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Review / Derleme

Neuroprotective Treatments in Parkinson's Disease

Parkinson Hastalığında Nöroprotektif Tedaviler

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Abstract

Parkinson's disease (PD) is a progressive disease due to dopaminergic cell loss in the substantia nigra and dopaminergic terminal lost in the striatum, which is the projection area of substantia nigra. It is characterized by resting tremor, bradykinesia, rigidity, and postural instability. In PD, non-motor symptoms such as cognitive impairment, anhedonia, apathy, and autonomic nervous system impairments affect quality of life as much as motor symptoms. PD may affect multiple systems and the underlying mechanisms are not known. However, developing new methods of treatment to slow or stop the rate of disease progression, to lessen or to cure the symptoms is crucial. The aim of this review was to discuss the alternative treatments that may be useful for both motor and non-motor symptoms. Symptomatic treatments with dopaminergic drugs aim to relieve motor symptoms and to increase the patient's life standards for a limited time. However, possible neuroprotective treatments that inhibit neuronal cell death can extend life span and provide higher quality of life. Lewy bodies, which are formed mainly from misfolded and native alpha-synuclein protein, is a pathologic hallmark of PD. Therefore, inhibiting the protein misfolding or clearing the aggregates could be a promising new therapeutic approach for the disease.

Keywords: Parkinson's disease, alpha-synuclein, drug therapy, neuroprotective agents

Öz

Parkinson hastalığı (PH), istirahat tremoru, bradikinezi, rijidite ve postural instabilite ile seyreden ve substantia nigradaki dopaminerjik nöron kaybı ve substantia nigranın projeksiyon alanı olan striatumda dopaminerjik terminal kaybı ile ilişkili ilerleyici bir hastalıktır. PH'de motor belirtilerin yanı sıra kognitif bozukluklar, anhedoni, apati, otonom sinir sistemi bozuklukları gibi motor-dışı belirtiler de hastaların yaşam kalitesini düşürmektedir. PH'nin altında yatan mekanizma tam olarak bilinmese de pek çok sistemin etkileniyor olması dolayısıyla elde olan bulgulardan yola çıkarak hastalığın ilerleyişinin yavaşlatılabilmesi ya da durdurulabilmesi, semptomların azaltılması ya da yok edilmesi için yeni tedavi yöntemlerinin geliştirilmesi oldukça önemlidir. Bu çalışmada PH'nin motor ve motor-dışı belirtilerine fayda sağlayacak tedavi seçenekleri üzerinde durulması amaçlanmıştır. Dopaminerjik ilaçlar ile sağlanan semptomatik tedavi hastaların yaşam kalitesini sınırlı bir süre düzeltebilmektedir. Öte yandan hastalığın ilerleyişi ile birlikte gözlenen nöron ölümünü engelleyebilecek olası nöroprotektif tedaviler hastaların hem yaşam süresini hem de kalitesini arttıracaktır. Yanlış katlanmış olan alfa-sinüklein proteininin agregatlar halinde birikmesi sonucu Lewy cisimciklerinin oluşumu PH'de anahtar rol oynamaktadır. Bu nedenle alfa-sinüklein proteininin yanlış katlanmasının engellenmesi ya da var olan agregatların yıkımı nöroprotektif tedavi için umut vadetmektedir.

Anahtar Kelimeler: Parkinson hastalığı, alfa-sinüklein, ilaç tedavisi, nöroprotektif ajanlar

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease with an increasing incidence with advancing age that affects almost 1% of the population over 60 years of age (1). Although the incidence increases after 60 years of age, PD of genetic origin affecting the young population between 20 and 50 years is seen more commonly in 5-10% of patients (2). Although the underlying pathophysiologic mechanism of PD is not known, environmental toxins are thought to have a role in the

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pathology of the disease when the initial regions of the disease are considered. Age is one of the major risk factors, but recent studies have shown that genetic factors as well as the environment play an important role in the disease pathology (3,4).

Four basic motor symptoms of PD are resting tremor, bradykinesia, rigidity, and postural instability (5). PD progresses slowly and it takes years for the symptoms to emerge (6). Before motor symptoms are seen and diagnosed, patients may present with many pre-motor symptoms and the initial onset of these symptoms may extend up to 10 years before the diagnosis (7). Basic motor symptoms begin to be observed only after the loss of up to 50% of dopaminergic neurons and up to 80% of terminals in the nigrostriatal system (2).

Non-motor symptoms as well as motor symptoms adversely affect the lives of patients with Parkinson's. These include autonomic dysfunction, cognitive impairment and behavioral disorders, sensory symptoms, and sleep disorders (4). The non-motor symptoms of the disease have been discovered to be caused by changes in neurotransmitters such as noradrenaline, serotonin, acetylcholine, as well as dopamine, and pathology in other brain regions such as the hippocampus, ventral tegmental area, cortex, as well as basal nuclei, such as substantia nigra pars compacta (SNpc) (8,9). In PD, neuronal loss occurs mainly in the brain stem in the early and mid-term, and related pathologic symptoms are observed (9). In later stages of PD, Lewy pathology is seen to spread to lateral hippocampus, intralaminar nucleus of the thalamus, cerebral cortex, and amygdala (10).

Although the pathophysiology of PD is not fully known, there are different hypotheses regarding the underlying mechanism. The most important of these hypotheses are mitochondrial dysfunction and oxidative stress injury, neuron death due to excitotoxicity, neuroinflammation, familial/genetic factors, and the prion hypothesis.

Mitochondrial Dysfunction and Oxidative Stress Injury

Mitochondrial dysfunction is mainly characterized by the production of excess reactive oxygen species (ROS), increased adenosine triphosphate degradation, caspase release, and disruption of the electron transport complex. An increase in the amount of ROS is observed due to disruption of mitochondrial function. ROS production causes damage to complexes 1 and 3. The production and release of neurotransmitters at the neuron terminals increases metabolic load due to synaptic transmission and activity and depletes mitochondrial respiratory reservoirs. Increased proteostatic load may increase the basal oxidative stress in neurons and cause degeneration to progress (9,11). Continuous mitochondrial oxidative stress causes the accumulation of mitochondrial DNA mutations and disruption of complex I function.

Studies after PD-like symptoms following exposure to 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) neurotoxin-contaminated drugs have shown that MPTP shows its toxic effect by mitochondrial complex 1 inhibition. In addition to MPTP, similar dopaminergic neuron death due to inhibition of mitochondrial complex 1 has been shown in animal models with PD induced by 6-hydroxydopamine, rotenone, and paraquat toxins (12,13,14). It has been shown that mitochondrial dynamics and quality control are impaired in the common autosomal recessive forms of PD (associated with Parkin, PINK-1 and DJ-1 gene mutations) (12).

Excitotoxicity

Excitotoxicity is one of the first theories about the pathogenesis of PD. Glutamate, which plays a key role in the central nervous system (CNS), is one of the neurotransmitters that cause excitotoxicity. The main inputs of the basal ganglia are dopaminergic or glutamatergic to neostriatum from the cortex, thalamus and substantia nigra. Dopaminergic innervation is derived from substantia nigra and glutamatergic innervation is mainly from the subthalamic nucleus and thalamus. Glutamate-mediated stimulation of N-methyl D-aspartic acid (NMDA) receptors in neurons during excitatory synaptic transmission eliminates magnesium block, so calcium and sodium enter the cell. Accumulation of calcium and mitochondrial depolarization in mitochondria causes excitotoxic cell death. Increased intracellular calcium causes nitric oxide synthase activation and increases NO and superoxide production (13). As a result, the amount of peroxynitrite increases. Peroxynitrite mediates oxidation of proteins, lipids and DNA, and nitration of structural enzymes (15).

Neuroinflammation

Neuroinflammation is also known to play a role in the pathogenesis of PD (3,16). Increased microglial activation, presence of reactive astrocytes and pro-inflammatory markers such as interleukin 1β, -6 in the SN and striatum suggest that inflammatory processes are effective in PD (3). The accumulation of alpha-synuclein aggregates in dopaminergic neurons causes microglia and astrocyte activation in regions with large number of dopaminergic neurons such as brain stem and midbrain. Activated microglia, however, cause release of ROS and pro-inflammatory cytokines in addition to neurotrophic factors during the cleaning of extracellular debris, so their benefits in PD are controversial (3).

Familial Genetic Factors

PD is a disease that increases with age, but genetically transmitted PD is seen in 10% of young age people (17). Fifteen genes and 25 genetic risk factors were defined as "PARK" and "non-PARK". The most common ones are α-sin, PARK1 and 4 (SNCA), parkin RBR E3 ubiquitin protein ligase, PARK2 (PRKN), PTEN-induced putative kinase 1 (PINK1), PARK6, PARK7 (DJ-1) and leucine-rich repeat kinase 2, PARK8 (LRRK2) (18,19).

In PD, Lewy bodies, the main component of which is the alpha-synuclein protein, accumulate in the neuronal cytoplasm. The alpha-synuclein protein is converted into tetrameric form by ubiquitinizing, phosphorylating and/or S-nitrosylating and forms aggregates as a result of incorrect folding (20,21). The role of alpha-synuclein in the disease is not fully understood. In some familial PD cases, point mutation, chromosomal triplications and duplications occurring in the alpha-synuclein gene have been found to be associated with early-onset PD (22,23). A non-genetic

disorder in the distribution and/or function of alpha-synuclein may also play a role in the pathogenesis of sporadic PD (20,24).

Prion Hypothesis

Another hypothesis about the mechanism of PD pathogenesis is the prion hypothesis (25,26). In the prion hypothesis, pathologic aggregates pass through neurons through synapses. Following the transplantation of a healthy neuron into the brain of a patient with PD, the observation of Lewy pathology in transplanted healthy neurons over the years and the passage of aggregates into the transplantation tissue evoke a prion-like mechanism (26).

Considering the hypotheses put forward, the fact that many systems are affected at the same time and that the disease is progressive with a long pre-symptomatic period suggest that PD is not due to a single mechanism, but that different molecular mechanisms act together. Therefore, the existing hypotheses alone are not sufficient to explain the pathogenesis of the disease.

Importance of Neuroprotective Treatment

There is no radical treatment for Parkinson's disease. The majority of medications given for treatment focus on motor symptoms, but the long-term use of symptomatic treatments of motor symptoms can cause adverse effects that negatively affect patients' lives. Therefore, there is a need for neuroprotective therapies to stop or slow down the neurodegenerative process, to benefit both motor and non-motor symptoms, and to affect the underlying pathogenesis.

The gold standard treatment for PD is L-DOPA, a dopamine precursor. L-DOPA and dopamine agonists are helpful in improving motor symptoms at the beginning. Motor complications such as dyskinesia and motor fluctuations are seen due to their long-term use and they are inadequate in the treatment of non-motor symptoms such as dementia, anxiety, and sleep disturbance (27). Therefore, new treatment options are needed. Selegiline and rasagiline, which irreversibly block monoamine oxidase (MAO) enzyme type B (MAO-B) in the brain, are used in the symptomatic treatment of PD because they provide improvement in motor fluctuations, freezing, and end-of-dose deterioration (28,29). Neuroprotective efficacy of MAO B inhibitors was evaluated in the "Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism" (DATATOP) study, the first controlled clinical trial to develop neuroprotective treatment in PD, and in the "Attenuation of Disease Progression with Azilect Given Once-daily" (ADAGIO) trial in 2007 (30,31). In DATATOP study, the use of 10 mg daily selegiline has been shown to delay the emergence of symptoms that would necessitate the use of L-DOPA (30). In the long-term follow-up of the DATATOP study, patients with PD receiving selegiline supplementation with L-DOPA for 7 years were compared with a group receiving selegiline for 5 years, which was then replaced with placebo, and a decrease in the rate of progression of the disease, less end-of-dose deterioration, less on-off phenomena, but more dyskinesia was observed in the group receiving selegiline (32).

The ADAGIO study demonstrated that patients in the early-start group receiving rasagiline at a dosage of 2 mg per day for 72 weeks had a slower rate of worsening in the Unified Parkinson's Disease Rating Scale (UPDRS) score compared with patients in the delayed-start group receiving placebo for 36 weeks followed by rasagiline (at a dosage of either 1 mg or 2 mg per day) for 36 weeks (31).

In addition to MAO-B inhibition, safinamide has different mechanisms of action such as sodium/calcium channel blockade, inhibition of dopamine, and glutamate release. Safinamide has been shown to provide more improvement in motor symptoms compared with both placebo and dopamine agonists (33). In the "Study 016" (34) and SETTLE (35) studies, safinamide was shown to improve UPDRS score and delay the use of L-DOPA or dopamine agonists (36). However, safinamide provides only symptomatic treatment rather than stopping the progression of the disease.

Vitamin E increases the cleansing of peroxy radicals with its antioxidant effect and protects the cell membrane against free radical damage by preventing oxidation of lipids, proteins, and DNA. In the early-onset PD model, vitamin E has been experimentally shown to protect against free-radical mediated neuron death in the locus ceruleus and toxin-induced neuron death in the striatal dopaminergic terminals (37). The neuroprotective effects of vitamin E have also been evaluated in the DATATOP study together with selegiline, but it has been shown to provide no additional benefit in correcting or preventing symptoms (30).

Adenosine A_{2A} receptor antagonists are another group of drugs that will be effective both in symptomatic treatment and neuroprotection (38). In the basal ganglia, A_{2A} receptors are involved in the indirect pathway and blockade of the receptor improves motor movements. Clinical studies using istradefylline, preladenant and tozadenant, which are adenosine A_{2A} receptor antagonists, have been performed and these agents have been shown to provide some reduction in freezing time and improvement in movement (39,40,41). There are controversial results as well as studies showing that adenosine A_{2A} receptor antagonists, when used in addition to L-DOPA or dopamine agonists, improve motor movements without worsening dyskinesia (39,40,41,42). The presence of adenosine A_{2A} receptors outside the basal ganglia and antagonists showing their effects of non-dopaminergic pathway suggest that these drugs may benefit motor functions and non-motor symptoms of PD. Non-motor symptoms are often overlooked in PD studies by focusing on correction of motor symptoms or symptomatic treatment with amantadine and anti-cholinergics. However, adenosine A_{2A} receptor antagonists have been shown to be useful in non-motor symptoms of PD, such as depression, anxiety, and cognitive dysfunction (43,44). Considering the association of adenosine receptors with PD, caffeine, a nonselective adenosine receptor antagonist, was thought to be effective in the treatment of PD. As the probability of developing PD has been shown to decrease in caffeine-consuming people by epidemiologic studies, studies focused on the relationship between caffeine-PD (43,45,46). Administration of caffeine at a dose of 10 mg/kg has been shown to protect dopaminergic neurons against MPTP toxicity in mice (47). The neuroprotective effect of caffeine has been investigated in clinical studies, and in a 6-week controlled study, it was observed that it decreased total UPDRS score but did not decrease motor fluctuations and dyskinesia or did not cause a decrease in daytime sleepiness (45,46).

It is thought that increased glutamatergic transmission in the corticostriatal pathway and in the subtalamafugal synapses within the cycle of the basal ganglia also plays a role in the pathophysiology of PD and therefore glutamatergic receptor blockade may be effective in the treatment of PD (48). Amantadine, an antiviral drug, also acts as an NMDA receptor antagonist and can be used as an anti-dyskinetic in PD treatment (49). In clinical studies on the effects of amantadine, it has been observed that it provides benefit in motor symptoms and dyskinesia, but causes an increase in non-motor symptoms (such as hallucinations) (45,50). Memantine, another NMDA receptor antagonist, is used in the treatment of dementia associated with Alzheimer's disease. Clinical studies have been conducted considering that memantine may be beneficial in dementia seen in advanced stages of PD and it has been shown not to provide a positive effect on dyskinesia in PD, but provide benefit in memory and attention (45). The possible neuroprotective effects of mGLu5 receptors, a glutamatergic receptor subtype, in PD have been studied *in vivo* in experimental animals and promising results have been obtained (50). In clinical studies related to this, it has been observed that it can alleviate dyskinesia due to L-DOPA use but cannot support the results obtained from experimental animals (50,51). In a study with 4-Fluorophenyl-{(2R,5S)-5-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]-2-methylpiperidine-1-yl}methanone (5PAM523) molecule, a positive allosteric modulator of the mGLu5 receptor, it has been shown that modulation of mGLu5 receptors in the hippocampus region can cause neurotoxic effects (51,52). In addition to the discussion of the effect-adverse effects of glutamate receptors in PD, another controversial point is the need for the use of antagonists for motor functions, and agonists for the treatment of non-motor symptoms such as anxiety, depression, and cognitive disorders.

Glial cell-derived neurotrophic factor (GDNF) is one of the neurotrophic factors known to be found in dopaminergic neurons and is thought to be effective in the modification of the disease. In clinical studies to evaluate the effects of GDNF in PD, intraventricular injection of recombinant GDNF or direct bilateral putaminal infusion has not been shown to be beneficial (53). Similarly, in a small clinical trial of 12 patients with bilateral putaminal injections of adeno-associated viral vector-2 (AAV)-mediated neurturine neurotrophic factor (CERE-120), some improvement was achieved in the clinical symptoms of the disease and in the UPDRS score, but the same success was not achieved in a later multicenter study (53,54).

Epidemiologic studies indicate that smoking may delay the onset of PD symptoms. It has been experimentally shown that nicotine inhibits alpha-synuclein aggregation and has a protective effect against nigrostriatal damage (55). On the other hand, controversial results were obtained from clinical studies with small groups on the effects of nicotine. It was reported to be ineffective in three of the five studies, to improve motor score in one study, and to worsen motor scores in the other study (56). The small scale of the studies and the different period of nicotine application may be the reasons why the results are contradictory. In a recent large-scale, open-label clinical trial, it was reported that transdermal nicotine patch improved motor score and slowed the progression of degeneration at dopaminergic terminals (56).

With the understanding of the role of neuroinflammatory processes in PD, anti-inflammatory drugs are thought to have the potential to slow the progression of the disease. Large-scale epidemiologic studies have been conducted following the success of cyclooxygenase inhibitors in experimental animals, but it has not been shown to be successful except that ibuprofen causes a 27% reduction in PD formation (57). Therefore, it is thought that immunomodulation in PD should be administered at an earlier stage rather than later. Minocycline, a broad-spectrum antibiotic, has been tested in both experimental animals and patients with PD. Minocycline showed a strong anti-inflammatory effect in experimental animals, and in clinical trials, it was also beneficial in the treatment early-onset PD. Therefore, phase 3 studies were thought to be beneficial (58,59). Successful results of anti-inflammatory drugs, therapies through LRRK2 enzyme inhibition or activation of peroxisome proliferator-activated receptor gamma co-activator 1-alpha with rosiglitazone, metformin and resveratrol are promising in PD (58).

Clinical studies have been conducted in line with the positive results obtained from molecules that are thought to be neuroprotective such as coenzyme Q10, creatine, vitamins A and C, and anti-apoptotic molecules such as TCH346, CEP-1347 in experimental animals, but no positive results could be obtained to stop the progression of the disease or decrease symptoms (37,60,61,62).

With the advancement of technology and the development of science, new treatment opportunities are emerging. Gene therapy is one of these methods. With gene therapy, it is aimed to change the expression of the target protein in certain brain regions by viral vector mediated gene transfer or to protect, regenerate or gain function of neurons by transferring cell grafts of different origin (63). AAV2-mediated glutamic acid decarboxylase (GAD) and aromatic L-amino acid decarboxylase (AADC) gene transfer therapies have been tried in clinical studies conducted for this purpose (64,65). In phase I studies of AADC injection to putamen, it has been shown to increase dopamine synthesis from L-DOPA and moderately improve PD symptoms, and injection of GAD into the subthalamic nucleus provided relief of motor symptoms, especially on the contralateral side of the injection by increasing GABAergic pressure on the thalamus, but phase 2 studies did not achieve the same success (63).

New Approach in Neuroprotective Therapy: Targeting Alpha-synuclein

Alpha-synuclein is a neuronal protein with a molecular weight of 14.46 kDa, which is highly presynaptically expressed in the brain. The physiologic role of alpha-synuclein is not fully known, but it is thought to play a role in the formation of synaptic vesicles, vesicular homeostasis, vesicle size adjustment, and synaptic transmission, and also in the release and storage of dopamine (66).

The fact that alpha-synuclein constitutes the main component of Lewy bodies and its association with cell death suggests that prevention of alpha-synuclein aggregate formation or destruction of aggregates may be a good therapeutic target (20). It is thought that new therapies can be developed to prevent the development and progression of PD through different mechanisms such

as inhibition of alpha-synuclein overproduction by RNA silencing (with siRNA), inhibition of the protein's conversion to oligomeric form deposited in aggregates by stabilizing the unfolded monomeric structure, or enhancing the clearance of aggregates by activation of protein degradation pathways (autophagic pathways) (63). The majority of studies that have been conducted or are currently underway in this area are at the pre-clinical stage. Alpha-synuclein is a structural protein and it is not known how suppression of its synthesis will affect normal physiologic functions or whether it has neuroprotective effect in stopping the progression of disease in humans. Treatments targeting alpha-synuclein can be classified according to their mechanism of action as follows:

1) Reduction of alpha-synuclein production:

Alpha-synuclein aggregates are found in many regions of the brain, from the medulla to the cortex, depending on the course of the disease. Since alpha-synuclein gene duplication and triplication are also known to be one of the causes of PD; it is considered that reducing alpha-synuclein production may be a good therapeutic approach. Reducing the level of cytosolic α-sin can also reduce the risk of oligomer formation of proteins, thus preventing aggregate formation and preserving the viability and function of neurons sensitive to PD (67). One way to reduce α-sin production is RNA interference. In a study in which ectopic expression of human alpha-synuclein was silenced, lentiviral vector-mediated *short hairpin* (sh) alpha-synuclein RNA was given to the rat striatum and the small inhibitor RNA (siRNA) was administered as a two-week infusion into the mouse hippocampus and direct reduction of endogenous alpha-synuclein expression was aimed, no toxicity was observed due to applications (68). As a result of the positive findings obtained from these studies, the effects of unilateral chronic siRNA infusion in reducing alpha-synuclein levels were tested in squirrel monkeys before starting clinical studies (69). As a result of the study, it was observed that alpha-synuclein levels in monkeys decreased by 40-50% compared with the untreated side (67,69). In rats, AAV vectors containing siRNA or control siRNA targeting alpha-synuclein were unilaterally injected into SNpc. It has been shown that the amount of alpha-synuclein is reduced in a short time such as 4 weeks, and that there is also a decrease in striatal dopamine and tyrosine hydroxylase positive cells, but that these decreases do not occur in AAV vector injections containing control siRNA (70). Reduction of the transcription of the alpha-synuclein gene, as RNA-mediated gene silencing, is thought to be effective in pathology, and therefore the effect of clenbuterol, a β2-adrenergic receptor agonist, on alpha-synuclein expression in neuroblastoma cell culture and rat cortical neurons was evaluated and it was shown to cause a decrease in SNCA mRNA level and alpha-synuclein protein level (71). Although there is no clinical study on the role of β2-adrenergic receptor agonists in the treatment of PD, four million Norwegians were screened in two large epidemiologic cohort studies and the use of β2-adrenergic receptor agonists was found to reduce the risk of PD development and vice versa (71). In addition to studies indicating that reduction of alpha-synuclein expression would be beneficial and it might be a new treatment method, there are also studies showing that dopaminergic neurons in SNpc and dopaminergic terminals in striatum decrease due to decrease in alpha-synuclein production, that neurodegeneration progresses and motor function deteriorates, and this raises controversy as to whether the reduction of alpha-synuclein production or the presence of alpha-synuclein is protective against the disease (63,68,70).

2) Inhibition of the formation of alpha-synuclein aggregates:

If the aggregate formation of alpha-synuclein can be prevented, it can maintain its normal function and its toxic effects due to aggregate formation can be prevented. For this purpose, heat shock proteins (HSP), especially small HSP2s are used (67). Although there are studies demonstrating its usefulness in preventing aggregation *in vivo* and *in vitro*, HSPs have not yet reached the stage of clinical studies. Another method used to prevent aggregation is the use of *intrabodies/nanobodies*, which show high selectivity to target epitopes. Intrabodies inhibit oligomerization by interfering with the non-amyloid beta component (NAC) or C-terminal regions of alpha-synuclein monomers, which tend to aggregate. VH14*PEST nanobody is directly targets the NAC region of the alpha-synuclein and NbSyn87 targets C-terminus. AAV vector-mediated VH14*PEST and NbSyn87 molecules were injected into the nigra of AAV vector-mediated alpha-synuclein overexpressed rats three weeks after the injection of alpha-synuclein. It has been shown that VH14*PEST and NbSyn87 molecules prevent nigral degeneration, provide some improvement in motor functions and that VH14*PEST protects striatal dopaminergic tone (72). Although studies using intrabodies have positive results, the need for direct injection of viral vector-mediated molecules into the CNS restricts its use as a treatment.

ANLE138b is an oligomer modulator, alpha-synuclein aggregation inhibitor. It has been shown in the PD mouse model that ANLE138b reduces alpha-synuclein aggregation and inhibits the progression of the disease even after a certain stage of the disease (73). The NPT200-11 molecule has been shown to reduce and prevent alpha-synuclein aggregation in cell models and to be safe and tolerable in healthy volunteers in a phase 1b study (67,73). NPT100-18A is the third preclinical molecule that reduces the formation of wild-type alpha-synuclein oligomers in the membrane. However, it has not been clinically tested yet (73).

3) Increasing intracellular degradation of alpha-synuclein:

Another approach to treatment over alpha-synuclein protein is to increase alpha-synuclein cleansing by activation of degradation mechanisms (autophagic pathways, ubiquitin-proteosome system). Specific degradation of this misfolded protein is thought to prevent neuronal death and improve both motor and non-motor symptoms. Autophagy is a closely controlled cellular death and recycling mechanism in all eukaryotic cells. By the activation of autophagic pathways, it is aimed to clean the accumulated aggregates that are misfolded and to reduce the cellular waste protein load and thus to sustain the vital activities of the cell. There are many pre-clinical studies conducted for this purpose (63,74,75). Rapamycin is one of the most important drugs known to activate the autophagic pathway. Rapamycin-mediated autophagy induction has been shown to increase degradation of alpha-synuclein aggregates, decrease cell death and synaptic damage, improve motor and mitochondrial

functions, and provide improvement in dyskinesia associated with the use of L-DOPA in many different models including cell culture, transgenic mouse models, and toxin-derived PD models (75). Increasing the breakdown of alpha-synuclein aggregates by administration of rapamycin is promising for treatment, but being non-selective, causing immunosuppression, and adverse effects such as respiratory infections, gastritis, leukopenia, hypertriglyceridemia, and hypercholesterolemia limit its long-term use (67). Besides rapamycin, metformin and *5-aminoimidazole-4-carboxamide ribonucleotide* in the Drosophila PD model, resveratrol and *2-hydroxypropyl-β-cyclodextrin* in the cell culture model, and prolyl oligopeptidase inhibitor KYP-2047 and *isorhynchophylline* in the transgenic mouse model have been reported to increase the degradation of alpha-synuclein aggregates by activation of autophagy and be neuroprotective (75,76,77,78,79,80). Trehalose has a natural simple sugar structure and is another important drug that causes autophagic activation like rapamycin, but performs it via chaperone independently of the mTOR pathway (63). It has been shown in animal models that trehalose increases the degradation of aggregates in neurodegenerative diseases by chaperone-mediated autophagy activation and has neuroprotective effect, but the mechanism of action has not been fully elucidated (63,81). In a cell culture study, it was shown that trehalose alone increased cell viability and caused an increase in autophagosome formation, but that there was no decrease in the formation or toxic effects of alpha-synuclein fibrils (82). Given all these results, its role and success in treatment remains controversial.

Reducing pyruvate transport to the mitochondria by using the mitochondrial pyruvate carrier modulator molecule, MSDC-0160, is another mTOR inhibition strategy. In a cell culture study conducted for this purpose, it has been shown that MSDC-0160 molecule is protective against MPP^+ toxicity by inducing autophagy and that it protects nigral dopaminergic neurons in *Engrailed-1* heterozygous *knock out* mice by increasing autophagy (67). However, there is no study on mammalian models created by alpha-synuclein aggregation.

It has been shown that gene transfer mediated overexpression of beklin-1, which is critical for regulation of autophagy and cell death, reduces alpha-synuclein accumulation in cell culture and mouse models (83). However, its reliability and tolerability need to be investigated.

Nilotinib is an anti-cancer drug that acts by inhibiting the Abelson murine leukemia virus oncogene (c-abl) and is involved in many physiological processes in the body, including cell growth, differentiation, proliferation and protein phosphorylation. In a study of brain tissues of Parkinson's patients, it was found that increasing c-abl activity increased alpha-synuclein phosphorylation and aggregation, and in another study, it was shown to reduce parkin gene activity (67). Nilotinib has been shown to reduce alpha-synuclein expression in the A53T transgenic mouse model and protect nigral dopaminergic neurons against viral vector-mediated alpha-synuclein toxicity (84). Despite the positive effects of nilotinib on autophagy induction-mediated aggregation, its pharmacokinetic properties such as failure to cross the blood brain barrier limit its therapeutic potential.

Together with a better understanding of the genetic forms of PD and the role of autophagic pathways in the disease, the association of glucocerebrosidase beta-acid 1 (GBA1) mutation and PD has attracted attention. The activation of β-glucocerebrosidase (GCase), which is effective in the lysosomal autophagic pathway, is thought to have therapeutic potential (63,75,85). Experiments with drugs such as ambroxol and isofagomin have been successful in cell culture and transgenic animal models (75). Ambroxol, of which mucolytic use is approved by the United States Food and Drug Administration, is thought to be effective in PD associated with the GBA1 mutation by regulating the activity of misfolded GCase by its chaperone feature (63).

4) Increasing extracellular alpha-synuclein degradation:

Studies have shown that alpha-synuclein is an intracellular synaptic protein and that it also exists extracellularly. Intercellular transfer of the misfolded alpha-synuclein may also be one of the important steps in increasing alpha-synuclein aggregates. Therefore, active and passive immunotherapy is an important choice among PD treatment approaches. Antibodies that cannot enter the cell target extracellular alpha-synuclein molecules. Both active and passive immunotherapy has been shown to reduce alpha-synuclein aggregation and associated behavioral disorders in animal models (63,86,87). Immunotherapy also triggers microglial activation and provides an anti-inflammatory effect against neurodegeneration. Active immunotherapy was administered to patients with early-onset Parkinson's with AFFITOPE PD03A, a peptide-formulated molecule mimicking the alpha-synuclein, in phase 1 clinical trials. Two different doses, high and low, were applied in a clinical study and both doses were well tolerated and did not create any serious adverse effects (63,67,88). Passive immunotherapy against alpha-synuclein with PRX002 has also passed phase 1a and 1b stages, and it was shown that serum alpha-synuclein level decreased in both stages and no serious dose-limiting adverse effects occurred (67,89). Then, the phase 2 study PASADENA was initiated in Austria, France, Germany, Spain, and the United States (73). In the alpha-synuclein passive immunotherapy study using BIIB-054 molecule, it was shown that this molecule was well tolerated in healthy volunteers and could be determined in cerebrospinal fluid (67). Phase 2 studies on the BIB054 molecule are continuing (73).

5) Inhibition of extracellular alpha-synuclein uptake:

There is little information about the molecules associated with the secretion of alpha-synuclein from neurons or glial cells into the extracellular space and uptake by other cells, thereby spreading the pathology between neurons. In a study, it was found that alpha-synuclein fibrils and tau fibrils were bound to cell surface heparan sulphate proteoglycans (HSPG) and taken by endocytosis, and that it was blocked in cultured cells by heparin, chlorate, heparinase, and genetic *"knock down"* of a key HSPG synthetic enzyme, Ext1 (90). Thus, restriction of extracellular uptake of alpha-synuclein is thought to slow down Lewy pathology.

Another strategy is to investigate the presence of a potential receptor for the uptake of alpha-synuclein fibrils or oligomers. In a study, it was shown that fibrillary alpha-synuclein, although not monomeric alpha-synuclein, bound to the lymphocyte-activation-gene 3 (LAG3) protein on the cell surface with high affinity, and pathologic alpha-synuclein was bound to neurons via endocytosis, causing structural and functional toxicity (91). It is

therefore thought that inhibition of LAG3 may also be effective in inhibiting alpha-synuclein aggregation by reducing binding.

Conclusion

PD is a complex disease due to its pathophysiologic mechanism. Currently, there are no treatment options for the etiology that can replace the L-DOPA and dopamine agonists that provide symptomatic treatment. Lewy bodies, the main pathologic marker of PD, and neuron death due to alpha-synuclein aggregates contained in it suggest that the degradation of aggregates in treatment may improve and even have a neuroprotective effect that may stop the progression of the disease. Many new methods and molecules are being studied for the treatment of PD. However, more successful results can be obtained when changing genetic factors and effects between individuals can be determined, the starting point of the pathology and the time of formation can be determined, and the mechanism of disease progression can be revealed. From this point of view, neuroprotective treatment methods, which have been studied intensively in recent years, show promise for PD and for many other neurodegenerative diseases.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.Ç., Design: E.Ç., G.Y.Ç., B.C.T., Data Collection or Processing: E.Ç., G.Y.Ç., B.C.T., Analysis or Interpretation: E.Ç., G.Y.Ç., B.C.T., Literature Search: E.Ç., Writing: E.Ç.

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