer to use mice as experimental animals for various reasons. However, these acute models do not substitute for the gradual accumulation of b-amyloid in humans over the years [7].

Streptozotocin-induced Alzheimer's model

Streptozotocin (STZ) is a glucosamine-nitrosourea compound that produces a cytotoxic content that destroys b cells in the pancreas when metabolized. The alkylating properties of streptozotocin metabolites result in reactive oxygen radicals. In Alzheimer's disease, use of glucose by brain reduces. This suggests that cognitive dysfunction may be associated with decrease in glucose metabolism and decrease in glucose levels are shown using intracerebroventricular STZ administration. This application was shown to cause insulin receptor

dysfunction in the hippocampus, leading to progressive cholinergic impairment, oxidative stress and neurodegeneration, and memory impairment. However, long-term development of b-amyloid and tau neuropathology is a disadvantage in this model [8].

Colchicine-induced Alzheimer's model

Colchicine is a neurotoxin substance that irreversibly binds to tubulin dimers and triggers neurofibrillary degeneration. It causes cognitive impairment due to damage in hippocampal granular cells and basal forebrain cholinergic neurons. It should be kept in mind that the implementation of this model requires a large number of animals due to long time needed and high mortality rate [8].

Scopolamine-induced Alzheimer's model

Scopolamine is a muscarinic receptor antagonist and it inhibits the activity of the muscarinic acetylcholine receptor, resulting in electrophysiological changes and transient cognitive amnesia similar to those observed in AD [9].

Adrenalectomy-induced Alzheimer's model

Degeneration of granular neurons in the hippocampus dentate gyrus has been demonstrated in adrenalectomized rats and this causes cognitive impairment [6].

Aluminum-induced Alzheimer's model

Peripheral or intracerebral administration of aluminum salts induced neurotoxicity resulting neurofibril tangles in studies performed with mice, rats, rabbits, cats and monkeys. This mechanism inhibits protein phosphatase 2A activity of aluminum, increasing tau phosphorylation resulting in the formation of neurofibril tangles. Aluminum also disrupts the Na⁺ / Ca²⁺ pump in the cells, leading to an increase in calcium levels in the mitochondria and accordingly inducing apoptosis through cytochrome C release and caspase activation [8]. In addition, experimental models have been established by inducing aluminum chloride (AlCl₃) and D-galactose, by administering zinc or by introducing lipids such as cholesterol, lipopolysaccharide [8].

Transgenic Alzheimer models

Non-transgenic models may be rats, dogs, monkeys while the majority of transgenic models are mice [7]. These models can be examined under two groups; b-amyloid models and tau models [6].

β-amyloid models

PSEN1: This is the first model in which height of Ab42 is shown for the first time in vivo selectively [10].

PDAPP: It is a preferred model for the trial of vaccine therapies and observation of intense plaque formation is important as it is one of the first models used [6].

Tg2576: In this most preferred transgenic model, mutant APP synthesis takes place under the control of the hamster prion

promoter. Cognitive impairment occurs, but no neurofibrillary tangles occur [6].

Tau models

JNPL3: In this model, the P301L mutation in the mouse produces 4R0N (4-repetitive tau isoform with no N-terminal) MAPT (microtubule-associated protein tau), and this is the first model proving neurofibrillary tangles and associated cell loss occur [6].

TAPP: This model is developed by crossing Tg2576 and JNPL3. MAPT pathology in the forebrain occurs more intensely compared to JNPL3 [10].

HUNTINGTON'S DISEASE

Huntington's disease (HD), one of the neurodegenerative diseases of the central nervous system, is also a trinucleotide repeat disorder. It is characterized by involuntary movements called chorea, memory loss, impaired motor coordination, and accompanying psychiatric symptoms. The loss of neurons in the basal ganglia is the main pathological finding of the disease. The gene that causes the disease is the HD gene (IT-15) found on chromosome 4 and encodes huntingtin protein. The likelihood of developing the disease increases with the level of CAG repeats resulting from mutation of the gene. GABAergic neurons in the striatum region of the brain are the main group of affected neurons [11]. While modeling the disease in experimental animals, transgenic animals have been created based on these genetic characteristics or damage of specific neuron groups has been tried by injection of neurotoxic agents [12].

Non-transgenic Huntington models

These models are based on the administration of glutamate receptor agonists by intrastriatal injections, leading to selective loss of GABAergic projection neurons [12].

Huntington model induced by Ibotenic acid and kainic acid

It is the first neurotoxin-based model used. When ibotenic acid-kainic acid and quinolic acid are co-administered, HD-affected neurons and unaffected striatal intermediate neurons can be separated [12]

Huntington model induced by malonate and 3-nitropropionic acid (3-NPA) Another model based on lesion formation is peripheral administration of malonate and 3-nitropropionic acid, mitochondrial toxins. It has been observed that the chronic application of these agents targeting the electron transport chain results mainly in bilateral striatum lesions. This model has also been used as an acute Huntington model in rodents and non-human primates [12] Animals treated with 3-NPA were shown to have deterioration in their spatial memory when evaluated with the elevated plus maze test.

Transgenic Huntington models

Rodents are the most commonly used animals in HH experimental models [12].

R6 / 1-R6 / 2

These transgenic animals express N-terminal fragments of the mutant huntingtin protein (mHTT). They express exon 1 of human HTT and the somatic instability of CAG repeats has been observed in both [20]. Among current models, R6 / 2 is the one with most rapid development of mouse symptoms and the most common form of huntingtin inclusions in the brain [13]. There are two R6 / 2 mouse models that constitute 110 and 250 CAG repeats [12].

N171

N171 mice express 82 CAG repeat truncated HTT cDNA. All N-terminal fragment models enable the rapid onset of motor, cognitive and behavioral symptoms [12].

YAC128 and BACHD

These models created with yeast artificial chromosome (YAC) and BAC technologies express the human mutant HTT gene. These two models develop progressive cognitive, motor and psychiatric impairment as well as striatal and cortical atrophy [12].

II. RESULT

Increasing life expectancy leads to an increase in the incidence of neurodegenerative diseases associated with combination of genetic and environmental factors. All these facts make the treatment of these diseases very important and popular nowadays. Transgenic and non-transgenic models are very valuable for elucidating the pathophysiology of diseases and drug development studies.

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