

Prevention of Neurological Disorders: A Novel Perspective

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COLUMN ARTICLE

Abstract

Neurological disorders are heterogeneous clinical conditions with variable course and outcome, representing a challenge as their prevalence increases with age. Some of these conditions such as migraine and stroke cause frequent disability and death. The available treatments are essentially symptomatic. Our understanding on the pathophysiology of neurological disorders is poor. Oxidative stress and neuroinflammation are recognized causes of neurological disorders. Treatments of neurodegenerative disorders include primary prevention, slowing or arrest of disease progression, and control of symptoms. Recent research focuses on the search for biomarkers for earlier diagnosis and preventative treatments to delay the onset of neurological disorders. For example, polyphenol dietary integration has been proposed for its potential anti-inflammatory and antioxidant activity. However, it seems that the limiting step in a real forward progress in preventing neurological diseases and developing efficient treatments is our lack of knowledge of brain metabolism and functioning. My recent research points at the existence of an aerobic metabolism outside the mitochondria in nervous tissue. However,

the downside of the expression of an ectopic respiratory chain is an increased risk of oxidative stress, which is in fact recognized cause of brain damage and the most recent target of drugs for neurological diseases.

Keywords: Neurological Disorders; Oxidative Stress; Neuroinflammation

More than 600 diseases of the nervous system are known. Table 1 summarizes the main neurological disorders. Cerebrovascular disease alone accounts for most of the deaths due to these diseases. These are difficult to treat due to late diagnosis, and limited distribution of medications into central nervous system (CNS). Moreover, symptoms often are lifetime. Immune-mediated inflammatory CNS diseases represent a rapidly evolving area of medicine. Dementing disorders, conditions in which altered cognitive functions associate with behavioural changes, are age-related and range from mild to severe cognitive impairment. Alzheimer's disease (AD) is the predominant dementia in the world, with the interesting exception of Japan, where the commonest cause of dementia in males is vascular [1]. Parkinson's disease (PD) is characterized by motor dysfunction, cognitive, sleep and olfactory disturbances. Amyotrophic lateral sclerosis (ALS) is a motor neuron fatal clinical condition.

Neurological Diseases
ALS
Alzheimer and other dementias
Arteriovenous Malformation
Brain Aneurysm
Brain and Spinal Cord Tumors
Cerebrovascular disease
Dural Arteriovenous Fistulae
Epilepsy
Migraine
Neuroinfections
Nutritional deficiencies
Multiple Sclerosis
Parkinson's Disease
neuropathies
Neurological injuries
Stroke

Table 1: List of the most common neurological diseases.

A risk factor for these neurodegenerative diseases is aging, as the brain appears to progressively acquire a pro-inflammatory phenotype (inflamm-aging). Neuroinflammation is a physiological response of microglia and astrocytes activated by various types of injury [2], now supposed to be an early cause rather than a consequence of neurodegeneration. Neuroinflammation can be primary or secondary, for example induced by the initial pathological insult of the disease.

Oxidative stress, resulting from the imbalance among the production of reactive oxygen species (ROS) and antioxidant systems triggers brain damage. Oxidative damage and hypometabolism plays a role in tissue injury in MS a chronic progressive demyelinating disease, associated with axonal degeneration, cause of disability. ROS are produced during mitochondrial oxidative metabolism, and in turn oxidative damage leads to mitochondrial dysfunction promoting inflammation, as mitochondria are a source of danger-associated molecular patterns (DAMPs) that can activate pattern recognition receptors [3].

My research line has shown the existence of an aerobic metabolism outside the mitochondria, in the nervous tissue. Myelin of both the peripheral and CNS would produce chemical energy for the axoplasm [4]. Notably, an ectopic aerobic metabolism, besides allowing the spread of five respiratory complexes on a wider surface, with greater ATP production capacity, would have the meaning of avoiding the inherent risk due to the presence of mitochondrial DAMPs. This new vision, while justifying the high oxygen consumption of nervous system, points to the existence of an unsuspected source of radicals: any disturbance of the respiratory chain function produces oxidative stress, which would diffuse in the cytosol [5].

The spread of neurological diseases sets the need for preventative interventions [6]. Recent research focuses on the search for both pathogenetic or diagnostic biomarkers [7]. Many modifiable risk factors include insulin resistance, elevated blood pressure, obesity, smoking, physical inactivity and high-sodium and hypercaloric diet. Dietary changes can be beneficial, as they can also affect the composition of the microbiome, which influences the development of autoimmune disorders and of PD. Among dietary interventions, intake of polyphenols, vegetable secondary metabolites, has been associated with reduction in the risk of PD and other neurological diseases. Polyphenols are candidates for neuroprotection. We have shown that, besides their capacity to scavenge ROS polyphenols can also suppress ROS formation by either inhibiting, enzymes involved in their production [8]. Most of the putative risk factors for multiple sclerosis, some other neurodegenerations and neurological diseases do not seem amenable to primary prevention. Many primary causes of neurological disorders such as pathogens or environmental factors proved inconsequential. It seems that the limiting factor in a forward step in the neurological diseases prevention and development of treatments is our lack of knowledge of brain metabolism and functioning. No primary preventive strategy improving physical and mental health is possible without a thorough understanding of nervous system metabolism and its role in oxidative stress generation. Interestingly, the current effective novel drugs for AD, ALS and PD are antioxidants.

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