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Pharmacology & Therapeutics 109 (2006) 42 – 56

Pharmacology & Therapeutics

www.elsevier.com/locate/pharmthera

Associate editor: K.W. Roche

Traffic accidents: Molecular genetic insights into the pathogenesis of the hereditary spastic paraplegias

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Abstract

The hereditary spastic paraplegias (HSPs) comprise a clinically and genetically diverse group of inherited neurological disorders in which the primary manifestation is progressive spasticity and weakness of the lower limbs. The identification of over 25 genetic loci and 11 gene products for these disorders has yielded new insights into the molecular pathways involved in the pathogenesis of HSPs. In particular, causative mutations in proteins implicated in mitochondrial function, intracellular transport and trafficking, axonal development, and myelination have been identified. In many cases, the proper intracellular trafficking and distribution of molecules and organelles are ultimately thought to be involved in HSP pathogenesis. In fact, deficits in intracellular cargo trafficking and transport are concordant with the length dependence of the distal axonopathy of upper motor neurons observed in HSP patients. Through a better understanding of the functions of the HSP gene products, novel therapeutic targets for treatment and prevention are being identified.
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Keywords: Mitochondria; Transport; Axon; Degeneration; Golgi apparatus; Vesicle trafficking; Myelin; Endocytosis; Motor; Chaperone

Abbreviations: BSCL2, Berardinelli–Seip congenital lipodystrophy 2; CGL, congenital generalized lipodystrophy; ER, endoplasmic reticulum; GEF, guanine nucleotide exchange factor; HSP, hereditary spastic paraplegia; Ig, immunoglobulin; L1 CAM, cell adhesion molecule L1; PLP, proteolipid protein; PMD, Pelizaeus–Merzbacher disease; TMD, transmembrane domain.

Contents

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0163-7258/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.pharmthera.2005.06.001

1. Introduction

Voluntary movement is widely regarded to depend upon the interplay between 2 major neuronal motor systems. One of these, the "extrapyramidal" motor system, comprises neurons and their processes in the deep cerebral nuclei, brainstem, and cerebellum; it influences motor function by modulating the "pyramidal" motor system. The neuronal pathways subserving movement through the pyramidal system can be divided into 2 main stages. In the first, neurons in the cerebral motor cortex, the upper motor neurons, send axons through the medullary pyramids, where most decussate to form the lateral corticospinal tract in the contralateral spinal cord. A small number of the fibers that do not decussate in the pyramids cross in cervical spinal segments and descend as the anterior corticospinal tract; an even smaller percentage descends uncrossed in the spinal cord in the ipsilateral lateral corticospinal tract. These axons project to, and synapse with, neurons in the spinal cord, most prominently the internuncial cells in the intermediate zone of the spinal gray matter, which themselves synapse with the lower motor neurons in the anterior horn; a smaller percentage of the corticospinal fibers establish direct connections with the lower motor neurons. In the second stage, axons emanating from the lower motor neurons of the spinal cord pass to the skeletal muscles, synapsing with muscle cells at the neuromuscular junction (Carpenter, 1991).

Injuries to the upper motor neurons, typically affecting cell bodies or the long corticospinal tracts, can result from a variety of conditions including ischemia, demyelination, and trauma. Such insults often result in a spastic paresis, characterized by weakness, increased muscle tone, and hyperreflexia. The pattern of neurological dysfunction is characteristically determined by the localization of the lesion—all limbs might be affected (spastic quadriparesis), legs only (spastic paraparesis), or leg, arm, and/or face on 1 side of the body (hemiparesis). In contrast, an intriguing subset of inherited neurological disorders, the hereditary spastic paraplegias (HSPs), is characterized by weakness and spasticity predominantly of the lower extremities (Harding, 1983), due not to a focal insult but instead to a pattern of distal axonal degeneration affecting predominantly those upper motor neurons with the longest axons. Indeed, the upper motor neurons responsible for lower extremity motor function are among the largest in the central nervous system, with axons extending to remarkable lengths of greater than 1 m in some cases and with axonal volumes that can exceed 99% of the total cell volume (Reid, 2003a, 2003b; Holzbaur, 2004). Investigating the pathogenesis of this group of disorders will clarify general themes of cellular dysfunction that have a propensity to cause "dying back" axonal degeneration by exploiting the unique vulnerabilities that highly polarized neurons face related to axon length.

Because protein and lipid synthesis occur largely in the cell soma, active anterograde transport is required to supply axons with these materials. Conversely, materials intended for degradation are transported in a retrograde fashion along axons from the distant presynaptic terminals to the cell soma. Intracellular signals, both anterograde and retrograde, face similar logistical challenges given the distances over which they must travel. Thus, neurons are particularly susceptible to impairment in cell processes such as trafficking, transport, energy utilization, signaling, cytoskeletal organization, and synaptic transmission (Crosby & Proukakis, 2002; Reid, 2003a, 2003b; Holzbaur, 2004). Those neurons with the longest axons can reasonably be considered to be particularly vulnerable to such insults, and in fact, the HSPs exhibit such a pattern of length-dependent axonal degeneration in the upper motor neurons. In this review, we summarize the clinical and pathological features of the HSPs and then present an overview of how the identification and subsequent functional studies of HSP gene products are providing fresh insights into mechanisms of axonal degeneration. Lastly, we discuss how these insights are leading to the identification of new targets for pharmacological therapy.

2. Clinical phenotypes of hereditary spastic paraplegias

2.1. Neurologic findings and classification

Although the HSPs as a group exhibit considerable clinical heterogeneity, their cardinal feature is bilateral spasticity and weakness of the lower limbs. Despite the fact that the reported prevalence of the HSPs has varied considerably in different studies (Polo et al., 1991; Mc Monagle et al., 2002), several studies employing similar criteria and methodologies have found a prevalence of about 3 people per 100,000 (Filla et al., 1992; Leone et al., 1995; Silva et al., 1997; McDermott et al., 2000). The HSPs have been classically termed "pure" or "uncomplicated" if the spastic paraplegia occurs in isolation and "complicated" if other neurological abnormalities are present (Harding, 1983). These other abnormalities can include significant urinary dysfunction, neuropathy, amyotrophy, ataxia, mental retardation, thin corpus callosum, retinopathy, and deafness. Common presenting symptoms of patients with HSP are gait disturbances and difficulty walking caused by lower limb spasticity and weakness, generally with gradual worsening over time. Symptom onset can vary dramatically, ranging from infancy to late in life, with prominent variability even within the same family. Still, in most cases, patients tend to develop symptoms in the years after adolescence through middle age. Although progressive spastic weakness is also found in other inherited disorders including leukodystrophies, Friedreich's ataxia, SCA3, multiple sclerosis, and familial Alzheimer's disease, other major associated neurological signs distinguish these disorders from the HSPs (Fink, 2003a, 2003b), and they will not be reviewed here. On the other hand, patients with an inherited form of amyotrophic lateral sclerosis, ALS2, can present predom-