Potential neuroprotective drugs for Parkinson’s disease

The Ravina et al. systematic review of potential neuroprotective agents for PD identified 59 potential neuroprotective compounds. Further detailed review points to 12 currently available compounds with various mechanisms of action that merit exploratory investigation for clinical use with a goal of neuroprotection early in the course of PD.

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Neuroprotective agents for clinical trials in Parkinson’s disease

A public policy experiment

Commentary by Roger L. Albin, MD

In this issue, Ravina et al. describe a process supported by the National Institute of Neurological Disorders and Stroke (NINDS) to identify candidate compounds for “neuroprotection” trials in PD. This is a particularly difficult task because our notions of pathogenesis remain vague, epidemiologic studies have failed to generate a list of potent risk factors, and preclinical models have uncertain relevance. Because of these limitations, other less scientific factors often have a greater role in the choice of potential treatments than they should. Chief among these other factors are business decisions by pharmaceutical companies that may reflect input from the marketing department more than the research department.

A major strength of the NINDS process is that it started by establishing a uniform set of criteria to help select agents most likely to have a therapeutic effect. Undoubtedly, this approach is only as good as the information guiding the decisions. If the assumptions about PD pathogenesis and the preclinical models used to select these agents are flawed, then the agents are unlikely to have the desired neuroprotective effect. Furthermore, available information about potential treatments is incomplete, reflecting unequal levels of interest in different agents and different types of preclinical assessments performed. As a result, potential treatments did not all have equal opportunity to make the cut. Despite these limitations, this is a valiant attempt to make rational decisions given the current state of knowledge. The fact that few of these agents have commercial interest is an interesting commentary on the usual selection process. The success of what appears to be a relatively unbiased approach will be measured, at least in part, by the effects these treatments demonstrate in clinical trials.

Designing trials to determine whether these agents actually have neuroprotective effects will not be easy. However, even the term “neuroprotection” has been clouded by so many arguments about pathogenesis and mechanisms of action that most clinical trialists prefer more concrete terms such as “course-modifying.” Designing a study that can clearly distinguish course-modifying effects from symptomatic effects is particularly difficult. No matter how clever the trial design, clinical measures of impairment and disability may not be adequate for this purpose, raising interest in potential biomarkers to be used as secondary or even surrogate endpoints. Even the most studied of these (e.g., β-CIT SPECT and fluorodopa PET imaging) have failed to produce unambiguous evidence of neuroprotection in recent studies. Thus, selecting promising agents to study is only the first of many daunting tasks on the road to neuroprotection in PD.

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Limb-girdle muscular dystrophy type 2I

Poppe et al. report the phenotype of a common type of limb-girdle muscular dystrophy (LGMD), LGMD2I, due to mutations in the fukutin-related protein gene (FKRP). Age at presentation varies widely and rate of progression may be slow. Cardiomyopathy and respiratory failure (from intercostal and diaphragmatic muscle weakness) are frequent.

In the original Tunisian family assigned the LGMD2I mutation, Driss et al. identified a novel homozygous FKRP mutation and abnormal expression of α-dystroglycan and laminin-α2 in their muscles, confirming that LGMD2I is due to FKRP defects.

The accompanying Editorial by Wicklund and Hilton-Jones considers these two papers and the (thus far) 15 LGMDs: 5 autosomal recessive LGMDs (denoted 1A through 1E); 10 autosomal recessive LGMDs (2A through 2J). The specific gene lesions have been defined for 13 of the 15 mutated proteins and include an enzyme (calpain), membrane signaling and repair (caveolin, dysferlin), sarcolemmal integrity (sarcoglycans), and contractile proteins (e.g., titin). They note that identification of genotype is important since certain LGMDs have a predilection for cardiopulmonary failure (as is the case in the LGMD2I report) and since widely varying treatment strategies will be required for successful gene therapy.

The pathogenesis of tremor in essential tremor and PD

Essential tremor

Pagan et al. used MRS to define differences in the cerebellum of essential tremor vs matched normals. The N-acetyl-aspartate to creatine ratio is low.

The accompanying editorial by Rottenberg contrasts the Pagan et al. studies of essential tremor with those published in Neurology 2003;60:601–605 by Doder et al. on Parkinson’s disease tremor. The Pagan et al. work suggests an oscillator in the cerebellum in essential tremor, whereas the studies of PD with PET imaging of 5-HT1A receptors pointed to an abnormality of serotonin-synthesizing neurons in midline raphe neurons being associated both with total and resting PD tremor.

Pregabalin for treatment of postherpetic neuralgia

Dworkin et al. conducted a double-blind trial of pregabalin in 173 patients with postherpetic neuralgia. Within 1 week, pregabalin treatment resulted in significant, clinically important pain relief and improved sleep compared with placebo.

Chromosomal abnormalities in ALS

Meyer et al. studied 85 ALS patients and identified five individuals each with different balanced chromosomal rearrangements. The unexpected frequency of chromosome abnormalities may represent a genomic risk for apparently sporadic ALS.
Outcome of trigeminal nerve section in the treatment of chronic cluster headache

Jarrar et al. followed 17 patients who underwent trigeminal root section for chronic cluster headache. Patients were symptomatic for a mean of 9 years, and, after a mean of 6.7 years follow up, 76% had complete or nearly complete relief. There was relatively little morbidity.

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Snoring and chronic daily headache

Scher et al. found chronic daily headache (CDH) strongly associated with frequent snoring episodes. CDH is a risk factor that appears to be independent of the usual risk factors for sleep-disordered breathing.

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Carotid dissection related to martial arts

Pary and Rodnitzky describe a patient who suffered a serious stroke due to dissection of the internal carotid artery as a result of participating in the martial art of taekwondo.

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