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The heterogeneity of diabetic neuropathy

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1. ABSTRACT

Diabetic neuropathy and its underlying pathogenesis are reviewed. It has been documented for some time that diabetic neuropathy differs in both human and experimental type 1 versus type 2 diabetes. Such differences are accounted for by impaired insulin action and signal transduction in type 1 diabetes, whereas hyperglycemia *per se* contributes equally to neuropathy in the two types of diabetes. Such differences in basic initiating factors and pathogenesis translate into differences in the functional and structural expressions of neuropathy in type 1 and type 2 diabetes. Type 1 neuropathy shows a more rapid progression with more severe functional and structural changes. Several experimental mono-therapies have been tested over the last decades which unfortunately have not been efficacious. Therefore discrepancies in underlying pathogenetic mechanisms in the two types of diabetic neuropathy will have to be taken into account in the design of future therapies, which should target several key pathogenetic mechanisms. Therapies that meet these criteria include replacement of acetyl-L-carnitine and replenishment of C-peptide in type 1 diabetic neuropathy.

2. INTRODUCTION

Diabetic polyneuropathy (DPN) includes several distinct syndromes. Sensory symmetric polyneuropathy, often accompanied by autonomic neuropathy, is the most common late complication of diabetes (1). Less common neuropathic syndromes include diabetic mononeuropathy and cachectic painful neuropathy. Both show acute onset and are self-limited (2,3). DPN is the result of hetergeneous underlying pathogenetic mechanisms, which differ according to the type of the underlying diabetic syndrome (1,4,5). Such differences are reflected in the prevalence of DPN, which occurs more predictably and progresses more rapidly in patients with type 1 diabetes, reaching close to 100% after 15 years duration of diabetes. In contrast, DPN in type 2 diabetes shows a prevalence of 30% after 25 years of diabetes (6-8).

Despite decades of clinical and experimental investigations, no accepted or effective therapy exists for DPN. In the last number of decades, several clinical trials employing various compounds targeting a single pathogenetic mechanism such as aldose reductase

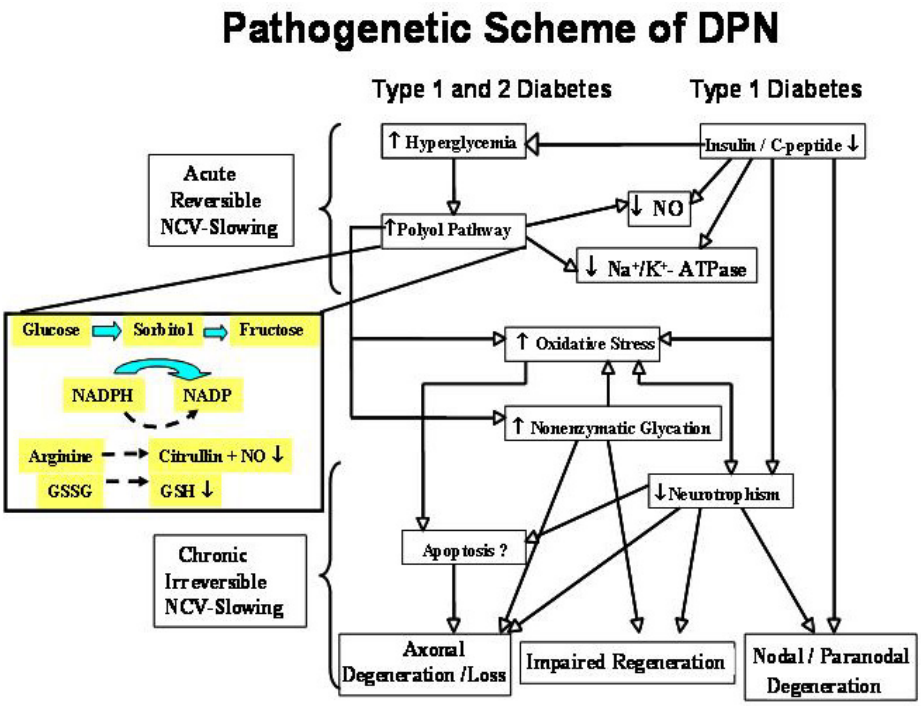

Figure 1. Scheme of pathogenetic mechanisms involved in DPN of type 1 and type 2 diabetes. The early metabolic abnormalities underlying the acute functional deficits are reversible. However, these become increasingly superimposed by progressive structural abnormalities, which are less responsive to metabolic corrections. For further explanation see text. (Redrawn from Sima and Kamiya (11).

inhibitors, antioxidants, substitution of nerve growth factor (NGF) or protein kinase C inhibitors have failed to demonstrate efficacy, whereas strict glycemic control has shown partial but significant therapeutic effects (6,9,10).

In hindsight, the reasons for these disappointing outcomes are related to the monotherapy approach and to initiation of therapy too late in the natural history of the disease as well as suboptimal potencies of employed drugs. Equally important has been the still lingering misconception that DPN in type 1 and type 2 subjects has been regarded as the same disease, implying that hyperglycemia is the only underlying causative mechanism for DPN (9,10).

Our understanding of pathogenetic mechanisms underlying DPN and its natural history has been obtained from experimental murine models. Unfortunately though, the most commonly used animal model, the streptozotocin-diabetic rat (STZ-rat), does not strictly model either type 1 or type 2 human diabetes. This fact alone may have fueled the assumption that DPN is caused by hyperglycemia alone. Within weeks of onset of diabetes, experimental models display nerve conduction velocity (NCV) abnormalities, increased polyol-pathway activity and decreased endoneurial blood flow (1,11). Such changes progress to oxidative stress, non-enzymatic glycation and initiation of a variety of progressive structural abnormalities with consequent impacts on nerve function (Figure 1). In exploring the differences in underlying mechanisms responsible for DPN in type 1 versus type 2 diabetes, our laboratory has utilized two rat models (the BB/Wor-rat and BBZDR/Wor-rat) with spontaneous onset of diabetes, closely mimicking human type 1 and type 2 diabetes, respectively (12,13).

It has thus become evident that DPN is the result of sequential, interacting and dynamic pathogenetic mechanisms, which may overlap or differ in the two types of diabetes (Figure 1). Some mechanisms may be prominent at one phase of the natural history of DPN, later to be replaced by other mechanisms (1,14). In both experimental diabetes and diabetic subjects there is an initial metabolic phase that is responsive to metabolic corrections, which however with progression of DPN is replaced by a structural phase which is increasingly non-responsive to therapeutic interventions (15-17).

3. THE REVERSIBLE METABOLIC PHASE OF DPN

Early metabolic abnormalities have been identified in diabetic nerve. Shunting of glucose through the polyol-pathway leads to intracellular accumulation of sorbitol and fructose with consequent depletion of other organic osmolytes such as taurine and myo-inositol (18,19). Depletion of the myo-inositol pool interferes with phosphoinositide turnover resulting in insufficient diacylglycerol for activation of Na^+/K^+-ATPase (Figure 1) (18). The type 1 BB/Wor-rat shows activation of the polyol-pathway, with consequent impairment of neural Na^+/K^+-ATPase activity, which is corrected by aldose

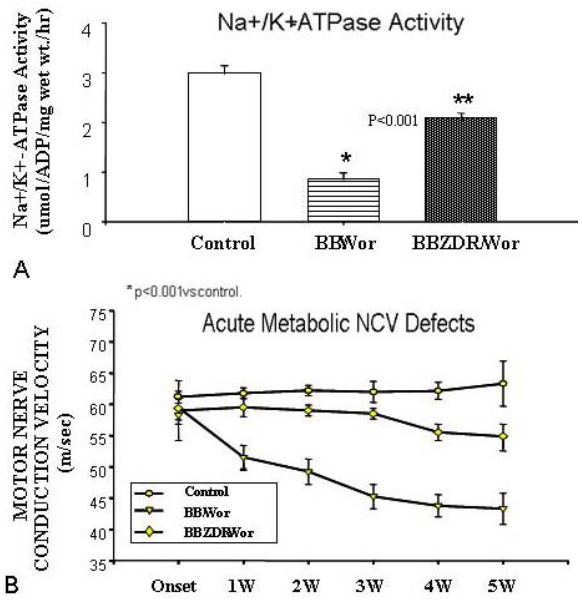

Figure 2. The defect in Na/K-ATPase activity is less expressed in type 2 BBZDR/Wor-rats (A), which translates into a milder nerve conduction velocity deficit as compared to type 1 BB/Wor-rats.

reductase inhibition (20). In the type 2 BBZDR/Wor-rat which shows the same magnitude of activation of the polyol-pathway, the impairment of Na^+/K^+-ATPase activity is significantly less (Figure 2). This difference in Na^+/K^+-ATPase activity is accounted for by impaired insulin signaling in type 1 diabetes adding to the polyol-pathway-induced defect. This has been confirmed by the insulinomimetic effect of proinsulin C-peptide (21). When type 1 BB/Wor-rats are replenished with C-peptide they show a dose-dependent correction of neural Na^+/K^+-ATPase activity and the acute NCV defect (22). Therefore the more severe defect in Na^+/K^+-ATPase activity and consequent nerve conduction slowing can be directly accounted for by insulinopenia and perturbed insulin signal transduction (Figure 2). Acetyl-L-carnitine replacement normalizes the acute Na^+/K^+-ATP-ase defect with consequent correction of the acute NCV defect (23,24).

Endoneurial hypoxemia due to impaired endoneurial blood flow has been ascribed to impaired expression of eNOS and NO activity. It has been proposed that mitochondrial dysfunction, superoxide over-production and oxidative and nitrosative stress underlie the depletion of NO and impaired nerve perfusion which contribute to nerve dysfunction (Figure 1) (25). In type 1 BB/Wor-rats both endoneurial perfusion and NCV are decreased and oxidative stress is increased. On the other hand, in the type 2 BBZDR/Wor-rat endoneurial nutritive blood flow and oxidative stress are similarly altered, whereas NCV is significantly less affected (26). C-peptide-substitution of type 1 rats corrects the NO-sensitive neurovascular function and nerve conduction velocity, without effecting oxidative stress or hyperglycemia (26). These findings suggest that nerve conduction deficits are not inevitably a consequence of increased oxidative stress and decreased nerve perfusion and indicate a dissociation between oxidative stress and endoneurial blood flow. Acetyl-L-carnitine has a corrective effect on the early diabetes-induced vascular dysfunction and metabolic imbalances (27,28).

These early metabolic abnormalities are associated with functional defects. The discrepancies in NCV slowing between type 1 and type 2 diabetes are related to differences in neural Na^+/K^+-ATPase activities (Figure 2). Since the excitation of the nodal membrane underlying the impulse propagation is caused by an inward flux of Na^+, the NCV is related to nodal Na^+ permeability. In the BB/Wor-rat there is a progressive defect in inactivation of $[Na^+]^i$ and a decline in the maximal peak of Na^+ permeability resulting in decreased nodal Na^+ equilibrium potentials (29). These changes result from the decreased Na^+/K^+-ATPase activity causing intra-axonal Na^+ accumulation (30). Intra-axonal Na^+ accumulation leads to a measurable swelling of the nodal axon, so-called nodal axonal swelling, one of the earliest but reversible structural changes (30). Interestingly, these biophysical abnormalities are corrected by insulin in acutely diabetic rats (30). Nodal axonal swelling, the early structural abnormality, is more prominent in type 1 than in type 2 BB-rats (12). It correlates with intra-axonal Na^+ accumulation and is reversed following insulin or C-peptide treatment and by acetyl-L-carnitine (21,23). However, the expression of voltage-gated α-Na^+-channels is not altered in sciatic nerve of diabetic rats (31). Therefore the early metabolic dysfunctions of myelinated fibers can be directly related to the Na^+/K^+-ATPase defect, whereas the contribution of impaired endoneurial blood flow is probably less as alluded to above.

Unmyelinated fiber dysfunction is reflected by thermal hyperalgesia. Again, the type 1 BB/Wor-rat shows a significantly more rapid decrease in the latencies to thermal stimuli (32). Damage to small myelinated Aδ and unmyelinated C-fibers underlie hyperalgesia and allodynia (33). Damage to axonal membranes of C-fibers induces increased formation of Na^+-channels and α-adrenergic receptors facilitating ectopic discharges (34,35). The varying degree of hyperalgesia in the two models correlates with significant differences in the expression NGF and NT-3 in sciatic nerve and of insulin receptor, IGF-1 receptor, high affinity NGFR-TrkA and TrkC receptors in dorsal root ganglion cells (DRG's) with consequent suppression of nociceptive peptides and synthesis of neuroskeletal proteins (32). These changes lead to degeneration and loss of nociceptive C-fibers. The abnormalities leading up to this series of events either do not occur or are significantly milder in the type 2 BBZDR/Wor-rat (32). Since the expression of neurotrophic factors and their receptors are intimately related to insulin signal transduction, it is not surprising that insulinomimetic C-peptide ameliorates these changes in type 1 diabetes (36,37).

4. THE INCREASINGLY IRREVERSIBLE STRUCTURAL PHASE OF DPN

From the acute metabolic abnormalities emerge progressive structural changes which become decreasingly

Table 1. Comparisons of quantitative structural changes in sural nerves from patients and BB-rats with type 1 and type 2 diabetes

A. Comparisons of quantitative structural changes in sural nerves from patients with type 1 and type 2 diabetes			
	Fiber density (#/mm^2)	Mean fiber size (μm^2)	Axo-glial dysjunction (%)
IDDM	2,464 + 440[1,4]	32.4 + 1.6[2,3]	40.1 + 1.8[1,3]
NIDDM	3,531 + 337[1]	38.6 + 2.0	12.3 + 1.3
Control	6,906 + 329	37.8 + 1.9	14.9 + 1.4
B. Comparisons of quantitative structural changes in sural nerves in type 1 and type 2 diabetetic BB-rats			
BB/Wor	9,085 + 207[5,6]	29.7 + 1.3[5]	44.2 + 4.3[5]
BBZDR/Wor	11,085 + 611	39.9 + 1.0[7]	11.8 + 1.8
Control	12,418 + 201	45.1 + 0.8	12.3 + 1.2

A. The data are adjusted for age and duration of diabetes. Note a more severe decrease in fiber density and mean fiber size in type 1 patients. Disruption of the paranodal ion-c hannel barrier (axo-glial dysjuntion (AGD)) is significantly increased in type 1 subjects but unaltered in type 2 patients. B. The same comparisons in type 1 and type 2 diabetic BB-rats show more severe decrease in fiber densities and size compared to type 2 rats. AGD is significantly increased in type 1 BB/Wor-rats but not in type 2 BBZDR/Wor-rats. [1] $p<0.001$, [2] $p<0.002$ vs control, [3] $p<0.001$, [4] $p<0.02$ vs NIDDM. [5] $p<0.001$, [6] $p<0.01$ vs BBZDR/Wor, [7] $p<0.05$ vs control.

responsive to metabolic interventions. One of the earliest detectable changes in myelinated fibers is nodal and paranodal axonal swelling which correlates with the early Na^+/K^+-ATPase defect and increased intra-axonal $[Na^+]^i$ (29,30). It is more expressed in type 1 BB/Wor-than in type 2 BBZDR/Wor-rats and is reversible (12,30). Other early abnormalities consist of malalignment of cytoskeletal structures reflecting aberrant synthesis, phosphorylation and assembly of neurofilaments (38-40). These changes lead to perturbed axonal transport and progressive axonal atrophy evident in the type 1 BB/Wor-rat after four months of diabetes. The axonal atrophy shows a proximal to distal gradient and ultimately results in distal axonal degeneration with secondary myelin breakdown and fiber loss (41). Axonal degeneration has been associated with impaired neurotrophic support by insulin itself, IGF-1 and neurotrophins (Figure 1), resulting in impaired synthesis of tubulins and neurofilaments and their assembly (39,40).

Significant fiber loss of 10% is already detectable in sural nerves of type 1 BB/Wor-rats after four months of diabetes increasing to 33% after 11 months (41). In contrast, the type 2 BBZDR/Wor-rat exhibits significantly milder axonal atrophy and fiber loss (Table 1) amounting to 11% after 14 months of diabetes. Primary segmental demyelination is rare in these models but is nevertheless more common in type 2 diabetic rats (12). Interestingly, early structural studies of diabetic nerve suggested that DPN was primarily a demyelinating disorder (42). These findings were later disputed and it is now generally agreed that DPN is primarily an axonopathy of dying back type (43,44). Differences in the severity of axonal degeneration and loss are also reflected by differences in the chronic NCV defects (Figure.3) in type 1 and type 2 diabetes. C-peptide substitution of type 1 BB/Wor-rats prevents and improves the nerve conduction defects, reflecting their insulinomimetic dependency. However, the defects are not totally prevented by C-peptide but show residual defects of similar magnitude as those encountered in the type 2 model (12). This has led us to suggest that the chronic functional defects in DPN consist of a hyperglycemic component, not responsive to insulinomimetic C-peptide, and an insulin/C-peptide deficiency component not present in type 2 diabetes (Figure 3) (45).

A characteristic structural change occurring in type 1 human and experimental diabetes is the progressive degeneration of the node of Ranvier and the paranodal apparatus (2,46). Such changes will affect nerve conduction velocity in a major way. They consist of progressive disruption of the paranodal ion-channel barrier allowing for lateralization of nodal voltage-gated Na^+-channels, thereby diminishing the initial Na^+ current of the nodal membrane (Figure 4). The abnormality of the paranodal ion-channel barrier is caused by decreased expression of key adhesive molecules, which make up the tight junctions of the barrier system, and their insulin-dependent postranslational modifications which underlie their protein-protein interactions (31). Similarly, the expression of ankyrin which through Na-β-channels mediate the anchorage of the α-Na^+-channels to the nodal axolemma is significantly suppressed, and allows then for the migration of α-Na^+-channel barrier beyond the now breached ion-channel barrier (Figure 4) (30,31). The insulin receptor is concentrated to the node and paranode and co-localizes with the paranodal adhesive molecules. The expression of the insulin receptor is significantly downregulated in chronically type 1 diabetic BB/Wor-rats. It is therefore not totally surprising that C-peptide replacement prevents these abnormalities (31). These changes do not occur in the type 2 model even after 14 months of diabetes or in human type 2 DPN (Table 1) (4,12). Therefore this degenerative process is specific for type 1 diabetes and contributes significantly to the more severe chronic NCV defect seen in type 1 diabetic rats.

The peripheral unmyelinated fiber population appears to be specifically sensitive to diabetic environments with changes preceding those of myelinated fibers. Even under prediabetic conditions as in the GK-rat, which shows impaired glucose tolerance and β-cell dysfunction, nociceptive neuropathy with C-fiber degeneration occurs (47). This is also reflected indirectly by the occurrence of painful diabetic neuropathy in patients with prediabetes or metabolic syndrome (48,49). In the type 1 BB/Wor-rat increased hyperalgesia to thermal stimulation is already present at two weeks duration of diabetes and increases progressively thereafter. This is accompanied by degenerative changes of C-fibers consisting of type 2 Schwann cell/axon relationships,

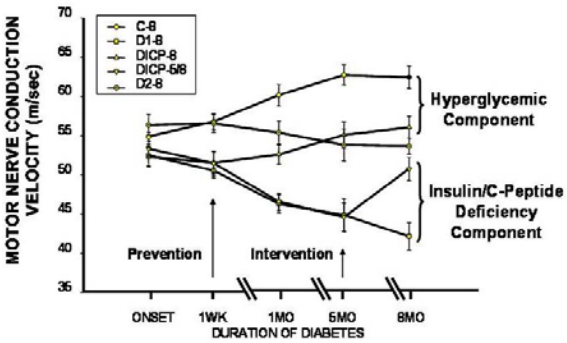

Figure 3. Longitudinal measurements of MNCV in type 1 BB/Wor- and type 2 BBZDR/Wor-rats. Also indicated are the preventive and interventional effects of C-peptide replacement, which does not influence hyperglycemia. Therefore the components of the nerve conduction deficits can be divided into a hyperglycemic component common to all diabetic groups and an insulin/C-peptide deficiency component only seen in type 1 rats.

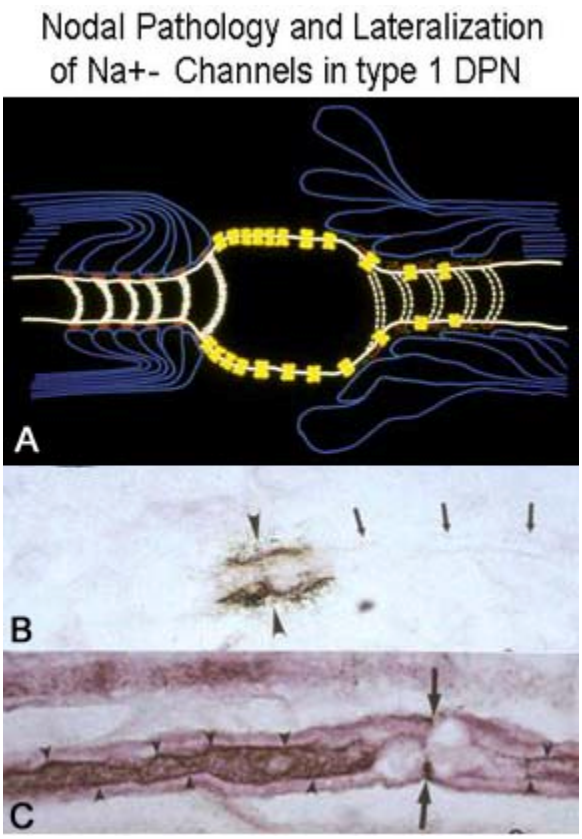

Figure 4. Schematic illustration of the disruption of the paranodal ion-channel barrier (right in A; the normal situation is illustrated on the left). The degeneration of the paranode allows for displacement of Na-channels into the internodal domain, hence depleting them at the node of Ranvier. This is illustrated in B and C showing immuno-localization of Na-channels in a control nerve fiber (B) and in a diabetic nerve fiber (C).

whereby the mesaxon degenerates leaving the axon directly exposed to the endoneurial environment. This is followed by axonal atrophy and loss, leaving behind collagen pockets and denervated Schwann cells (32). This series of events is preceded by suppressed expression of the insulin receptor in dorsal root ganglion (DRG) cells, impaired exposure to NGF, IGF-1, NT-3, and their respective receptors NGF-RTrkA, IGF-1R, and TrkC (32). The consequences of this impairment of wide neurotrophic support are impaired synthesis of nociceptive neuropeptides such as substance P and CGRP, axonal atrophy and loss of their parent DRG ganglion cells. The neuronal loss is not apoptosis-induced but correlates with progressive degeneration of the Golgi apparatus resulting in vacuolar degeneration and eventually neuronal loss (50). These changes progress at a significantly slower pace in the type 2 BBZDR/Wor-rat, with an almost normal expression of neurotrophic receptors in DRG ganglion cells and milder suppression of nociceptive neuropeptides. Hence, these differences between the two models can again be traced to differences in insulin action and its downstream regulatory effect on neurotrophic factors and their receptors (Figure 1). This is confirmed by the beneficial effects of C-peptide replacement on nociceptive sensory neuropathy in the type 1 rat model (37).

In human DPN, replenishment with C-peptide in type 1 patients show significant improvement in C-fiber and myelinated fiber functions (51). Similarly, treatment with acetyl-L-carnitine significantly improved diabetic neuropathic pain in a large multi-center trial with 1,346 patients (52). There is also recent evidence to suggest that acetyl-L-carnitine may prevent neuropathic pain prospectively (53). These effects are most likely related to the effects of acetyl-L-carnitine on the expression of neurotrophic factors and nociceptive neuropeptides (52).

5. REPARATIVE CHANGES

Once nerve degeneration has taken place, nerve regeneration is the natural reparative response. Nerve regeneration is subdued under diabetic conditions, which relates intimately to the expression of neurotrophic factors and their action upon synthesis of neuroskeletal proteins (39,40). It has become clear that abnormalities in insulin and IGF's are involved in impaired neurite outgrowth and regeneration under diabetic conditions. It has been shown in the model of crushed sciatic nerve that both IGF-II and IGF-I significantly increase the distance of motor axon regeneration, whereas infusion of insulin alone was only marginally effective (54-56). However, there is evidence to suggest that insulin has indirect effect on both IGF-I and its receptor via gene regulatory effects (6). Interestingly, insulin alone is mainly neurotrophic for small sensory neurons, whereas insulin receptors are sparse on motor neurons (57). On the other hand, IGF's have a more ubiquitous neurotrophic influence on all sensory neuronal sub-populations as well as motor neurons.

Systemic IGF-I is decreased in both type 1 and type 2 diabetes, whereas both endogenous IGF-I and its receptor are significantly downregulated in dorsal root

ganglia of type 1 BB/Wor-rats but not in type 2 BBZDR/Wor-rats (58). Following sciatic crush injury in these models, the type 2 model exhibits an almost normal immediate upregulation of both IGF-I mRNA and protein in the sciatic nerve, whereas this is delayed by 24 hrs. in type 1 diabetic rats followed by a progressive decline in both mRNA and protein expression over the next six days (36,59). In this model these perturbations are accompanied by a lack of upregulation of β-II and β-III tubulin as well as impaired downregulation of low- and medium-molecular neurofilaments and decreased rate and size of regenerating axons (40). Interestingly, proinsulin C-peptide prevents this series of events in type 1 diabetes, probably via its insulinomimetic gene-regulatory effects on IGF-I and its receptor (36,60). Hence, marked differences occur in the regenerative capacity of peripheral diabetic nerve in type 1 and type 2 diabetes, which is likely to contribute to the more severe DPN in the former type of diabetes.

6. THOUGHTS ABOUT FUTURE THERAPIES

As outlined here, DPN is a complex heterogeneous disorder with several underlying metabolic mechanisms which provide potential targets for therapeutic interventions. As mentioned, several clinical trials have been undertaken in the past targeting one mechanism alone in the pathogenetic web, and have unfortunately been disappointing. The reasons for these failures may be multiple; such as the timing of the intervention in relation to the dynamic disease process with correction of one mechanism but not others.

It is obvious that hyperglycemia is a major contributing factor to DPN and that its control should be a major goal. In this review, I have referred to the effects of C-peptide and acetyl-L-carnitine substitution. Both these substances are deficient in diabetes. Hence replacement with C-peptide in type 1 patients corrects via its insulinomimetic effects a series of insulin-deficiency related abnormalities, such as endoneurial blood flow, Na^+/K^+-ATPase activity, gene expression of neurotrophic factors, their receptors, as well as that of cell adhesive molecules involved in nodal degenerative changes characterizing this type of DPN. These positive effects were born out in a clinical trial with C-peptide demonstrating significant improvements in nerve conduction velocities and small fiber function (51). Acetyl-L-carnitine also provides effects on multiple pathogenetic targets by correcting Na^+/K^+-ATPase activity, endothelial NO, lipid peroxidation, with further effects on prostaglandins, neurotrophic factors, nociceptive neuropeptides and upregulation of mGlu2 metabotropic glutamate receptors. A clear advantage of these substitution therapies is their low incidence of adverse effects, which at times have been substantial and limiting in the employment of earlier targeted therapy. Finally, the approach to therapy should as we expand our knowledge of underlying mechanisms and their differences in the two main types of DPN be more ubiquitous either through multi-therapy or by replacement of key natural molecules that become deficient under diabetic conditions as outlined above.

7. SUMMARY

In summary, this review has outlined differences in metabolic abnormalities and their magnitudes in type 1 and type 2 experimental diabetes models, which closely mimic the human conditions. The development of differing structural changes relates to different sets of underlying molecular changes and differences in the severities of neurotrophic support, which can be directly related to differences in insulin action. Therefore, despite exposure to the same magnitude of hyperglycemia over prolonged periods of time the resultant outcome is different in the two types of DPN. This means that apart from hyperglycemia, perturbations of insulin action and signaling play equally important roles in the development of type 1 DPN. Such differences have to be taken into account in future approaches to the treatment and/or prevention in this common complication of diabetes.

8. ACKNOWLEDGEMENTS

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