Structural-Functional Interactions in the Therapeutic Response of Diabetic Neuropathy

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Studies in experimental diabetic rat attribute the acute reversible nerve conduction defect as well as the early structural abnormalities of the node of Ranvier and myelinated axons to changes in nerve metabolism secondary to hyperglycaemia and activation of the polyol pathway.[1–8] The early readily reversible slowing of nerve conduction velocity in the diabetic rats correlates with a decrease in nerve Na,K-ATPase activity,[3] which induces a selective conduction block of large rapidly conducting fibres by inactivating voltage-dependent sodium channels.[9] A further progressive impairment of nerve conduction velocity correlates with the progressive development of axo-glial dysjunction, a characteristic structural lesion of the paranodal region in experimental diabetic rats and diabetic human subjects.[6,8,10] This structural defect is associated with an acutely irreversible marked reduction in nodal sodium permeability.[11] Impaired Na,K-ATPase activity and axo-glial dysjunction are normalized or prevented by aldose reductase inhibition in the diabetic rat,[11,12] in whom axo-glial dysjunction shows a strong correlation with the slowed nerve conduction velocity.[12] These data indicate that the nodal delay of the impulse propagation is associated with axo-glial dysjunction and is superimposed on the slowing of nerve conduction velocity related to abnormalities in nerve fibre metabolism.

The neuroanatomical abnormalities associated with peripheral polyneuropathy in diabetic human subjects are similar to those of the diabetic rat including axo-glial dysjunction.[10] The mechanisms underlying the electrophysiological abnormalities in diabetic patients are less well defined, but it is believed that they include both metabolic and structural components.[13] The rapid improvement in nerve conduction velocity following strict glycaemic control probably reflects improvements in nerve metabolism.[13]

Fibre atrophy and progressive loss of myelinated fibres are the structural hallmarks of advanced diabetic neuropathy in humans.[10,14] Decreased fibre diameter has been suggested as the basis for nerve conduction slowing in human diabetic neuropathy.[15] This laboratory has previously demonstrated that the progressive loss of myelinated fibres correlates with a progressive decrease in evoked potential amplitude,[16] and that the improvement in myelinated fibre density in sural nerve biopsies following aldose reductase inhibitor treatment correlates significantly with the improvement in sural evoked potential amplitude.

However no light-microscopically identifiable lesions correlate with nerve conduction velocity or its improvement following metabolic interventions.

In the present studies we examined sural nerve biopsies electron microscopically to determine if ultrastructural lesions such as axo-glial dysjunction and/or axonal atrophy might provide a structural basis for nerve conduction slowing in diabetic neuropathy.

Twenty-seven patients with overt diabetic polyneuropathy participating in an aldose reductase inhibitor trial with the experimental drug Sorbinil underwent electrophysiological studies and sural nerve biopsies at the entry into the trial. After 1 year of the placebo-controlled study, 16 of these patients underwent renewed sural nerve conduction studies and a second biopsy.

Antidromic sural nerve conduction velocity were measured using surface electrodes. Supramaximal stimuli of 0.2 ms duration was applied and compound action potentials were obtained using averaging technique.

The sural nerve biopsies were examined electron microscopically and assessed as to the frequency of axo-glial dysjunction as previously described in detail.[8] Axonal atrophy was examined using three independent morphometric techniques:

1. electron-microscopic assessment of myelin/axon ratio;
2. frequency of excessively wrinkled myelinated fibres examined from single teased fibres;
3. internodal length/diameter ratio measured from single teased fibres.[8,10]

Correlations between the baseline nerve conduction and morphometric data demonstrated highly significant negative correlations between nerve conduction velocity and the product of the natural logarithm of the frequency

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of axo-glial dysjunction and the natural logarithm of the extent of axonal atrophy. These significant correlations remained unchanged regardless of how axonal atrophy was assessed; either as myelin/axon ratio, or excessive myelin wrinkling or internodal length/diameter ratio. These correlations are similar to those obtained in the diabetic rat, in whom nerve conduction velocity showed an exponential correlation with axo-glial dysjunction.[12] Following 1 year of aldose reductase inhibition with Sorbinil, patients treated with active drug showed a significant improvement in sural nerve conducting velocity ($p < 0.05$), whereas placebo-treated patients showed a small but statistically significant decrease in nerve conduction velocity ($p < 0.05$). Morphometrically patients treated with active drug showed improvements in axo-glial dysjunction ($p < 0.012$) and in axonal atrophy whether this was measured as axon/myelin ratio ($p < 0.0001$), excessive myelin wrinkling ($p < 0.0001$), or internodal length/diameter ratio ($p < 0.0000$). Placebo-treated patients showed no change in any of the morphometric parameters over the 1 year clinical trial period.

The data of all patients who demonstrated a measurable nerve conduction velocity at baseline and follow-up were then used to calculate the change in nerve conduction velocity, and the change in magnitude of axo-glial dysjunction and axonal atrophy as measured by the three independent parameters. The change in nerve conduction velocity was correlated with the product of the natural logarithm of the change in axo-glial dysjunction and that of axonal atrophy. These calculations revealed highly significant positive correlations between the change in nerve conduction velocity and that of axo-glial dysjunction and axonal atrophy suggesting that axo-glial dysjunction and axonal calibre are major determinants for nerve conduction velocity.

The present data therefore suggest that specific structural changes in peripheral nerve form the basis for nerve function as measured by electrophysiological means.

Hence, evoked compound action potential appears to reflect the density of myelinated nerve fibres in diabetic nerve and the slowing of nerve conduction velocity in overt diabetic neuropathy appears to occur as a result of a combination of nodal delay of the impulse due to axo-glial dysjunction and slowing of the internodal electrical transmission secondary to axonal atrophy.

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