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Review

Mechanisms of distal axonal degeneration in peripheral neuropathies

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ABSTRACT

Peripheral neuropathy is a common complication of a variety of diseases and treatments, including diabetes, cancer chemotherapy, and infectious causes (HIV, hepatitis C, and *Campylobacter jejuni*). Despite the fundamental difference between these insults, peripheral neuropathy develops as a combination of just six primary mechanisms: altered metabolism, covalent modification, altered organelle function and reactive oxygen species formation, altered intracellular and inflammatory signaling, slowed axonal transport, and altered ion channel dynamics and expression. All of these pathways converge to lead to axon dysfunction and symptoms of neuropathy. The detailed mechanisms of axon degeneration itself have begun to be elucidated with studies of animal models with altered degeneration kinetics, including the slowed Wallerian degeneration (Wld^S) and Sarm knockout animal models. These studies have shown axonal degeneration to occur through a programmed pathway of injury signaling and cytoskeletal degradation. Insights into the common disease insults that converge on the axonal degeneration pathway promise to facilitate the development of therapeutics that may be effective against other mechanisms of neurodegeneration.

Contents

Abbreviations: AGE, advanced glycation end products; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; CIDP, chemotherapy induced peripheral neurotoxicity; ddC, 2′,3′-dideoxycytidine; ETC, electron transport chain; G6P, glucose-6-phosphate; G6PD, glucose-6-phosphate dehydrogenase; GBS, Guillain–Barré syndrome; HCV, hepatitis C virus; IGF-1, insulin-like growth factor-1; IFN-α/γ, interferon α or γ; MPTP, mitochondrial permeability transition pore; Nmnat, nicotinamide mononucleotide adenylyltransferase; PARP, poly(ADP-ribose) polymerase; RAGE, receptor of advanced glycation end products; RNS, reactive nitrogen species; ROS, reactive oxygen species; TLR, toll-like receptor; Ube4b, ubiquitination factor E4B; Wld^S, slowed Wallerian degeneration gene.

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1. Introduction

Peripheral nerve degeneration is a common disorder of the nervous system whereby sensory and/or motor axons no longer effectively communicate between the periphery and central nervous system. The prevalence of peripheral neuropathy in the United States has been reported to be nearly 15% in adults over the age forty [108].

Peripheral neuropathy is not a single, homogenous disease, but is instead a mix of different clinical presentations, natural histories, and pathologies. Patients may present with motor insufficiency (weakness), sensory abnormalities (numbness, paresthesias, hyperalgesia/allodynia, pain), autonomic symptoms, or a combination of all, often depending on the particular disease. These various constellations of neurological symptoms suggest motor, sensory, and autonomic axons have differing susceptibilities to various disease processes. Additionally, while most neuropathies are chronic, slowly progressive conditions, some neuropathies have a more acute onset and gradual recovery [111] (reviewed in [140,275,293]). The heterogeneity of peripheral neuropathies is likely secondary to the initiating event. Few neuropathies are present in isolation, but, rather, are often secondary to other systemic illnesses, including diabetes and infectious causes such as human immunodeficiency virus and hepatitis C virus. Additionally, peripheral neuropathies may be iatrogenic, arising from the toxicity of drugs given as part of antiretroviral or chemotherapy regiments.

Despite the great variety of cause and symptoms, the pathophysiology of peripheral neuropathies is limited to only a handful of mechanisms. In this article, the pathophysiological mechanisms of various types of peripheral neuropathy – diabetic neuropathy, chemotherapy induced peripheral neurotoxicity (CIPN), HIV- and non-HIV infectious neuropathies – will briefly be reviewed in an effort to examine how many different disease process converge onto a handful of cellular targets involved in the axonal degradation pathway to produce peripheral nerve dysfunction. As it is among the most heavily studied, diabetic neuropathy will serve as the prototypical example for many of the mechanisms, then additional detail added for particular diseases.

1.1. Clinical overview of selected diseases

1.1.1. Diabetic neuropathy

Diabetes mellitus is a very common chronic disease. In 2014, over 9% of the United States population (21 million people) has been diagnosed with diabetes [47], and the prevalence is expected to increase [220]. Diabetes is the most common cause of peripheral neuropathy, accounting for over half of the cases in a recent Dutch study [207].

Diabetic peripheral neuropathy is classically a sensory neuropathy presenting as numbness and paresthesias in a length dependent "stocking glove" distribution, whereby the feet are affected earlier and more severely than the hands (as reviewed in [51]), but painful, autonomic, or motor neuropathies may also occur (reviewed in [249]). In two studies of patients with type-I diabetes, intense glucose control reduced the risk of peripheral neuropathy by 60% [102,110]. This finding suggests that the elevated glucose levels in the body may be pathogenic. While hyperglycemia may be a large component of the pathogenesis of diabetic neuropathy, non- hyperglycemic effects of diabetes, including reduced trophic support (hypoinsulinemia in type I and advanced type II diabetes) and mitochondrial health and function, may also be important.

1.1.2. Chemotherapy induced peripheral neurotoxicity

While improved cancer treatment regimes and higher rates of remission are a boon to modern medicine and cancer biologists, many of the commonly used anti-neoplastics have long term toxic effects that currently are not well mitigated during treatment [45]. Indeed, chemotherapy induced peripheral neurotoxicity (CIPN) has increased in incidence as cancer remission rates continue to climb due to improved cancer therapies (as reviewed in [12,45]). While the incidence and prevalence of CIPN varies by agent, in general, 30–80% of treated patients develop a peripheral neuropathy (as reviewed in [96]). Patients experience motor and sensory symptoms, including numbness, pain, and weakness [248], so severely that they may be dose-limiting. The wide variety of symptoms suggests chemotherapeutic agents may harm multiple types of neurons, as well as different parts of neurons, including the axon (axonopathy) or the soma/ganglion (ganglionopathy) (as reviewed in [118]). The most common causes of CIPN include taxanes, such as paclitaxel, platinum agents including cisplatin and oxaloplatin, and proteasome inhibitors such as bortezomib and will, thus, be the focus of discussion. For other compounds, readers are referred to Argyriou et al's excellent, recent review [12]. Within a pharmacological class, there is also heterogeneity. For example, cisplatin has chiefly chronic affects, but oxaliplatin has toxic neurological effects in both the acute and chronic setting, suggesting different processes may underlie early and late pathology. Thus, the particular pathophysiology of CIPN depends not only on the family of chemotherapeutic but also on the specific member of the family.

1.1.3. Human immunodeficiency virus neuropathy

The global prevalence of the human immunodeficiency virus (HIV) in 2009 was found to be 33.3 million [1], and nervous system defects, including a peripheral neuropathy, is common in the disease [159,229]. Interestingly, while control of the virus has improved over the past few decades, the incidence of neuropathy has increased from 13% in 1993 to 42% in 2006 [229]. This increase in prevalence during the era of effective treatments suggests that the neuropathy is not caused by the virus alone, but also by the drugs used to treat it [87]. HIV neuropathy is chiefly a sensory neuropathy of pain, paresthesias, and absent ankle reflexes [67]. Direct viral infection of neurons or Schwann cells has not been well demonstrated, but the virus has been recovered from some nerve samples [52,74]. Viral concentration in these samples is remarkably low, suggesting viral particles and proteins must enter the nerve through other cells, such as macrophages or T-cells. Indeed, careful studies of viral tropism have shown that particles recovered from nerve are consistent with macrophage and T-cell infectious particles, [127] and that viral proteins colocalize with macrophages in vivo [115]. These findings suggest the virus is brought to the nerve by immune cells, but does not directly infect neuronal cells [66,115]. The viral proteins gp120 and protein R (VPR) are especially important toward the observed neurotoxicity. The primary mechanisms of the neuropathy appear to be immune damage from viral proteins and mitochondrial toxicity from the antiretrovirals (as reviewed in [131,133]).