Microangiopathy, Diabetes, and the Peripheral Nervous System

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SUMMARY

This chapter reviews how disease of small nerve and ganglia microvessels, or microangiopathy, relates to the development of diabetic peripheral neuropathy. Microangiopathy involving vessels of the nerve trunk and those of dorsal root ganglia (that house sensory neuron cell bodies), does develop in parallel with neuropathy and is likely to eventually contribute to it. It is debatable whether early polyneuropathy in models or in humans can be exclusively linked to reductions in the blood supply of nerves. More likely, diabetes targets neural structures and vessels concurrently. There might be chronic ganglion ischemia altering neuronal function such that terminal branches of the nerve can no longer be properly supported. Downregulation, in turn, of critical structural and survival proteins in the sensory (or autonomic) neuron tree might account for early sensory dysfunction and pain (or autonomic abnormalities). There might also be exquisite sensitivity of vessels to vasoconstriction as an early functional abnormality. Rises in local endothelin levels, for example, might trigger acute nerve trunk and ganglion ischemia, and damage. Finally, failed upregulation of blood flow to injured nerves after acute injury might impair their ability to regenerate. Future therapy of diabetic polyneuropathy will require attention toward both direct neuronal degeneration and superimposed microangiopathy.

Key Words: Diabetic neuropathy; ganglion blood flow; ischemia; microangiopathy; nerve blood flow; nerve injury; regeneration; vasa nervorum.

INTRODUCTION

Microangiopathy, or dysfunction of small blood vessels, is closely linked to diabetic complications, such as nephropathy and retinopathy. Microangiopathy is also closely associated with the third complication of this triad, polyneuropathy, but its exact role in the development of nerve disease is uncertain. It is probably incorrect to conclude that microvascular disease is the primary trigger of neuropathic complications, an assumption that ignores direct neuronal damage. Instead, there is significant evidence that a unique neuroscience of diabetic neuropathy exists. The evidence that diabetes has direct impacts on sensory neuron structure and function independently of microangiopathy is reviewed in depth elsewhere (1). Overall, it might be more accurate to depict chronic diabetes as involving nerve trunks, ganglion, and their respective microvessels in parallel, a process that can eventually lead to a vicious interacting cycle of damage. In some situations, such as focal nerve trunk ischemic insults or
mechanical nerve injury, the relative contribution of microangiopathy might be higher. Although, a detailed technical appraisal of relationships between nerve blood flow in published work and experimental neuropathy has been recently published separately, this review will highlight and summarize some of this controversy (2). In this work, aspects of nerve and ganglion blood flow and its measurement, models of ischemia, and evidence for diabetic peripheral nerve and ganglion microangiopathy are emphasized and reviewed.

**BLOOD FLOW OF NERVE TRUNKS AND GANGLIA**

The characteristics of the blood flow in nerve trunks and ganglia are unique and are distinguished from those of the central nervous system. Nerve trunks are supplied upstream by arterial branches of major limb vessels that share their supply with other limb tissues. At some sites, the overlapping vascular supply from several parent vessels renders zones of susceptibility to ischemia, or watershed zones. In the rat, and probably human sciatic nerve, a watershed zone can be found in the proximal tibial nerve (3). In some nerve trunks, the centrofascicular portion of the nerve trunk might be the most vulnerable to ischemia, accounting for corresponding centrofascicular patterns of axon damage. However, ischemic damage of large multifascicular nerve trunks is more commonly multifocal, with irregular zones of axon damage that depend on specific features of their perfusion and the exact vessels that are involved in causing ischemia (4,5). In general, nerve trunks are well-perfused from multiple anastamosing parent arteries that ultimately form a rich epineurial vascular plexus on it. Such a rich vascular supply explains why long segments of nerves can be “mobilized” by surgeons without major sequellae. Arteriovenous anastamoses are common in the epineurial plexus, but some might also exist in the endoneurium (6). Because of this rich complex of vessels, it can be surprisingly difficult to distinguish arterioles from venules in the epineurial plexus when they are directly visualized in vivo.

Spinal dorsal root ganglia are supplied from segmental radicular arteries and anastamoses with branches of spinal arteries (7). Unlike the peripheral nerve trunk, they do not have a prominent extracapsular plexus. Neuron perikarya that entrain higher metabolic requirements are most often located in the subcapsular space, whereas axons eventually entering roots are more frequently found in the core of the ganglia. Given this structure, microanatomic susceptibility of the ganglia to ischemia is probably even less predictable than that of nerve trunks.

Peripheral nerve trunks are supplied by blood vessels from two distinct compartments: the epineurial vascular plexus and the intrinsic endoneurial blood supply. Although, extrinsic epineurial blood flow is ultimately responsible for “downstream” blood flow in the endoneurial compartment, each compartment has distinct physiological and morphological characteristics. The epineurial plexus, as discussed, is well-perfused by arterioles, has prominent arteriovenous shunting, has innervation of its arterioles, discussed further below, and has a leaky blood–nerve barrier. This plexus supplies segmental arterioles that penetrate into the endoneurium directly or that arrive there from a remote origin traveling in a longitudinal centrofascicular pattern. Although not an absolute rule, the endoneurium is largely supplied by noninnervated capillaries that respond passively to changes in blood flow. Pericytes, smooth muscle-like contractile cells, are associated with some endoneurial capillary segments, but