Future of Brain's Health: Prevention of Neural Inflammation with Traditional Chinese Herbal Medicine

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Abstract

Inflammation in the central nervous system is commonly responsible for many serious neurological diseases and inflammatory responses in microglial cells specifically can result in harmful neurotoxic effects. Although activation of microglial cells is neuroprotective to a certain degree, excessive activation of microglia can result in neurodegeneration and can create disorders such as Parkinson's, Alzheimer's, or amyotrophic lateral sclerosis (ALS). Pharmacological strategies are being explored to inhibit microglial activation and any harmful associated inflammation predominantly through natural remedies derived from Traditional Chinese Herbal Medicine. In this review, the characteristics of microglial cells and their importance in immune function as well as natural products derived from Traditional Chinese medicinal herbs that inhibit microglial activation will be discussed. Development of new drugs from well known herbal remedies show promise in alternative drug discoveries and measures to prevent excessive neural inflammation and degeneration.

Keywords: Microglia, Microglial activation, Traditional Chinese Medicine, neurodegeneration, neuro-inflammation, herbal remedies, Parkinson's, Alzheimer's

1. Introduction

Inflammation in the central nervous system (CNS) is known to cause neurodegenerative disorders and diseases. Inflammation in the body arises when white blood cells are generated in the presence of a foreign pathogen to combat infection and maintain homeostatic integrity. Additionally, inflammation can arise from autoimmune disorders such as arthritis or more serious neurological diseases such as Alzheimer's and Parkinson's as well as many more [1].

The function of inflammation is to enclose injury and to ultimately restore tissue but it can be harmful since many chemical inflammatory mediators can also produce hypersensitivity reactions leading to progressive organ damage. Based on research so far it is evident that microglia, the immune cells of the CNS, are involved in neurodegeneration caused by excessive inflammation [2]. The central nervous system, which consists of the brain and the spinal cord, is especially susceptible to inflammation and oxidative stress[1], ensuing irreversible neuronal and glial damage [1]. Microglial activation and chronic inflammation creates greater risk of elevated levels of neurotoxic molecules and pro-inflammatory cytokines that can further contribute to neurodegeneration [2].

Although damage to the CNS cannot be fully reversed, it can be decelerated with the use of neuroprotective compounds derived from anti-inflammatory herbal agents. These herbal anti-inflammatory agents developed from Traditional Chinese Medicine (TCM) remedies, play role in reducing inflammation and neurological impairment from oxidative stress and neurotoxin secretions. TCM has used compounds from herbs such as *Glycyrrhiza uralensis and Ganoderma lucidum* to cease neurotoxin secretions and to combat inflammation by downregulation of neuroinflammatory responses [2]. By using such compounds, comorbid disorders such as depression and anxiety associated with CNS cell inflammation could also be moderated [3]. Here we review recent literature on Traditional Chinese herbal inhibitors of microglia-mediated neurotoxicity.

2. Microglial Cells and Microglial Immunopathology

A variety of specialized cells compose the nervous system including neurons, ependymal cells, and microglial cells[2]. Of the three types of microglial cells, astrocytes are the most numerous glia in the brain and coexist with oligodendroglial cells in the CNS whereas Schwann cells reside solely in the peripheral nervous system [4]. Unlike neurons which are mostly responsible for transmitting chemical and electrical impulses for information processing, microglial cells act predominantly as phagocytes to remove excess debris from the brain left by dead or dying neurons [4] Additionally, microglia are essential for maintaining the stability of neurons, add a protective barrier for neurons against foreign

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[1] *An inability for the body to produce antioxidants at an equal or faster rate in which free radicals are being created. Free radicals are uncharged molecules that accelerate aging.*

[2] *Types of microglial cells include astrocytes, oligodendroglial cells and Schwann cells. (Bear et. al 46)*

objects or physical distress, and myelinate[3] neuronal axons to speed up electrical impulse transmissions. Microglia are always active and continuously survey their local microenvironment [5].

Over the last decade, microglial cells have been studied more thoroughly because most neurological disorders have been attributed to microglial activation and dysregulation [6]. Interestingly, microglia may not only be involved in neurological disorder development, but they also potentially contribute to inflammatory and adaptive immune responses in non-specific CNS regions [6]. Microglial cells undoubtedly have innate immune functions and play a large role in nervous system immunopathology. The CNS has ultimately evolved[4] to protect itself from immune-mediated inflammation that can damage its delicate and vital functions [6].

There are a variety of immune responses and protective measures in the brain in order to defend it, such as the blood brain barrier that prevents blood-borne substances from entering cerebral extracellular fluid [4]. Additionally, Microglial cells serve considerable homeostatic and reparative functions as well because of their ability to respond quickly to physiological and stressful stimuli while also secreting cytokines and neurotrophic factors[5]. Microglia quickly alter their phenotype in response to a nervous system homeostatic disturbance and become activated when their cell surface antigens change morphology or expression [5]. Lastly, microglia can become phagocytic when neurons are damaged or dead and need to be removed from the CNS as not to cause toxicity [6].

Although microglia already appear to have a plethora of functions, they are also responsible for host-defense. When the CNS becomes infected, inflammatory stimuli and interaction with blood- derived cells activates microglial cells to induce inflammation, cytotoxicity and initiate T-cell action through antigen exhibition, ultimately supporting the theory of microglial importance in CNS immune surveillance [6].

Microglia do not, however, function alone to protect the CNS, but rather, communicate extensively with neurons to achieve both their quiescent and reactive states [6]. Unlike in other bodily immune responses, microglia are tightly monitored by chemical responses[6] and react in different degrees of inflammatory reactions based on these neurochemical ratios [6].

Microglia and Cytokines

As aforementioned, microglial cells secrete cytokines and neurotrophic factors when exposed to physiological or stressful stimuli. Cytokines are proteins secreted by non-inflammatory leukocytes and non-leukocyte cells that are responsible for acting as intercellular mediators. These non-antibodies differ from other hormones because they are produced by varying tissue cell types rather than from lymph nodes or other specific glands making them autocrine and paracrine proteins rather than endocrine proteins (nih.gov).

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[3] *Myelin is a membranous wrapping, or sheath, around axon provided by oligodendroglia in the central nervous system and Shwann cells within the peripheral nervous system (Bear et al. 806)*

[4] *CNS evolution is both anatomical and physiological (Aloisi 165)*

[5] *e.g. Neurotrophic tumor necrosis factor (TNF-α)*

[6] *CNS signaling molecules include ATP, neuropeptides, and neurotransmitters (Aloisi 2001)*

Microglia are able to recognize cytokine production intracerebrally during CNS inflammation [6]. On the surface of microglia, certain receptors are able to distinguish between pro and anti-inflammatory cytokines and the balance between these two types result in microglia inducing the appropriate immune function [6].

One particular Cytokine tested for is tumor necrosis factor (TNF-α). TNF-α is a pro-inflammatory cytokine that when released, activates macrophages (astrocytes) to promote glial phagocytosis in the CNS. Additionally, with TNF-α release into the CNS, the production of additional pro- and anti- inflammatory cytokines has been observed [6].

TNF-α and Inflammation

TNF-α is produced when TH1 cells, microglia and macrophages become activated. With its release, TNF-α attaches itself to two similar receptors TNFRI and TNF-RII [6]. Additionally, TNF-α activates a variety of transcription factors such as (nuclear factor kappa B) NF-κB to induce transcription of immune genes [6]. NF-κB transcribes TNF-α while also allowing TNF-α to activate it [3]. NF-κB is usually harvested in the cytoplasm of inactivated cells but must be transmitted to the nucleus to have any effect [3]. This activation and cascade suggests that TNF-α and NF-κB act together during immune inflammatory responses as seen predominantly when observing numerous microglia and CNS macrophages [6].

TNF-α production in the CNS is ultimately harmful because it has depressive effects. Asthma sufferers, for instance, exhibit high incidence of anxiety and depression due to increased levels of TNF-α in the peripheral and central nervous systems [3]. TNF-α promotes neuroinflammatory cascades and is toxic to oligodendroglia, causing them to demyelinate and eventually die [3]. The suppression of TNF-α prevents excess inflammation and the occurrence of associated anxiety and depression [3]. Ultimately, Cytokines are essential regulators of innate and adaptive immune responses and in both infection and autoimmune disorders of the CNS, macrophages, microglia and astrocytes have produced these cytokines to generate CNS-specific inflammation [6]. Taking a closer look within this particular inflammatory cascade, we can easily learn what herbal treatments we can utilize to stop it.

3. Traditional Chinese Medicine and Inflammation

Traditional Chinese Medicine is a practice that originated in Ancient China and evolved over thousands of years, transforming it into what we consider herbal medicine today. In recent years, the re-emergence of these remedies have been researched extensively and authenticated by their long-term use over centuries as compared to newer supplements [2]. Because of their already trustworthy ethnopharmacologial properties, these traditional herbs have been revisited in research and have been confirmed to contain neuroprotective and neurotrophic capacities useful in preventing neurodegeneratory and neuroinflammatory diseases [2]. Furthermore, during the last two decades, it was observed that various botanicals have exhibited anti-inflammatory and antioxidant functions to potentially protect the brain from inflammatory impairment [2]. These herbal extracts can generate neuroprotective effects with varying mechanisms but those specifically targeted to block microglial activation may be most effective at improving neurodegeneration and

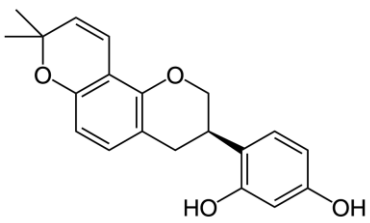
neuroinflammation caused by microglial activation. In the sections to follow, emphasis will be placed on traditional herbal products with discussion on their active constituents specifically in reducing inflammation and inhibiting microglial activation.

3.1 Chinese Licorice - *Glycyrrhiza uralensis and Glycyrrhiza glabra*

Chinese Licorice, referred to as *Gancao* in China, is a flowering plant native to Mediterranean, central and southern Russia and Asia Minor, used often in herbal Chinese medicine for its remarkable uses [7]. Utilized alongside 50 other fundamental herbs used in TCM, *Glycyrrhiza uralensis* has been traditionally used in the respiratory system and the gastrointestinal tract to reduce inflammation [8]. The family of licorice has been used medically since 500 BC and has been nicknamed "The grandfather of herbs" for its extensive medicinal history [7]. Several studies also suggest that Glycyrrhiza can be useful in treating Alzheimer's disease, a very prevalent neurodegenerative disorder [8]. Within Glycyrrhiza, the triterpene saponin GA and the aglycone GRA, have demonstrated neuroprotective and anti-inflammatory characteristics capable of reducing such inflammation commonly found culprit in patients with Alzheimer's [8]. The licorice root itself has an abundance of triterpenoid saponins (4-20%) known best as glycyrrhizin as well as potassium and calcium ions forming glycyrrhizic acid [7]. Furthermore, glycyrhhiza uralenisis contains a series of potent flavonoids capable of interacting with biomolecules via hydroxyl groups, modifying proteins to generate neuroprotective effects [8]. Some of these potent flavonoids include liquiritin, liquiritigenin, rhamnoliquiritin, neoliquiritin as well as several more [7]. For instance, the flavonoid ILG (isoliquiritigenin) demonstrated anti-inflammatory and neuroprotective effects. An isomer of ILG, LG (liquiritigenin) showed anti-depressive properties in murine models and inhibited neurotoxicity created by Aβ (amyloid-beta) peptides [8].

Glycyrrhiza glabra

Also a species of licorice, the flavonoids extracted from *Glycyrrhiza glabra* have also demonstrated attenuation of cerebral injuries in stroke animal models [9]. Just like many other neurodegenerative disorders, stroke can cause inflammation and neurotoxicity since blood is inherently toxic to the brain tissue. Very similar to Gycyrrhiza uralensis, the flavonoid glabridin in Glycyrrhiza glabra can enhance the survival of neurons and prevent their apoptosis [9]. Glabridin specifically, is an isoflavan and the major active flavonoid in *Glycyrrhiza glabra*.



Glabridin

Isoflavans are placed in a subclass of the flavonoid compounds and have a unique structure in which an A, C and B ring are connected respectively through a Carbon 3 [9]. The hydroxyl group on the B-ring has the most anti-oxidative properties and is the most useful factor in bio-actively combating bodily inflammation [9]. In a murine model, *Glycyrrhiza glabra* flavonoids and isoflavans demonstrated reduction in brain malyonyldialdehyde (MDA) while elevating two internal antioxidants in the brain; superoxide dismutase(SOD) and reduced gluthathione (GSH). Also, glabridin isoflavan significantly inhibited cytotoxicity and apoptosis in cortical neurons insinuating the neuroprotective effects of *Glycyrrhiza glabra* and its resourcefulness in traditional and contemporary medicine [9].

3.2 Reishi Mushroom (*Ganoderma lucidum)*

Throughout history, mushrooms have been used greatly within culinary practice, but also have been utilized specifically for the treatment of diseases [10]. In addition to plants, fungi have been studied for their anti-inflammatory and neuroprotective compounds. The Reishi Mushroom, commonly known for its anti-cancer properties is particularly well known in Traditional Chinese Medicine. Further in vitro evidence suggests, that this mushroom's potent anti-inflammatory characteristics also can protect against prevalent neurodegenerative disorders such as Alzheimer's and Parkinson's [10].

Although lifespan is increasing dramatically, with increased lifespan comes greater possibility of developing neurodegenerative diseases. It is estimated that nearly eighty million individuals will suffer from dementia by 2040 where Alzheimer's accounts for about sixty percent of the cases [10].

Like with Glycyrhhiza uralensis, Ganoderma lucidum has the ability to moderate Aβ hypersensitivity [10]. Furthermore, mushrooms such as *G. lucidum* have been shown to promote axon growth during brain development in the striatal region. This is possible because *Ganoderma lucidum* like many fungi contains palmitic, oleic, and linoleic fatty acids that have the ability to generate and promote axonal growth [10]. Unlike newer medications, studies on cell lines suggest taking high doses of fungal and herbal supplements has no adverse effects [10]. By taking extracts of *Ganoderma lucidum*, neurodegenerative diseases could be prevented earlier rather than attempting to cure them in later stages of development [10]. In *Ganoderma lucidum* alone, over 140 different triterpenes have been discovered, all of which can inhibit the production of free radical and act as anti-oxidative agents[7] [10].

With dietary supplement usage *G. lucidum* has demonstrated its ability to delay Alzheimer's onset - a very big step in the field of preventive medicine [10]. In addition to delaying Alzheimer's, *Ganoderma lucidum* has been studied in murine Parkinson's models as well. Previous studies on rats fed with *G. lucidum* oil have shown that they had fewer characteristic symptoms. Those rats who were fed *G. lucidum* also downregulated the neurotoxin 1- methyl-4 phenyl-1,2,3,6-tetrahydropyridine(MPTP), a neurotoxin highly responsible for the originating Parkinson's [10]. A lack of dopamine in both the substantia nigra and striatum is what results in Parkinson's symptoms so by reducing neurotoxin MPTA levels with *G. lucidum*, dopamine levels could be partially restored [10]. With

[7] ganoderic, lucidenic, ganodermic, ganolucidic, applanoxidic acids,lucidones, gadoderals, and ganoderols.

Ganoderma treatments, these dopamine levels in mice increased in these two brain areas and involuntary movement was considerably reduced [10].

Testing Neuroprotective effects of Ganoderma Lucidum

Using a variety of lab techniques to test the neuroprotective effects of *Ganoderma lucidum* gives us confidence in its effectiveness. To test the effects of *G. lucidum*, dopaminergic neuronal cell line MES23.5 and LPS-activated microglia were used after being treated with 1-methyl-4-phenylpyridinium (MPP+)[10]. MPP+ being a metabolite of neurotoxin MPTP would have the same effects as using MPTP directly. After treatment, *G. lucidum* extracts inhibited microglia from producing inflammatory and cytotoxic cytokines such as TNF-α and Aβ [10]. This inhibition of microglial cells producing cytokines makes *G. lucidum* a potentially useful agent in reducing inflammation and thus neurodegerative disorders like Parkinson's as well [10].

3.3 Anti- inflammatory effects of *Sophora flavescens* and *Sophora japonica*

Sophora flavescens is a flowering plant of the Leguminoseae (bean) family and is widely distributed in Asia and Oceania. From the fifty-two species in this family, fifteen of them have been used extensively within TCM. Although *S. flavescens* has anti-inflammatory effects on other portions of the body, purer compounds allow for anti-inflammatory function in the central nervous system as well [11]. From *S. flavescens*, pure compounds including matrine, kurarione, and oxymatrine and Sophoraflavanone G. have been extracted [11].

Oxymatrine is one pure compound that has been studied in depth. This compound derived from *Sophora japonica*, a subspecies of *Sophora flavescens* possesses anti-inflammatory characteristics [12]. Oxymatrine(OMT), is a monosomic alkaloid derived from *Sophora japon*ica and has a unique tetracyclic quinolizine structure [12]. Possessing anti-inflammatory, immune regulatory, antivirus, anticancer, anti-apoptosis and anti-fibrous activity, oxymatrine can be used to treat a plethora of illnesses including neurological ones [12].

In one particular study conducted by Nanjing Medical University researchers investigated the effects of oxymatrine on nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) in Lipopolysaccharide activated BV2 microglial cells [12]. In the investigation, Nitric Oxine (NO), prostaglandin E2 (PGE2), tumor necrosis factor (TNF-α), interleukin-1beta (IL-1β) and interleukin- 6 (IL-6) were derived from the supernatants of BV-2 cell cultures. In the study, oxymatrine inhibited the production of NO,PGE2, TNF-α, IL-1β, and IL-6 while also diminished levels of inducible nitric oxide synthase (iNOS) and cycloozygenase-2 (COX-2), cytosolic inhibitor of kappa B-alpha (I-κBα)and phosphate I-κBα in the MAPK molecule kinases [12]. Furthermore, the nuclear levels of phosphate fifty-six (p65), the extracellular signal- regulated kinase (ERK), phosphate thirty-eight (p38) and c-Jun N- terminal kinase (JNK) pathways were blocked by oxymatrine [12]. After treatments with varying doses of *S. japonica* to this cell lines and released aforementioned cytokines, it was evident that oxymatrine attenuated inflammatory responses in microglia. Thus it is capable of reducing inflammation in various brain disorders [12].

3.4 Berberine

Berberine, an alkaloid extracted from plants like *Berberis aquifolium*, *Berberis aristata*, *Hydrastis Canadensis*, *Coptis chinensis*, *Xanthorhiza simplicissima* as well as several others has also been extensively researched for its anti-inflammatory properties. First known for its use in TCM, berberine has been used to treat a host of diseases including bacterial, fungal and viral infections. Because of berberine's ability to reduce inflammation in the central nervous system, it also acts inherently as an anti-depressant and can also act as a neuroprotector against neural disorders. In mice that have experienced traumatic brain injury (leading to neurodegeneartion), berberine has shown promise in reducing the severity of associated negative symptoms [2]. Mice who received a controlled cortical impact injury and had been treated with berberine 10 minutes after injury showed that berberine significantly diminished functional deficits and brain damage even up to 28 days post-injury [2]. Additionally, berberine reduced neuronal death, apoptosis, BBB permeability, and brain edema a day after injury [2]. While reducing any of these undesired symptoms of TBI, a significant reduction of leukocyte infiltration, microglial activation and inflammatory mediator expression was observed [2]. Berberine treatment did not have any effect on the ERK pathway, however it did reduced NF-κB signaling [2]. Additionally, after administering berberine *in vivo* to mice, it was observed that berberine reduced TBI brain damage by limiting glial inflammatory mediator production as well [2]. Furthermore, berberine was able to reduce the infiltration of neutrophils and slow IL-1β NO production in glia and BV-2 cells [2]. Because of this research, the notion that berberine can inhibit glia-mediated inflammatory responses following brain injury is very likely and can be a primary herbal treatment for inflammation resulting from central nervous injury [2].

3.5 Ginseng

Ginseng is a plant from the Araliacea family and it is found in a lot of locations in the world. Ginseng, or *Panax ginseng*, has an interesting name that means "all healing" [2]. In modern society, Ginseng has become a very popular commodity not only in Chinese medicine, but in Western culture as well because of its easy preparation such as in tea [2]. Although there are two known types of ginseng, white and red, TCM believes the red ginseng is more potent and effective in treatments, however now it is believed both white and red are equally as effective [2].

P. ginseng is truly an "all healing" plant because it has the ability to inhibit DNA damage, induce cancer cell apoptosis, and even inhibit cell proliferation [2]. Furthermore, the chemotherapeutic effects of ginseng are also very strong and the consumption of ginseng significantly decreased several types of cancers in the pharynx, stomach, liver, pancreas and colon in a variety of studies [2]. Ginseng extract, like that of berberine and *S. flavescens* all have the ability to suppress the NF-κB and MAP kinase neuroinflammatory cascades [2]. Furthermore, ginsenosides Rh2, Rh3 and compound K extracted from *P. ginseng* inhibited LPS-induced nitric oxide synthase (iNOS) and cytokine activation, demonstrating their potential benefit in combating neurodegenerative disorders [2]. *P. ginseng* not only inhibits LPS in (iNOS) ,but also inhibited the tumor necrosis factor (TNF-

α) and pro-inflammatory cytokines produced by inflamed macrophages and specifically in BV-2 microglial cells [2].

Ginsenosides and inflammation prevention

The Rg3 ginsenoside was a promising compound in treating inflammatory responses. The single compound Rg3 inhibited phorbol ester-induced cyclooxygenase-2 (COX-2) as well as NF-κB generation [2]. Rg3 attenuated neuroinflammation in primary, murine dopaminergic neurons and glia [2]. Additionally, the polysaccharide ginsan extracted from *P.ginseng*, inhibited p38 MAP kinase pathways and NF-κB during *in vitro* studies while also inhibiting pro-inflammatory cytokines *in vivo* [2]. A fermented extract of ginseng named BST204 inhibited iNOS expression and NO production in LPS RAW macrophages as well. Because these ginsenosides demonstrated their ability to reduce NO formation, PGE2 synthesis and interfere with iNOS and COX-2 expression, it is possible that they can be useful in treating many neurodegenerative disorders such as Parkinson's and Alzheimer's [2].

3.6 Cammelia Sinensis

Green tea is a very popular drink around the world now, however not many people know from which plant it is produced. Green tea, produced by the leaves of *Camellia sinensis*, is one of the oldest beverages in the world while also having a variety of benefits helping with for example cardiovascular disorders, obesity, cancer and it also slows the aging process [2].

From observing the effect of green tea in humans and in laboratory research, it was determined that polyphenol epigallocatechin-3 galate (EGCG) is the most therapeutic component [2]. EGCG can inhibit the production of many inflammatory cytokines such as TNF-α, IL-6, and IL-1β [2]. Because green tea compounds can also cross the blood-brain barrier, it makes it a great compound in antioxidant activity, inflammation reduction, and mediation of cell apoptosis [2]. Although there are many anti-oxidant compounds such as vitamins E and D, EGCG is more potent and more effective in reducing free radical levels [2]. Furthermore, EGCG inhibited NF-κB activities and was a neuroprotective agent in autoimmune disorders such as encephalomyelitis [2]. Like berberine, green tea also can protect against neuronal injury induced by N-methyl-D aspartate (TRAIL), inhibited LPS-induced microglial activation and protected against neuronal injury of dopaminergic neurons [2]. Lastly, EGCG inhibited LPS activated microglia secretions of both NO and of TNF-α by down-regulating iNOS and TNF-α gene expression while significantly protecting against microglial activation-induced injury both in mice and humans [2]. Based on this evidence, green tea and EGCG extract specifically, could be very effective in treating and preventing neuroinflammation and neurodegeneration [2].

10. Conclusions

Although Western medicine is used prevalently in modern medicine, a new era of using traditional medicine to find cures has been on the rise. By using the time-tested

techniques of Traditional Chinese Medicine to cure and prevent illnesses, scientists have discovered a great deal about herbal remedies and their potential in curing and preventing illnesses equally if not more effectively than modern techniques. A few herbs, mushrooms and plants have been studied in depth and their therapeutic effects along with their safety, affordability, and availability have made them very desirable. Recently, these studied remedies have demonstrated that regular consumption can prevent or diminish the development of neurological diseases caused by excessive microglial activation and inflammation. Excessive microglial activation can induce neuroinflammation capable of causing neurodegenerative diseases such as Parkinson's and Alzheimer's and using herbal remedies could prevent and slow down epidemics of these disorders. By observing herbal remedies and studying them further, new neuroprotective agents could be discovered and the complex pathology of neurodegenerative disorders could be uncovered.

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