Review

Diabetic Autonomic Neuropathy

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Introduction

Diabetes is probably the commonest cause of autonomic neuropathy, and causes functional changes in many systems including the cardiovascular, urogenital and gastrointestinal systems. Fainting, postural hypotension, gastroparesis, atonic bladder, and erectile dysfunction may all be associated with autonomic dysfunction in diabetes, and there may also be defective sweating and pupillary reflexes. All of these may depend on damage to the small fibres in peripheral autonomic nerves, but it is increasingly clear that there are many disturbances in synaptic transmission and end-organ responses as well. Indeed many of the studies of 'autonomic neuropathy' depend on the measurements made of the function of effector organs rather than of the autonomic nerves themselves. Provocation tests which investigate end-organ activity during reflex manoeuvres, such as the Valsalva manoeuvre, postural tilting or cystometry, may allow the investigator to observe changes in reflex functions that are generally interpreted as being due to a disorder of the nerves themselves. Similarly changes in gastro-intestinal transit times and tests of secretory responses may indicate changes in the digestive system in diabetes. However it is difficult to exclude changes in the synaptic or end-organ function in many of these investigations, and the conclusion that the pathophysiology in diabetes resides in the autonomic nerves is somewhat of an extrapolation. Nevertheless, damage to the small fibres in peripheral somatic and visceral nerves may be an important causal factor in many cases, and may be due to functional or structural changes in the nerves themselves. Some of these changes in neuronal function may possibly be due to an alteration in blood supply to the nerves, while other mechanisms, including inflammation of immunological origin,[1] may also contribute to the neuropathology. Some of the functional changes are reversed when the blood sugar is corrected, while other features of the diabetic state are not.

The pathology in autonomic neurones may also be paralleled by disturbances in other small fibre systems, particularly the small sensory fibres that mediate pain and thermal sensation. In diabetes the thermal sensitivity may be reduced, while mechanical hyperalgesia may be demonstrated. Indeed, reduced thermal sensation is thought to be a very early marker of diabetic neuropathy, and the disturbances in pain sensation can be manifested by the presence of

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neuropathic ulcers and Charcot's joints.[2] While large myelinated axons show a reduction in conduction velocity and a variety of morphological changes including axonal loss, segmental demyelination and a reduction in cross sectional area, the anatomical changes in the unmyelinated fibres that compose the vast majority of autonomic nerves are less easy to quantitate. The peptide content, and the functional characteristics have proved to be a more useful method of study of these conditions, as has the changes in trophic factor production by the effector organs that regulate their growth. This review will briefly describe some of the changes that occur in autonomic nerve function in experimental diabetes, induced by the injection of alloxan, or more commonly streptozotocin (STZ).

Peripheral nerve function: Neural trophic factors and neuropeptides

The response to poor nutrition of axonal endings caused by poor intracellular axonal transport, peripheral ischaemia or other factors includes the retraction of nerve endings, and the possible regrowth (sprouting) of axons, which may be encouraged by the production of trophic factors produced by denervated tissues. This type of reorganisation of the autonomic nervous system is postulated in autonomic neuropathy and may be caused by variations in the levels of trophic factors such as the neurotrophins, a group of molecules that has expanded in number greatly in recent years. The first of these trophic factors to be discovered was nerve growth factor (NGF; Neurotrophin–1) which is produced by myocytes and other cells, but there are at least six members of the neurotrophin family. They are believed to interact with receptors such as those of the tyrosine kinase series, *trk-a*, *trk-b* and *trk-c*, to produce a complex that is transported back to the neuronal cell body, where the expression of various genes is altered in such a way that regrowth of axonal terminals is facilitated.[3,4] Kanki et al[5] found that the levels of NGF mRNA increased in the heart of diabetic animals, suggesting there is a trophic stimulus that would favour re-growth of sympathetic and other neurones. In another study of STZ-diabetic rats, cardiac sympathetic denervation was described, to a greater degree distally than proximally. This denervation was associated with a gradient of NGF protein production, which was greater distally in the tissue.[6] Schmidt et al[7] observed the effects of two neurotrophins (NGF and Neurotrophin-3) on STZ-diabetic rats that have an autonomic neuropathy characterized by the occurrence of pathologically distinctive dystrophic axons in prevertebral sympathetic ganglia and ileal mesenteric nerves.

Treatment of these animals with NGF or Neurotrophin -3 did not normalize established neuroaxonal dystrophy (NAD). They suggested that, in adult sympathetic ganglia NGF may contribute to the pathogenesis of NAD rather than its amelioration, perhaps as the result of inducing intraganglionic axonal sprouts on which dystrophic changes are superimposed. Administration of Neurotrophin-3 resulted in a significant decrease in NAD in control superior mesenteric ganglia. However, Neurotrophin-3 did not alter the frequency of NAD in diabetic animals, and the authors warned that delivery of excessive levels of growth factors may produce untoward effects.

Diabetes causes changes in the peptide content of some sensory and autonomic nerves. In the skin of STZ diabetic animals Karanth et al[8] reported a marked increase in the number of calcitonin gene-related peptide (CGRP)-immunoreactive fibres present in

epidermis and dermis, and of vasoactive intestinal polypeptide (VIP)–immuno-reactive fibres around sweat glands and blood vessels in early diabetes. There was no change in the NPY innervation of the skin, but in other tissues, viz., the myenteric plexus, an increase in the number of neuropeptide Y and vasoactive intestine polypeptide immunoreactive myenteric neurons was present in diabetic animals.[9] The levels of substance P and methionine-enkephalin are markedly reduced throughout the intestine, while VIP content is dramatically increased in diabetes.[10] These examples indicate that the changes that occur in different tissues are not uniform and there may be specific factors operating in each tissue to influence the content of different types of peptidergic innervation.

Another possible neuronal mechanism that may alter the functional reactivity of axons in the diabetic state is a change in the activity of the sodium pump: Na-K ATP-ase levels are reduced in diabetes in the sciatic and vagus nerves.[11] Unmyelinated axons have a high turnover of sodium and this may be altered as a consequence of changes in intracellular metabolism in diabetes.

Changes in cardiovascular function in experimental diabetes

Studies of the intrinsic heart rate of rats following pharmacological blockade of the sympathetic and parasympathetic systems were performed by Maeda et al; [12] these experiments allowed the investigators to observe the resting intrinsic heart rate, i.e. that of the cardiac pacemaker. The intrinsic rate fell by around 25% in the diabetic animals, and there was also evidence for depressed sympathetic (22%) and vagal (50%) tone. These authors concluded that changes in arterial pressure and baroreflex control are present in diabetic animals, but their data also suggests there may be some intrinsic changes in the heart itself. Minor ultrastructural changes that may be important in the handling of calcium ions have been observed in myocytes taken from the heart of STZ-diabetic rats; these changes may explain some of the significant changes in the contractile properties of single myocytes that occur in diabetes.[13] It is clear that at least some of the changes in cardiac function in diabetes may reside in the myocytes themselves, rather than just in their innervation.

Heart rate variation

Schaan et al[14] compared untreated and insulin-treated STZ diabetic rats in a study of arterial pressure, heart rate and their variability. Changes in heart rate variability are commonly interpreted in human studies as indicating a change in vagal tone. In this animal study, the authors concluded that the changes in autonomic control of HR and MAP were reversible with insulin treatment and better metabolic control. Another mathematical treatment of arterial pressure and heart rate variations in diabetic rats by Fazan et al[15]suggested that sympathetic modulation of the cardiovascular system is impaired.

Changes in parasympathetic nerve function in the heart.

There is evidence that human diabetics have lower heart rates than controls and this has generally been interpreted as indicating a reduction in vagal tone.[16] To a certain degree there was also an association between serum insulin, serum glucose and heart rate present within this study. Animal studies in normal dogs also indicate that changes in serum insulin and glucose can affect cardiac function: increased insulin levels which were accompanied by normoglycaemia by the infusion of glucose, were

associated with a negative inotropic response, but had no effect when blood sugar was allowed to increase. In the same study, reduction of insulin levels to one fifth of normal had no effects on cardiovascular function.[17] However no chronotropic changes were reported. It is believed that vagal Na-K ATP-ase levels are reduced in diabetes, and this may be a consequence of metabolic changes in the nerve induced by variations in plasma glucose and/or insulin.[11]

In STZ diabetic rats, bradycardia was present as indicated by increased R-R interval; however the atrio-ventricular transmission time was unchanged. The change started at 1 week after diabetes induction and remained until 20 weeks.[18] Bilateral vagotomy, in both diabetic and non-diabetic rats resulted in no difference between the diabetics and controls in either parameter, which indicated that an alteration in parasympathetic tone was present and could be the cause of the observed bradycardia in diabetics. A further observation that implicated the vagus was the impairment of effects of vagal stimulation on the R-R interval. While those results suggest there might be some impairment of vagal release of acetylcholine, other studies suggest that the release of acetylcholine from vagal nerve endings in the atria appears to be normal in diabetic animals, at least when presynaptic pharmacological stimulation was used.[19]

Failure of release of a neurotransmitter is often associated with post-synaptic supersensitivity of the tissue to that transmitter. Supersensitivity to the negative chronotropic effects of acetylcholine, carbamylcholine and bethanecol has been demonstrated in STZ-diabetic rats by Carrier and Aronstam.[20] These authors described chronotropic changes in diabetes; however inotropic responses to these drugs were unaltered by the presence of the metabolic disorder. Acetylcholinesterase activity was reduced but there was no change in the rate and extent of neuronal choline uptake. The binding of ligands to muscarinic binding sites was also studied using [3H]N-methyl-scopolamine. In the atria from both diabetic and control rats the receptors had the same high affinity, but the density of the binding sites was reduced in the atria from STZ-diabetic rats, and binding affinity was lower in diabetes. These authors concluded that the supersensitivity of right atria to the muscarinic agonist may be a consequence of altered coupling of muscarinic receptor to intracellular signal transduction mechanisms in diabetes. There is evidence from functional studies for altered activity of sarcoplasmic reticulum calcium transport in diabetes, which may underlie some of the time-dependent changes in the amplitude and kinetics of contraction of myocytes taken from diabetic hearts.[21]

Changes in sympathetic neuro-transmission in the heart and blood vessels.

The sympathetic supply to the heart and blood vessels has been investigated in diabetic rats. Sunagawa et al [22] found evidence that both adrenergic receptor-mediated and cholinergic receptor-mediated responses of the heart are significantly depressed in the diabetic heart. STZ-diabetic and insulin-treated STZ-diabetic animals were compared with controls, and the plasma glucose in the insulin treated group was between that of the control and the diabetic levels. The sensitivity of control, STZ diabetic and insulin-treated STZ-diabetic perfused isolated hearts to dobutamine (DOB) and acetylcholine (ACh) was studied. The increase in tension development by dobutamine was greatest in the control

group and least in the untreated diabetic group. A similar order was found when the bradycardia development by acetylcholine was investigated.

Increased contractile responses of the isolated caudal artery to noradrenaline have also been reported in diabetic rats by Weber and Macleod.[23] This is in contrast with the responses of same artery to sympathetic nerve stimulation by Hart et al[24] who found no changes in the sensitivity to noradrenaline. This group found that the caudal arteries from diabetic animals also accumulated and released more tritiated noradrenaline than did the arteries of control rats. Their interpretation was that neuro-vascular function of the isolated caudal artery of diabetic rats is abnormal, and that the ability of sympathetic nerves to store and release noradrenaline may play a role in this phenomenon. The increased release of tritiated noradrenaline from the tail artery of diabetic rats was also observed by Katovitch et al. [25]

The microvasculature of the sciatic nerve of normal and diabetic rats has been studied by van Buren et al,[26] who investigated the sensitivity of the vasa nervorum to tyramine and phenylephrine. The reduced response to adrenergic stimuli was investigated and the authors concluded that the defect lay in the presynaptic endings of sympathetic nerves, which suggests a problem with the release of noradrenaline. It is hypothesised that changes in the microvasculature of nerves contribute to diabetic neuropathy.

Alterations in Baroreceptor and other Cardiovascular Reflexes in Diabetic animals

The central control of the circulation appears to be defective in a number of studies on 'autonomic neuropathy'. The baroreceptor and chemoreceptor reflex responses mediated by the carotid sinus nerve are examples of the overall depression of reflex function. Dall'Ago, et al[27] used baroreflex sensitivity to test the reflex responses of diabetic animals. Heart rate changes induced by increasing or decreasing arterial pressure with phenylephrine and sodium nitroprusside injection allowed the effects of baroreceptors on heart rate to be determined; baroreflex sensitivity or gain was reduced in diabetic animals. Injections of potassium cyanide into the arterial chemoreceptors were used to stimulate the carotid body, which resulted in reflex bradycardia and raised arterial pressure. The sensitivity of this reflex was also compared in diabetic and control animals. STZ-diabetes resulted in reduced resting heart rate combined with a reduced sensitivity of the baroreflex to both increases and decreases in arterial pressure. Bradycardia induced by the chemoreceptor reflex was also attenuated in the diabetic rats. These authors concluded that the baroreflex and chemoreflex responses of the cardiovascular system are impaired in diabetic rats. A similar response was observed by Van Buren et al[28] who studied arterial pressure, heart rate and the baroreflex control of heart rate after induction of diabetes with STZ. Changes induced by changes in blood pressure induced by the vasoconstrictor phenylephrine, and the vasodilator sodium nitroprusside were again investigated in animals that had been diabetic for 2-42 weeks. Both the depressor response and maximal vasodilator activity in response to sodium nitroprusside were significantly ($P<0.05$) reduced in the diabetic animals. The maximal decrease in heart rate and

sensitivity of baroreflex-mediated bradycardia were reduced in the diabetic rats. Another reflex mechanism of great importance in cardiovascular control is the cardiovascular response to postural hypotension, which is largely due to changes in baro-reflex sensitivity. Karakida et al[29] recorded a greater incidence of hypotension during tilting of diabetic rats: the blood pressure fall was greater and the rate of return to normal was slower than in normal animals.

Central mechanisms

An alteration in opioid neurotransmission using the mu-opioid receptor within the CNS or the ganglia was observed in STZ diabetic animals by Severson and Tackett.[30] The opioid agonist DAME produced a significantly greater reduction in blood pressure, increase in hindlimb blood flow and decrease in hindlimb vascular resistance in diabetic rats, and the responses were reversed by naloxone. The responses were reversed by insulin treatment.

Autonomic control of the gastro-intestinal tract in diabetes.

The gastrointestinal tract of the STZ-diabetic rat is hypertrophied, and this appears to be associated with a reduction in the influence of the parasympathetic nerves[31] and changes in the sympathetic innervation which may be consistent with a pattern of denervation and re-innervation.

A decrease in parasympathetic supply to the GI-Tract tract remains a distinct possibility, and in the parotid gland, Anderson and Garrett[32] found a reduction in the secretory response to stimulation of the parasympathetic nerves in diabetic rats. This was attributed to an increase, at least in part, in acetylcholine-esterase. In studies of diabetic mice, Murai et al[33] also found a decreased secretory response of sublingual and submandibular glands to pilocarpine. However there was also an increase in the concentrations of acetylcholine and noradrenaline in these tissues in the diabetic group, which maybe indicate a difficulty with exocytosis of acetylcholine during nerve stimulation.

There is also evidence that the cholinergic supply of the stomach is less effective in diabetic than in normal rats; there was an increase in sensitivity to acetylcholine, and the dose-response curves for VIP isoprenaline and noradrenaline were shifted to the right.[34] A slowing of gastro-intestinal motility is consistent with this picture: a delayed stomach to caecum transit time was found by Chesta et al[35] using the non-invasive hydrogen excretion method. The transit time was significantly delayed, starting at one week following the STZ injection. Hyperglucagonaemia produced a similar result, and while this may be part of the explanation, the possibility of a role for autonomic dysfunction remains to be clarified.

The gut and other viscera have a sympathetic supply that utilises the intra-abdominal pre-vertebral ganglia, such as the coeliac and mesenteric ganglia. There are reports that changes in these neurones include an elevation of tyrosine hydroxylase activity, which may be related to increased catecholamine turnover and increased sympathetic influence on the gut of diabetic animals.[36,37] Paravascular mesenteric nerves (the extrinsic innervation) and the intramural nerves of diabetic rats contained numerous, markedly swollen dystrophic axons which stained intensely for tyrosine hydroxylase and dopamine-beta-hydroxylase. Both these enzymes are involved in noradrenaline synthesis. This change was fairly specific, because axons containing vasoactive intestinal polypeptide, gastrin-releasing

peptide/bombesin, substance P, leu-enkephalin, met-enkephalin, dynorphin B, neuropeptide Y and somatostatin showed no evidence of comparable changes.

One role of the sympathetic nerves to the liver is the regulation of liver carbohydrate metabolism and blood flow. In diabetic rats the ability to release glucose by the infusion of noradrenaline or sympathetic nerve stimulation is lost, whereas the effects of noradrenaline, but not sympathetic nerve stimulation, on hepatic blood flow are unaltered.[38] This group have also produced evidence that there is a change in the chain of intracellular signalling within enterocytes and associated with a disordered autonomic innervation of the liver and small intestine in STZ diabetic rats.[39]

Changes in urogenital function in diabetes

Bladder function and innervation in diabetes

In many species, the response to bladder distension is a reflex micturition contraction that is repeated many times if the distension is not relieved. The relationship between bladder pressure and volume in these circumstances is known as the cystometrogram, and the pressure or volume at which the micturition contractions first occur is known as the micturtition threshold. The diabetic bladder differs from the normal in that the capacity of the bladder is much greater, and this may be a compensatory increase as a result of polyuria, but may also be associated with nerve damage. The micturition volume, compliance and bladder weight are increased in the diabetic group.[40,41] Paro and Prosdocimi[42] found that the micturition threshold also increased in diabetic animals. The contractions at volumes greater than the threshold normally occur with a regular pattern and increase in frequency with increasing volume. However, in the diabetic group, the contractions became irregular and the degree of irregularity increased with the duration of the condition. Paro et al[40] compared the alloxan-diabetic with the sucrose-fed rat, in order to compare diabetic animals with another polyuric model. They found that the bladder contractions were normal in the polyuric group, which suggests that the responses of the diabetic rats was not simply due to polyuria. They also studied bladder strips *in vitro* and found that the ability of the strips to contract during stimulation of the autonomic (parasympathetic) nerves was reduced in diabetics compared with control and sucrose-fed animals. Morphological studies of the pelvic and hypogastric nerves suggested some abnormalities in the diabetic but not the other groups. The authors concluded that these alloxan diabetic rats had an autonomic neuropathy.

Other studies of detrusor muscle strips *in vitro* involved the use of acetylcholine, rather than nerve stimulation. Kamata et al[43] found that the maximal contraction in response to ACh was significantly enhanced in STZ- diabetic rats. In addition the density of muscarinic receptors measured in binding studies with tritiated -QNB was significantly higher in the bladder from diabetic rats compared to age-matched control rats.

The group also studied the role of calcium in acetylcholine-induced detrusor contractions, and concluded that the enhanced contractions may be due to increased influx of calcium ions through the ligand-gated calcium channels in the smooth muscle.

The actual concentrations of acetylcholine and noradrenaline in the bladder was studied in STZ diabetic

animals by Nakamura et al.[44] These authors found a two-fold increase in acetylcholine concentration in the bladder base, but no increase in noradrenaline. Taken together with the previous results it may be that there is a failure to release acetylcholine in these bladders, and possibly an impaired development of the cholinergic system, as was suggested by the authors.

The state of the micturition reflex in diabetes has been studied by Steers et al.[41,45] This reflex involves a pathway from the pelvic nerve afferents to the spinal cord and dorso-lateral pontine reticular formation, and an efferent path that includes a bulbo-spinal connection and the parasympathetic efferent supply to the bladder. Activity in this pathway is normally facilitated during bladder distension. They found that there was no change in the electrical thresholds or of the conduction velocities of the bladder postganglionic nerves. There was also no change in synaptic transmission in the major pelvic ganglion of the rat or in the latency of the supraspinal reflex that is normally associated with bladder contractions. However the normal facilitation of the supraspinal reflex by bladder distension was absent in the diabetic animals. Morphological studies however did indicate changes in the micturition pathway of diabetic animals. The size of the major pelvic ganglion cell somata was increased in diabetics, although the numbers of perikarya were similar. In contrast there was evidence of changes in the afferent pathways of the micturition reflex, because the size of pelvic neurone perikarya in the L6/S1 dorsal root ganglia was reduced (rats have six lumbar segments, and the pelvic nerve enters the cord at L6 and S1). There was also a reduction in trans-synaptic labelling of spinal cord neurones in the L6/S1 segments with wheat germ agglutinin labelled with horseradish peroxidase. Substance P concentrations measured by radio-immunoassay in the dorsal root ganglia were diminished in the dorsal root ganglia, but not within the bladder itself. Their main conclusion was that the sizes of the perikarya of afferent and efferent neurones in the micturition pathway of diabetic rats are reduced; there were also quantitative changes in the process of axonal transport and trans-synaptic transport within the spinal dorsal horn, resulting from the diabetes.

Erectile function in diabetes

Erectile function depends on a combination of events including increased blood flow to the corpus cavernosum, increased resistance in the venous outflow of the penis, and contraction of the somatic smooth muscle of bulbocavernosus and other muscles. Recently there have been studies which indicate that there is a defect in the autonomic control of the corpus cavernosal smooth muscle in diabetic animals. This muscle relaxes under the influence of cholinergic stimuli and parasympathetic nerve stimulation, which allows the erectile tissue to fill with blood. In diabetes these responses are diminished, partly because of the inability of the endothelium to release nitric oxide, which relaxes the smooth muscle using a cGMP mechanism. The balance of parasympathetic input, which causes erection, and of sympathetic input, which antagonises the response appears to be important.

Azadzoi and Saenz[46] concluded that diabetes impairs neurogenic and endothelium-mediated relaxation of rabbit corpus cavernosal smooth muscle. Nitric oxide was shown to act as the non-adrenergic non-cholinergic relaxatory neurotransmitter in the penis,

and it was suggested that this impairment of neurogenic and endothelium-dependent relaxation was due to diabetes and is mediated by alteration in the synthesis or availability of nitric oxide in corporeal tissue. Which aspect of diabetes causes the changes is not fully clear. Certain aspects of cavernosal response to constrictors and vasodilators are potentiated in hyperglycaemic media,[47] while there is also an impairment of the ability of the corpus cavernosal smooth muscle to relax in the presence of glycosylated human haemoglobin *in vitro*.[48]

In another study of corpus cavernosum and aortic rings in diabetic rats, Keegan et al[49] observed that STZ- diabetes caused about a 30% reduction in maximum aorta endothelium-dependent relaxation to acetylcholine and about a 40% reduction in corpus cavernosum endothelium-dependent maximum relaxation to the cholinergic transmitter. Cavernosal non-adrenergic, non-cholinergic nerve stimulation caused frequency-dependent relaxation to a maximum of about 40%, which was reduced in diabetic animals to about 25%. These studies point to changes in the muscarinic function in the aorta and penis, which were dependent on the production of nitric oxide. These authors found some reversal of the diabetic changes by antioxidative agents.[49,50]

In other studies on the diabetic rat, Mills et al[51] also found there was a loss of alpha-adrenergic responses to phenylephrine within the cavernosal circulation.

There have also been some studies on the changes in the vas deferens in diabetic animals. Longhurst [52] studied insulin-treated diabetic BB rats and diabetes-resistant BB rats (which did not require insulin treatment). Vasa deferentia from STZ-diabetic animals showed impaired responsiveness to nerve stimulation and some supersensitivity to contractile agents. However the insulin-treated diabetic BB showed only increased contractile responses to nerve stimulation and carbachol. Kamata and Kirisawa[53] studied the changes in sympathetic innervation of the vas in STZ-diabetic animals and found changes in junctional potentials and in the dose-response curves for noradrenaline. The affinity of the receptors for noradrenaline was decreased. These results were interpreted as indicating some degeneration of the sympathetic nervous system in these animals: the greater amplitude of the junctional potentials may be related to increased calcium mobilization. In the seminal vesicle, there is anatomical evidence of a reduction in sympathetic nerve fibres and an increased density and fluorescence intensity in NPY-containing fibres, but no change in acetylcholinesterase-containing nerves of diabetic animals.[54]

Ocular changes in diabetes

There are differences in the diameter of the pupil in the eyes of STZ-diabetic animals that have been attributed to changes in the autonomic innervation. Observations were made after a crush lesion of the parasympathetic innervation of the iris, which results in a state in which the autonomic control of the pupil is entirely due to the sympathetic nerves. In such a state, the pupils were smaller in diabetic animals, presumably due to the lack of a sympathetic mydriatic action. This change was attributed to a failure of the sympathetic innervation to function in this tissue in the diabetic animals.[55] However, anatomical studies do not show any changes in the distribution of adrenergic nerves in the iris in diabetes. Crowe and Burnstock[56] studied the innervation of the iris of diabetic and

control rats, and found no evidence for a change in the nor-adrenergic or the substance P -containing terminals. However there was an increase in the density of NPY-containing nerve terminals, and to a lesser extent, the VIP terminals within the iris of diabetic animals.

Ocular vascular reactivity shows some changes in the diabetic eye, and it is not clear how autonomic neuropathy contributes to this. The basal vascular resistance in diabetic eyes is similar to the controls, but there is altered reactivity to noradrenaline, adrenaline, prostaglandin F2 alpha and serotonin. The threshold concentration of these compounds necessary to cause a change in vascular resistance was less in diabetic eyes, but the contribution of blood flow and oxygen supply was uncertain.[57]

Conclusion

It seems sensible to ask the question 'What is Autonomic Neuropathy?'. Unlike the somatosensory neuropathies associated with diabetes, there is not an easy functional definition in terms of altered conduction velocities of the peripheral nerves; nor is there consistent evidence of morphological changes in the autonomic nerves themselves. Peptide content and distribution in nerves may change in diabetes, but the changes differ between tissues, and it is difficult to identify one anatomic change that is universally present in all tissues.

Diabetic autonomic neuropathy is a clinical diagnosis that is applied when patients show a variety of functional changes that may be attributed to the autonomic system. Fainting, postural hypotension, gastroparesis, atonic bladder, and erectile dysfunction may all be associated with autonomic dysfunction in diabetes. It may seem that the parasympathetic system is more involved than the sympathetic, but there is evidence for both in experimental and in human studies. Some of the functional changes are simply related to hyperglycaemia, swings in glycaemic status or the presence of glycosylated haemoglobin, and occur too early in the disease to be attributable to a reorganisation of nerve function.

The synthesis, release, breakdown, turnover and/or re-uptake of autonomic neurotransmitters or their products may change in diabetes, and there are many studies that indicate an impairment of autonomic neurotransmission. Changes in the post-synaptic receptors for these transmitters are also documented: supersensitivity is a common finding, and alterations in the binding characteristics of the receptors is reported in many tissues. Finally, the link between the ligand-gated receptors and the signalling systems within the cell may also be changed. All of these factors may contribute to the syndrome of autonomic neuropathy.

In contrast with the somatosensory peripheral neuropathy in diabetes, there is evidence of some changes in the function of some central nervous pathways that regulate the function of viscera, and it may be that at least some of the changes in reflex function may be affected within the central nervous system. Changes in baroreflex sensitivity, and in the micturition reflex are examples where a central component cannot be excluded.

Finally, there is the possibility of plasticity in the peripheral organisation of the autonomic system: the retraction and re-growth of autonomic nerves, and changes in axonal transport. It is believed that the integrity of autonomic connections with the target organs depends on trophic factors such as nerve

growth factor (neurotrophin-1). The fact that in diabetic tissues, there is a synthesis of these trophic factors and the expression of mRNA for the growth factors in sites that appear to be denervated does suggest that some reorganisation of neuronal connections may take place in diabetes.

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