The Pathogenesis and Prevention of Diabetic Neuropathy and Nephropathy

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The chronic complications of diabetes are thought to be caused by an interaction between hyperglycemia, or other metabolic consequences of insulin deficiency, and independent genetic or environmental factors that are poorly defined. Several potentially relevant biochemical sequelae to hyperglycemia have been identified in tissue susceptible to diabetic complications. Among these, a rise in tissue sorbitol secondary to concentration-dependent activation of polyol pathway activity by glucose, and an accompanying fall in tissue myo-inositol and Na-K ATPase activity have recently been linked to a self-reinforcing cyclic metabolic defect that accounts for rapidly reversible slowing of conduction in peripheral nerve in diabetes. Impaired Na-K-ATPase activity also appears to be responsible for intracellular Na+ accumulation and resultant localized axonal paranodal swelling that characterizes diabetic neuropathy in both humans and laboratory animals. These swellings are thought to be responsible for the subsequent disruption of the nodal apparatus (axo-glial disjunction) and some component of the loss of large and small myelinated fibers. Recent studies have suggested that microvascular insufficiency may also contribute to diabetic neuropathy, especially in non-insulin-dependent diabetes. Aldose reductase activity is concentrated in endoneurial vessels, and similar biochemical mechanisms (i.e., sorbitol accumulation, myo-inositol deficiency, and impaired Na-K-ATPase activity) are thought to be operative in the endoneurial microvessels in diabetes. Administration of an aldose reductase inhibitor to patients with diabetic neuropathy is associated with repair of damaged nerve fibers and the appearance of newly generated fibers, presumably secondary to metabolic correction within the nerve fibers themselves or their supporting microvasculature. Components of this same biochemical pathway have now been identified in the renal glomerulus and the retina, which may implicate this metabolic sequence in the pathogenesis of multiple diabetic complications.

ONE OF THE MOST persistent, controversial, and important questions concerning diabetes is whether the so-called glucose hypothesis of diabetic complications is correct. Essentially, the hypothesis is that hyperglycemia and/or insulin deficiency leads to secondary biochemical abnormalities in target tissues, which are followed by alterations in the functions of these tissues, the appearance of structural lesions, and, ultimately, clinical complications. In addition, at each point in this sequence of events, independent genetic or environmental variables seem to alter the expression of these complications. The results of one study indicate that male diabetics are more likely to develop diabetic neuropathy than their female counterparts, despite similar duration of disease and degree of hyperglycemia, and that taller individuals are more likely to develop diabetic neuropathy than shorter ones, even after correction of glycated hemoglobin and duration of diabetes. Other studies indicate that the development of diabetic neuropathy seems to be accelerated by alcohol consumption and nutritional deficiencies.

If the modified glucose hypothesis of diabetic complications is correct, there should first be a logical sequence of events that starts with glucose and ends with a clinical complication. Secondly, this hypothesis should in some way address the well-known clinical variability of diabetic complications. Diabetic neuropathy embraces a tremendously varied spectrum of disease. A patient with an acute onset of paresthesia and distal symmetric polyneuropathy presents an example of diabetic cranial neuropathy, a condition that has a good chance of resolving within a year or so. In contrast to this, the more common chronic indolent distal symmetric polyneuropathy arising over 10 to 15 years tends to be progressive, despite temporary periods of remission. Symptoms such as pain or paresthesias may resolve, but sensory deficits generally worsen from paresthesia to anesthesia.

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AUTONOMIC NEUROPATHY

Autonomic neuropathy, which can involve virtually any of the visceral organs, tends to be progressive. One patient may present with severe gastroparesis with little clinical evidence of cardiovascular autonomic neuropathy, and another may present with orthostatic hypotension without obvious delayed gastric emptying.

Widespread subclinical autonomic dysfunction is present in almost all patients with symptomatic autonomic neuropathy. Again, the disease may express itself differently in each person. The chronic progressive forms of diabetic neuropathy, distal symmetric polyneuropathy and autonomic neuropathy, exhibit widespread loss of large and small myelinated and unmyelinated fibers, as does autonomic neuropathy. Indeed, it is not uncommon for patients to lose two thirds or more of their myelinated nerve fibers. This loss is accompanied by proliferation of endoneurial connective tissue and a series of vascular abnormalities, including thickening of the vascular basement membrane, capillary closure, and thrombotic occlusion within the peripheral nervous system.

Is this chronic destructive process related to blood glucose abnormalities? A study by Troni et al demonstrated that reducing hyperglycemia acutely improves nerve conduction velocity (Fig 1). Other studies have had similar results, suggesting that glucose or a glucose metabolite may acutely impair nerve function in diabetics. But what is the biochemical mechanism responsible for changes in nerve function?
Quantitatively, the most impressive abnormality in nerve metabolism in diabetes is a diversion of glucose metabolism from oxidative to reductive pathways. Under normal circumstances, glucose is primarily oxidized to carbon dioxide and water for efficient derivation of energy in the form of adenosine triphosphate (ATP) (Fig 2, left panel). When hyperglycemia is present, excess glucose enters the nerve because its transport is neither rate-limiting for metabolism nor insulin dependent. Glycolytic pathways become saturated and there is a marked increase in the reduction of sorbitol by the enzyme aldose reductase once glucose levels are elevated within peripheral nerves. The sorbitol is then metabolized to fructose by sorbitol dehydrogenase.

THE SORBITOL PATHWAYS

Is there a link between abnormal glucose metabolism through the sorbitol pathways and reversible abnormalities in nodal (nodes of Ranvier) function? It has been established that the enzyme aldose reductase is localized in the nodes of Ranvier, but to understand the effects of sorbitol pathway on nerve conduction, it is first necessary to understand another biochemical abnormality of diabetic peripheral nerve. When the sorbitol pathway was first intensively studied in diabetic peripheral nerve, independent studies were being conducted on the metabolism of myo-inositol in peripheral nerve. In studies of diabetic rats, myo-inositol levels were decreased in peripheral nerve, but administration of insulin prevented this decrease and improved nerve conduction velocity. Furthermore, myo-inositol depletion did not lower elevated nerve glucose and sorbitol levels, restored normal nerve conduction velocity. Understandably, the so-called sorbitol hypothesis and the myo-inositol hypothesis were originally considered to be two independent hypotheses that attempted to explain acute and reversible changes in nerve conduction in experimental diabetic neuropathy. However, increasingly compelling evidence suggested that the biochemical defects were tightly intertwined.

In virtually every tissue prone to diabetic complications, a rise in sorbitol level is accompanied by evidence of myo-inositol depletion within the tissue; however, the exact mechanism for this seesaw interrelationship is still not clear. The observation that myo-inositol depletion occurs in diabetic complications preceded our recognition that myo-inositol metabolism plays a unique role in cellular regulation. Myo-inositol belongs to a class of compounds called phosphoinositides, which are metabolically labile phospholipids consisting of myo-inositol in phosphodiesterase linkage to a glycerol moiety containing two fatty acids, which are usually arachidonic and stearic acid.

PHOSPHOINOSITIDE METABOLISM

Phosphoinositide hydrolysis is initiated by a variety of specific receptor mediated stimuli, yielding two important metabolically active intracellular metabolites, diacylglycerol and inositol polyphosphates, which modulate an array of cell functions. Diacylglycerol, a lipid-soluble metabolite, is an activator of protein kinase C, which phosphorylates a large number of intracellular proteins, thus modulating their activity. Inositol polyphosphates, the water-soluble derivatives of phosphoinositides, have marked effects on intracellular calcium metabolism. Therefore, myo-inositol through its incor-
Intracellular transport of sodium and potassium plays a very important role in transmembrane signaling and in the regulation of intracellular metabolism. Thus, hyperglycemia stimulates polyol pathway activity, which leads to myo-inositol depletion, which in turn leads to derangements in phosphoinositide-mediated transmembrane signal transduction, which then leads to interference with cell function.

Do alterations in phosphoinositide metabolism contribute to abnormal function of the nodes of Ranvier? A node of Ranvier contains three important functional elements: (1) the axonal membrane, (2) a sodium pump or Na-K-ATPase that generates an electrochemical sodium gradient across the membrane, and (3) a series of voltage-sensitive sodium channels that become permeable to sodium in the presence of a depolarizing voltage and discharge the gradient generated by the Na-K-ATPase (Fig 3). As has been demonstrated in a series of biophysical and neurochemical studies, Na-K-ATPase activity is reduced in diabetic nerve, but if an accumulation of sorbitol is prevented by means of an aldose reductase inhibitor, the impairment of Na-K-ATPase is prevented. In addition, if sorbitol is allowed to accumulate, but myo-inositol depletion is prevented by administration of myo-inositol, the abnormalities of Na-K-ATPase and nerve conduction are also prevented. Thus the Na-K-ATPase impairment in diabetic nerve is the result of myo-inositol depletion induced by sorbitol-pathway activation.

The rapidly reversible component of nerve-conduction slowing can be largely attributed to impairment of the Na-K-ATPase, which in turn is secondary to myo-inositol depletion, sorbitol accumulation, and, ultimately, hyperglycemia (Fig 4).

Although these processes may explain the rapidly reversible slowing of nerve conduction in diabetic animals or patients, do they relate to the pathogenesis of clinically overt diabetic neuropathy? Obviously, painful paresthesias or clinically detectable sensory deficits are not easily explained simply on the basis of sodium pumps that are turned off. More likely, symptomatic diabetic neuropathy reflects the loss or severe damage to the majority of peripheral nerve fibers in patients with long-standing diabetes.

Does the biochemical sequence clarify the development of severe structural abnormalities in peripheral nerve? Because the sodium pump plays a major role in the maintenance of the intracellular ionic environment, it is understandable how impairment of Na-K-ATPase function would lead to the swelling of cells. Indeed, the swelling of nerve fibers in the nodal and paranodal regions is the earliest structural lesion that occurs in diabetic rats. Persistent swelling is thought to lead to subsequent disruption of the structural elements of the nodes of Ranvier (Fig 5). Under normal conditions, the myelin sheath is tightly applied to the axon membrane in the paranodal region, thereby maintaining the sodium channels in high concentration there. Persistent swelling of the nodes of Ranvier is associated with loss of these axo-glial junctions, which leads to early paranodal demyelination and loss of sodium channels from the nodal region (Fig 5). This is a relatively poorly reversible structural lesion, since once these channels are lost, metabolic correction does not rapidly restore their normal distribution, and hence nodal function and structural integrity remain impaired.

Does this sequence of events occur in human patients with diabetic neuropathy? As part of a recent multicenter trial of...
Diabetes, then interruption of that mechanism might yield diabetic neuropathy: Baseline analysis of neuropathy in the feasibility phase of the Diabetes Control and Complications Trial (DCCT).

Preliminary data suggest that specific interruption of the biochemical abnormalities is likely to lead not only to stabilization, but also to at least partial reversal of this clinically overt complication of diabetes. The possibility that therapies that interrupt this biochemical sequence may become important elements in the prevention and reversal of the three major diabetic complications holds great promise for the future.

REFERENCES


