Experimental Therapeutics of Neurodegenerative Disorders: Unmet Needs

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VIEWPOINT

The experimental therapeutics of neurodegenerative disorders is in its infancy, but neuroprotective strategies are already being applied in healthy persons at high risk of developing disease as well as in patients with manifest illness. Knowledge of etiology and pathogenesis, improved design of clinical trials, the development of biological markers, the advent of genetic animal models, the enhanced identification of susceptibility factors, and more effective drug delivery—such advances have improved the prospects for forestalling onset of illness and clinical decline in the growing numbers of people affected by neurodegenerative disorders.

Alzheimer's disease (AD) is the most common cause of dementia in adults, affecting about 4 million persons in North America. Symptomatic treatment is largely palliative. Based on knowledge of degeneration of forebrain cholinergic pathways, rational treatments have been developed that increase central cholinergic neurotransmission and temporarily improve cognitive and functional performance (*1*, *2*). However, the benefits of cholinergic therapies are modest, associated with potential adverse effects, and short-lived in the setting of progressive neurodegeneration.

Parkinson's disease (PD) affects nearly 1 million persons in North America. Treatments that enhance central dopaminergic neurotransmission ameliorate PD signs and symptoms and temporarily improve quality of life (*3*). However, the symptomatic benefits of dopaminergic therapies are temporary and accompanied by adverse motor and mental effects. No treatments lessen the progressive pace of nigrostriatal degeneration, postpone onset of illness, or substantively slow disability.

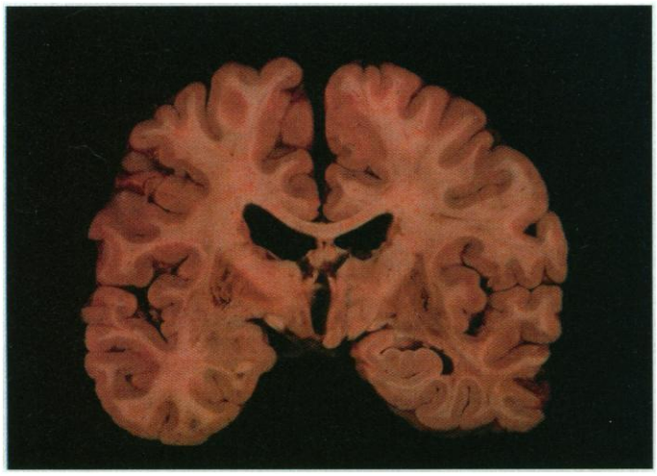

Fig. 1. In Wilson's disease toxic levels of copper accentuate and damage many tissues and organs, including the basal ganglia of the brain.

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder, resulting from mutation of the IT15 gene (4p16.3) and excessive repetition of CAG trinucleotide codons near the 5′ end of the IT15 transcript. About 30,000 persons in North America are affected by HD, and an additional 150,000 bear a 50:50 risk of having inherited the mutant gene. Similar CAG expansions coding for polyglutamine account for mutations in other neurodegenerative disorders, including dentato-rubro-pallido-luysian atrophy (DRPLA), forms of spinocerebellar ataxias, and spinobulbar muscular atrophy (*4*). Agents that retard dopaminergic neurotransmission, such as dopamine receptor blockers or depletors, may lessen the severity of involuntary (choreic) movements accompanying HD, but the benefits are largely cosmetic and fleeting (*5*).

Neuroprotective Therapeutic Strategies

Patients and families affected by these neurodegenerative disorders face many unmet needs, especially in combating problems with cognition, mobility, and behavior. But symptomatic treatment remains a daunting task in the setting of progressive neurodegeneration. Increasing knowledge of etiology and pathogenesis has provided an unprecedented opportunity to develop therapies aimed at protecting neurons from underlying degeneration.

The term neuroprotection has taken on a popular mystique, but in therapeutic terms refers to "interventions that produce enduring benefits by favorably influencing underlying etiology or pathogenesis and thereby forestalling onset of illness or clinical decline" (*6*, p. S160). Pathogenetic mechanisms may involve propagating factors, which may in turn be self-sustaining. Propagating mechanisms that appear common to the neurodegenerative disorders include oxidative stress, free-radical activity, excitotoxicity, accumulation of intracellular aggregates, immunogenecity, mitochondrial dysfunction, and apoptosis (*7*). Mutant proteins identified in AD, PD, and HD (Table 1) also have self-aggregating properties that may predispose to neuronal disturbances in transport and synaptic function (*8*). Preventing self-aggregation or combating its consequences is a rational tactic for therapeutic discovery, but to date no clinical trials have been mounted that address the common pathogenetic mechanisms of these disorders. Nonetheless, agents that are found to be neuroprotective for one disease may prove protective for other neurodegenerative disorders.

Although, neuroprotection remains a largely unrealized therapeutic goal, decoppering therapy for Wilson's disease (WD) can be considered a prototype of neuroprotective therapy (Table 1). WD is a relatively rare (prevalence of about 30 per million) autosomal recessive disease resulting from a disturbance of copper incorporation into ceruloplasmin and the eventual accumulation of copper in the liver, kidney, brain, and cornea (Figure 1). Untreated, homozygotic gene carriers eventually develop hepatitis, cirrhosis, aminoaciduria, and progressive neurologic deterioration characterized by movement disorder, as well as speech and swallowing problems. In persons with manifest illness, decoppering therapies slow and may even reverse neurologic deficits. WD is also a prototype for prevention strategies whereby decoppering therapies can prevent the clinical manifestations of illness in healthy persons who are known homozygotic gene carriers (*9*). Notably, penicillamine decoppering therapy was developed more than three decades

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before the mutant gene for Wilson's disease was eventually identified on chromosome 13.

Knowledge of the pathogenesis of copper accumulation in WD led to the rational development of neuroprotective and preventive treatments. This experience argues strongly for continued investment in basic research in order to provide essential clues about the proximal etiologic events involved in the induction of disease, the intermediate events accounting for the presymptomatic latency and the prodromal phase of illness, and the more distal events paralleling clinical onset and phenotypic expression. But the pathogenetic mechanisms accounting for AD, PD, and HD are not as straightforward as are those for WD. Basic science advances, although necessary, are insufficient for developing neuroprotective interventions. Other factors, perhaps not as obvious, are critical for achieving successful neuroprotective and preventive therapies.

Better Designs and Outcome Measures

The DATATOP (deprenyl and tocopherol antioxidative therapy of Parkinsonism) study has been one of the most comprehensive clinical trials aimed at slowing disability resulting from neurodegeneration. Initial findings from this trial in patients with early PD indicated that deprenyl (selegiline), a type B monoamine oxidase inhibitor, significantly delayed disability associated with early PD; however, therapeutic effects were not sustained or translated into enduring benefits such as reduced levodopa-related adverse effects or extended lifespan. The slowing of disability may have been due in part to weak dopaminergic effects of deprenyl. The antioxidant α-tocopherol had no benefit in slowing disability or extending life. Notably, research participants in DATATOP, regardless of treatment assignment, lived as long as age-matched controls without PD (*10*).

A similar controlled trial was carried out in patients with AD of moderate severity. After post hoc adjustments for imbalances at the time of randomization, both deprenyl and tocopherol were found to delay disability as measured by relevant milestones (activities of daily living, cognitive changes, institutionalization, and death) (*11*). These findings have yet to be replicated, and it is not known if the observed effects on disability have been sustained or have had a favorable influence on the underlying disease process. It is unclear why tocopherol benefited the AD patients but not the PD patients participating in the DATATOP trial.

These clinical trials were designed to detect relatively small therapeutic effects, largely measuring disability, in the setting of considerable variability. Accordingly, relatively large sample sizes were required to detect relatively modest treatment effects. It is reasonable to argue for more robust and less variable outcomes, but even small clinical benefits may prove worthwhile in the incremental process of clinical trials. Some authorities have suggested that testing a large number of combined agents in a small number of selected patients will improve the efficiency of clinical trials, but cocktails of drugs may produce negative interactions as well as the desired synergistic effects. In the long run, whether or not experimental treatments prove enduring will be critical in determining neuroprotective value.

The recent initiative of a pilot trials program by the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) (*12*) is an important effort to help fashion more effective designs and relevant outcome measures. Other NINDS-sponsored controlled trials are under way in early-PD patients to assess the consequences of earlier versus later levodopa therapy (NS34796) and the impact of enhancing mitochondrial electron transport with coenzyme Q treatment (NS36714).

An important challenge is to develop valid and reliable biological markers of neurodegeneration. Surrogate markers that detect the progression of brain disease in the living patient have enhanced the experimental therapeutics of demyelinating disorders wherein magnetic resonance imaging (MRI) has helped monitor the distribution and load of demyelination (*13*). Other neuroimaging tools have already shown promise as markers of neurodegenerative activity, helping to place the impact on disability observed in the clinical trial in biological perspective (*14*). But biological markers should be

Table 1. Comparison of familial neurodegenerative disorders.

Disease	Genetic transmission	Chromosomal localization	Mutant gene product or genetic susceptibility	Primary pathway degeneration (intracellular aggregates)	Clinical features	Symptomatic therapy	Neuroprotective therapy
Alzheimer's (AD)	Autosomal dominant						None
	Early onset	21	Amyloid precursor protein (APP)	Cortical and basal forebrain (neurofibrillary tangles, neurites)	Adult-onset dementia, ± movement disorder	Cholinergic agents	
		14 and 1	Presenilins 1 and 2 (PS1 and PS2)				
		12	α-2 Macroglobulin (A2M)				
	Late onset	19	Apolipoprotein E4 (apoE4)				
Parkinson's (PD)	Sporadic, autosomal dominant	4q21–23	α-Synuclein	Nigrostriatal (Lewy bodies)	Adult-onset movement disorder, ± dementia	Dopaminergic agents	None
Huntington's (HD)	Autosomal dominant	(4p16.3) CAG repeat (single gene mutation)	Huntingtin	Striatonigral, striatopallidal, cortical (Intracytoplasmic, intranuclear)	Adult-onset movement disorder, dementia	Dopamine blockers and depletors	None
Wilson's (WD)	Autosomal recessive	(13q14.3) point and frameshift mutations	P-type ATPase	Hepatolenticular (copper)	Juvenile-onset movement disorder	Decoppering agents	Decoppering agents
			Impaired copper incorporation with ceruloplasmin				

viewed as an enhancement of neuroprotective inquiry rather than a substitute for relevant and enduring clinical outcomes.

Better Definition of the At-Risk Population

The CARE-HD (coenzyme Q_{10} and remacemide evaluation in Huntington's disease) clinical trial, sponsored by the NINDS (NS35284), is in progress to examine the effects of coenzyme Q_{10}, a substrate for mitochondrial electron transport, and remacemide, an NMDA (*N*-methyl-D-aspartate) glutamate antagonist, on the pace of disability in patients with early HD. This trial is based on the rationale that mitochondrial energy defects and glutamate-mediated excitatory neurotransmission act alone or in combination to promote the neurodegenerative process (*15*). If either intervention were found to benefit patients with manifest HD, this would help justify a prevention trial aimed at postponing the onset of illness in healthy, presymptomatic gene carriers. Because an individual whose parent is affected by HD can be screened for the presence of the IT-15 mutant gene, preventive therapeutic trials aimed at forestalling the clinical onset of HD should be possible. Studies are under way to better define the clinical characteristics, predictability, and biologic correlates of the onset of HD.

As genetic risk, susceptibility factors, and prodromal features of illness are better characterized, prevention strategies will increasingly be directed at healthy cohorts in an effort to postpone the onset of illness. Under the sponsorship of the NIH, National Institute of Aging (AG15922), such a strategy is being undertaken in healthy, nondemented, women, 65 years of age or older, with a family history of AD in an immediate relative. Research subjects are being enrolled to participate in this randomized, double-blinded, placebo-controlled clinical trial of estrogen alone or combined estrogen and progesterone and followed systematically for the occurrence of cognitive decline.

More precise definition of susceptibility factors, the prodromal phase of illness, and clinical onset will provide powerful paradigms to test putative neuroprotective therapies. But cautions are appropriate. The prevention model carries the added risk of inadvertently hastening the onset of illness in healthy individuals. This risk underscores the need for placebo treatment, adequate controls, and independent prospective monitoring of prevention trials.

Better Screening of Promising Interventions

The advent of genetic mouse models of neurodegenerative disorders has invigorated the search for neuroprotective interventions, providing the potential to characterize in vivo the onset and course of neurodegeneration (*16*, *17*). Theoretically, these models should accelerate the screening of promising neuroprotective interventions. However, the types of genetic models vary considerably, depending largely on the genetic construct used. Producing adequate numbers of these models is expensive for therapeutic screening, especially when fewer animals are needed for fundamental biological studies. The development of neurodegenerative polyglutamine disease models in *Drosophila* (*18*) enhances the prospects for conducting therapeutic trials, provided that the phenotype and experimental therapeutics of the fruit fly are relevant to the human condition.

Drug Delivery, Targeting, and the Blood-Brain Barrier

It is obviously futile to develop a drug that will not reach its target. For the desired central nervous system (CNS) effects to be achieved, a systemically administered compound must pass through the capillary endothelium of the blood-brain barrier (BBB). Invasive strategies may circumvent the BBB through neurosurgical approaches to implant cells, tissues, or drug-delivery systems. Pharmacologic-based strategies are being developed to deliver drugs, polymers, or liposomes to their CNS targets, and innovative physiologic-based approaches make use of intrinsic pathways of carrier-mediated transport of nutrients (for example, levodopa via the neutral amino acid transport system) or receptor-mediated transport of peptides (for example, insulin and transferrin) (*19*). Regardless of delivery strategy, neuroprotective therapy will ultimately rely on the capacity of interventions to reach and interact with the intended CNS system target.

Patience as Well as Patients

Several intangible factors may potentially compromise neurotherapeutic discovery. A mounting sense of urgency and desperation among patients and families may lead to getting it fast rather than right. The general urgency among patients and families is understandable, given the broad and increased risks of neurodegenerative disease among expanding and aging populations. Pressures may also come from well-intentioned therapeutic developers who may place personal financial interests and prestige above the standard to develop safe and effective treatments. Preliminary data (usually derived from small samples and brief observation), often overstated by the media, may further heighten concerns and desperation.

Reaffirming a position taken a decade ago about neurotransplantation for PD, there is an ever-present need for patience as well as patients in experimental therapeutics (*20*). It is important to follow research subjects for a sufficiently long duration (months or even years) to confirm genuine neuroprotective effects. It may be time-consuming and costly to conduct therapeutic trials with proper placebo or sham groups, but such controls are reality checks that in the long run are time savers. Adequate controls also provide the safety net to ensure that experimental treatments do not inadvertently hasten the onset of illness or clinical decline. Patients and families naturally hope for quick fixes, but these should not come at any risk or cost.

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