Science plus technology to address challenges in determining the efficacy of neuroprotective/neurorestorative therapies

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Introduction

The main challenge in neuroprotection is to demonstrate in humans the efficacy of any neuroprotective therapy. Exploration of Neuroprotective Therapy (ENT) highlights interest in the classical pharmacology, in sophisticated techniques such as deep brain stimulation and in traditional medicine tools (herbal medication, meditation...), etc.

While Alzheimer’s disease (AD) and Parkinson’s disease (PD) require neuroprotective interventions to reduce neuronal death whereas amyotrophic lateral sclerosis, spinal cord injuries, autism, etc. may require restoration or both protection and restoration. The challenges are manifold and the 21st century should be able to provide answers to many of the diseases that currently do not have an effective therapy to treat or slow down disease progression.

Nervous system diseases’ diversity, risk assessment and the discovery of successful therapeutic strategies

Diseases affecting the peripheral or central nervous system share some features: alteration of energetic balance, and/or local depletion of a given neurotransmitter, and/or alteration of brain circuits and/or neuronal death and/or glial cell death, etc. Similarly, measuring the effectiveness of a given intervention is a challenge whose solution may vary from one nervous system disease (NSD) to another, but there may be shared parameters to measure, e.g., the level of glucose in the cerebrospinal fluid (CSF).

Oomics approaches provide a large amount of data that, in fact, provides valuable information. In terms of NSD, genomics provides risk factors. For late-onset degenerative diseases (e.g., non-inherited AD and PD) it is questionable whether knowing the risk is desirable or not [1-9]. Personally, I would not want to live knowing that I am at high risk for AD to live in fear and end up with a healthy brain but a fatal heart attack.
The two phases in NSDs

In some NSDs in which neuronal death occurs, two phases appear that may require differential therapeutic approaches. Although targeting neurons may be good in prevention and first clinical stages, targeting glial cells is instrumental at advanced stages. Among them microglia, upon activation, may be proinflammatory (M1 phenotype) or neuroprotective (M2 phenotype) [10]. Time may be a factor convert M1 into M2 cells and, also, there is in vitro evidence of interventions that can skew the M1 into the M2 phenotype. Combining these two discoveries it would be interesting to explore time windows of therapeutic intervention.

Positron emission tomography (PET) is advancing to detect neuroinflammation in the human brain through the use of probes that interact with microglial molecules. As far as we know, these procedures are not routine, that is, they are already in the experimental phase [11-20]. The development of M1 and M2 PET ligands would help decide when therapies should temper neuroinflammation and when they should be addressed to boost neuroprotection.

Learning from other diseases

Along with age-related neurodegenerative diseases, three other common diseases are on the rise in recent decades, namely diabetes (type II), hypertension, and hypercholesteremia. There are interventions for all of them that do not cure the underlying cause, but allow patients to enjoy relatively normal lives. Parameters to evaluate the efficacy of therapies to combat these therapies are well defined.

Centuries back when nobody knew what a carbohydrate was, diabetes was diagnosed by the sweetness of the urine. After discovering that sweetness was due to sugars, and that glucose was the culprit, the last two centuries allowed progress in simple tests to determine glucose in blood urine and CSF [21, 22]. It should be also noted that it is possible to assess whether the patient has the disease under control by measuring A1c glycosylated hemoglobin [23-26].

Can surrogate parameters for NSD be found in blood? This is one of the main questions although the answer is likely not. Desirable but very difficult. Therefore, other body fluids should be considered and the field must be open to develop strategies to measure parameters in the CSF.

Telemetry and nanotechnology to measure CSF components

In the case of NSDs, the two legs to support the therapeutic corpus are neuroscience and bioengineering. While advances in neuroscience are difficult to predict, engineers can design and build almost any device. The results of Neuroscience in the case of some NSDs have been poor, but the technological advances in Medicine have been notable. ENT welcomes articles from neuroscientists who think of useful devices to address neuroprotection/neurorestoration and that can be built by bioengineers. Telemetry (see below) is one of the techniques that show potential and neuroscience must benefit of telemetry and any other technological advance that is deemed necessary. The diabetes research field is gaining momentum due to tools that allow real-time measurement of glucose levels by telemetry [27-30] thus avoiding changes due to stress in animal handling, circadian rhythms, etc. Who would not want to know whether CSF glucose levels, that in a healthy individual are 60-70% of those in blood, are altered in neurodegeneration and are restored by a given neuroprotective therapy?

Technology has advanced enormously in the last decades and the Neuroscience field must take advantage of its present and future possibilities. ENT journal will welcome papers showing bioengineers and nanotechnology researchers the way to assess parameters measuring the efficacy of neuroprotective therapies.

Longitudinal studies

Coffee/tea consumption reduces the risk of suffering from PD or AD; there are solid longitudinal studies show that natural methylxanthines: caffeine in coffee (or cola drinks) and theophylline in tea are neuroprotective (via blockade of adenosine G protein-coupled receptors) [31-41].
Natural compounds or approved drugs considered as nootropics, i.e. those that improve brain function, must be subjected to longitudinal studies to show neuroprotective potential \([42-50]\). Ideally these studies should be performed in humans but ENT is open to receive submissions of epidemiological-like longitudinal studies in animals. Taking AD models, which require time to manifest cognitive deficits: could these deficits manifest themselves later in animals that consume nootropics?

Finally, another version of longitudinal studies to address neuroprotective potential is to analyze data of aged people that take pills (antihypertensive, antidiabetic, etc.). Do some pills reduce/increase the age at which a certain NSD occurs? Do patients on memantine have accelerated cognitive decline or live longer or shorter than patients taking another anti-AD drug? The data is there, and Governments, Institutions and Hospitals should make possible access to the data (preserving the identity of the individuals). Similarly, do ethnic groups present less impact from NSDs due to their lifestyle? Do societies that started few years ago to take pills have more/less affectation of NSDs?

**Conclusions**

ENT is born with the spirit of serving as a platform to accelerate the translation of therapies to patients with diseases of the peripheral or central systems. The added value of the journal consists of going beyond the publication of an article. The journal will be successful to the extent that published studies, opinions, reviews, etc. take into account the greatest challenge in the field, namely how the efficacy of therapy may be demonstrated. Certainly, articles that convincingly show advances in any therapeutic aspect related to NSDs are welcome. Reports on potential biomarkers whose measurement can be carried out in a living human being (rather than in postmortem tissue) will be critical in overcoming the challenges of demonstrating the efficacy of neuroprotective therapies. Articles in which novel strategies to determine efficacy are pursued, e.g., longitudinal trials in humans and/or animal models, are very welcome. Finally, the journal would like to include innovative ideas on technological developments to discover biomarkers that can be measured in living humans, e.g., using probes and nanotechnology or telemetry to detect in real-time glucose and oxygen levels in the cerebrospinal fluid.

**Abbreviations**

AD: Alzheimer’s disease  
CSF: cerebrospinal fluid  
ENT: Exploration of Neuroprotective Therapy  
NSD: nervous system disease  
PD: Parkinson’s disease

**Declarations**

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The author contributed solely to the work.

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