Nerve conduction velocity in man: influence of glucose, somatostatin and electrolytes

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Summary Insufficient metabolic control in diabetes mellitus is associated with a reversible reduction in nerve conduction velocity, but the mechanism behind this phenomenon is unknown. To examine the effect of acute hyperglycaemia on nerve conduction eight non-diabetic men (20–49 years of age) with no signs of peripheral neuropathy were studied before and after 3 h of hyperglycaemic clamping (plasma glucose ≈ 15 mmol/l), while insulin secretion was suppressed by somatostatin [Study 1]. Nerve conduction velocity, as determined in the proximal part of the median nerve, fell by 2.8 ± 3.0 m/s ($2p$ -value: 0.033). However, during euglycaemic clamping (plasma glucose ≈ 5 mmol/l) in five non-diabetic men (19–38 years of age) infused solely with somatostatin [Study 2], a comparable decrement in nerve conduction velocity was found (1.7 ± 1.3 m/s, $2p$ -value:

0.043). In both studies relative hypoinsulinaemia was present. Serum-sodium decreased significantly (143 ± 1 mmol/l vs 137 ± 1 mmol/l [Study 1] and 143 ± 1 mmol/l vs 142 ± 2 mmol/l [Study 2]), while serum-potassium increased. In conclusion, the slight but significant reduction in nerve conduction velocity observed in both studies appears to be correlated to electrolyte changes. However, an effect of hyper-somatostatinaemia or the hormonal changes associated with this cannot be excluded, while short-term hyperglycaemia per se seems to be without effect on nerve conduction velocity. [Diabetologia (1994) 37: 1216–1220]

Key words Diabetes, diabetic neuropathy, electrolytes, hyperglycaemia, nerve conduction, somatostatin.

Clinical neuropathy is a major complication of long-term diabetes mellitus [1, 2]. Assessment of neuropathy is often made by measuring nerve conduction velocity (NCV), which has been found to be reduced in diabetic patients with and without clinical neuropathy [3, 4]. In the late stage, diabetic neuropathy is characterized by axonal degeneration, demyelination and fibre loss [5]. In early diabetes a modest and partly reversible decrease in NCV is seen. This condition appears to be associated with metabolic control

[6], but the cause of this decrease is unknown. Even in diabetes of long duration there seems to be a reversible metabolic component superimposed on the late structural neuropathy, as restoration of near-normoglycaemia improves nerve conduction [4, 7]. The present study was performed to gain further insight into the pathogenesis of nervous abnormalities in diabetes by examining the effect of hyperglycaemia on NCV while other hormonal and metabolic variables were controlled or closely monitored.

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Abbreviations: NCV, Nerve conduction velocity.

Materials and methods

Subjects and experimental design. Two different study protocols were employed (Fig.1). In a hyperglycaemic study (Study 1), eight healthy lean men, with a mean age of 34 ± 9 years (range 20–49 years) were studied. All participants had been fasting since 24.00 hours. At 08.00 hours (t: –60 min),

Fig. 1. Plasma glucose was clamped at either 15 mmol/l (hyperglycaemic study $\approx$ Study 1) or 5 mmol/l (euglycaemic study $\approx$ Study 2) with infusion of somatostatin (400 μ g/h). In Study 1 sodium chloride was also infused. Nerve conduction velocity was measured before (-30 – 0 min) and at the end (180–210 min) of the clamps

two intravenous cannulae were inserted. One placed in an arterialized hand vein was used for blood sampling, the other for infusions. Proximal and distal sensory NCV, proximal motor NCV and distal motor latency were determined in the median nerve twice, i.e., at the start of the experiment (-30 min to 0 min) and after 3 h of hyperglycaemia (180 to 210 min). At 09.00 hours ($t=0$) plasma glucose was acutely raised to 15 mmol/l (Fig. 1) and then maintained at this level by a variable glucose infusion (200 g/l). To suppress endogenous insulin secretion, somatostatin (Ferring AB, Malmö, Sweden) was infused at a rate of 400 μ g/h. Moreover, isotonic sodium chloride was infused (250 ml/h) to reduce the hyperglycaemia-induced increase in serum osmolality.

Plasma glucose was measured every 5 min by a glucose analyser (Beckman Instruments, Palo Alto, Calif., USA). Serum-insulin was measured as shown in Figure 2, while blood for determination of serum-electrolytes, osmolality, creatinine, urea, bicarbonate, protein, C-peptide and growth hormone was drawn at -60 , 0 , 60 , 180 and 210 min. As no significant fluctuations in blood chemistry were seen to occur before the infusion the values at $t: 0$ min were used as the before-value. The after-value was defined as the mean value of the measurements $t: 180$ to $t: 210$, i.e., the period during which nerve conduction was evaluated. In the euglycaemic study (Study 2) five healthy lean men with a mean age of 28 ± 8 years (range 19–38 years) were examined according to the same study protocol as described above, the only differences being that plasma glucose was clamped at euglycaemia (5 mmol/l) and no sodium chloride was infused.

None of the participants had symptoms or signs of peripheral neuropathy. All had given informed consent and the study was approved by the Regional Ethical Committee.

Nerve conduction measurement. For stimulation of sensory fibres surface electrodes were placed on digits I and III. Recording needle electrodes were placed near the left median nerve at the wrist and elbow. The needles were left in place during the experiment. The distal sensory NCV were measured from digit I to the wrist and from digit III to the wrist. The proximal sensory NCV was measured from wrist to elbow after stimulating at the digits. The values given in Table 2 are the mean between values obtained by stimulating at digits I and III, respec-

Fig. 2. Plasma glucose, serum insulin and rate of glucose infusion (GIR) during a hyperglycaemic $\circ$ and euglycaemic clamp study ($\bullet$) with infusion of somatostatin. Values are mean $\pm$ SEM

tively. The motor latency and the motor NCV were measured by stimulating with needle electrodes placed at wrist and elbow, and recording from a needle electrode placed in the thenar.

Analytical methods. Plasma glucose was determined by a glucose oxidase method, and serum growth hormone and insulin as previously described [8]. Serum C-peptide was assayed employing a commercial kit (Immunonuclear Corp., Stillwater, Minn., USA).

Table 1. Concentration of glucose in plasma, osmolality of the serum, and concentration of creatinine, carbamide, HCO₃⁻, protein, hormones and inorganic ions in serum before and after 3 h glycaemic clamping (Study 1 ≈ 15 mmol/l, Study 2 ≈ 5 mmol/l)

Group No.	Unit	Study 1				Study 2			
		Eight subjects				Five subjects			
		Before	After	Change	2p-value	Before	After	Change	2p-value
Glucose	mmol/l	5.1 ± 0.5	15.3 ± 0.2	10.2 ± 0.6	< 0.001	5.1 ± 0.3	5.8 ± 1.5 ^b	0.7 ± 1.5 ^b	N.S.
Osmolality	mOSM/kg	283 ± 2	288 ± 3	4.9 ± 1.5	< 0.001	288 ± 4 ^b	288 ± 2	-0.4 ± 2.3 ^b	N.S.
Creatinine	mmol/l	89 ± 4	88 ± 5	-0.8 ± 3.3	N.S.	94 ± 7	92 ± 4	-2.3 ± 2.6	N.S.
Carbamide	mmol/l	4.3 ± 0.7	3.7 ± 0.6	-0.59 ± 0.16	< 0.001	4.5 ± 0.5	4.3 ± 0.5	-0.24 ± 0.11 ^a	0.0029
HCO ₃ ⁻	mmol/l	24 ± 1	23 ± 1	-1.3 ± 1.6	N.S.	26 ± 2	25 ± 1 ^a	-1.2 ± 1.3	N.S.
Protein	g/l	68 ± 4	61 ± 3	-7.4 ± 2.2	< 0.001	65 ± 4	65 ± 3 ^a	0.5 ± 2.8 ^b	N.S.
Insulin	mU/l	14.8 ± 6.1	17.0 ± 4.7	2.2 ± 8.2	N.S.	19.6 ± 5.5	9.5 ± 11.1	-10.1 ± 9.0 ^a	(0.066)
C-peptide	µg/l	1.16 ± 0.31	1.28 ± 0.26	0.12 ± 0.32	N.S.	1.84 ± 0.93	0.84 ± 0.22 ^b	-1.00 ± 0.74 ^b	0.039
Growth hormone	µg/l	1.40 ± 0.63	1.99 ± 0.74	0.59 ± 0.51	0.013	3.60 ± 3.74	2.37 ± 1.22	-1.23 ± 4.05	N.S.
Sodium	mmol/l	143 ± 1	137 ± 3	-5.8 ± 2.2	< 0.001	143 ± 1	142 ± 2 ^b	-1.5 ± 0.7 ^b	0.0091
Potassium	mmol/l	4.30 ± 0.32	4.64 ± 0.26	0.34 ± 0.25	0.0064	4.16 ± 0.23	4.52 ± 0.42	0.36 ± 0.54	N.S.
Calcium	mmol/l	2.39 ± 0.32	2.19 ± 0.12	-0.20 ± 0.07	< 0.001	2.37 ± 0.10	2.38 ± 0.09 ^b	0.01 ± 0.04 ^b	N.S.
Magnesium	mmol/l	0.84 ± 0.06	0.79 ± 0.04	-0.05 ± 0.03	0.0037	0.85 ± 0.03	0.85 ± 0.05	0.00 ± 0.03 ^a	N.S.
Chloride	mmol/l	105 ± 2	104 ± 2	-0.8 ± 1.6	N.S.	106 ± 2	107 ± 2	0.9 ± 0.9	N.S.
Phosphate	mmol/l	1.17 ± 0.19	1.00 ± 0.14	-0.17 ± 0.16	0.019	0.97 ± 0.11	1.25 ± 0.06 ^b	0.28 ± 0.10 ^b	0.0034

^a Significantly different from the value of the hyperglycaemic group, 2p-value < 0.05;

^b Significantly different from the value of the hyperglycaemic group, 2p-value < 0.01

Values are mean ± SD

Statistical analysis

The values before and during hyperglycaemia were compared by Student's *t*-test for paired samples using a 5 % limit of significance. A bivariate correlation analysis was used to analyse the connection between the different measurements. A step-wise regression analysis was used to analyse the dependence of the nerve conduction velocity of different factors. By each step the most significant factor was chosen and the remaining variation was correlated to the remaining factors.

Results

Glucose, hormones and electrolytes (Table 1, Fig. 2). Basal plasma-glucose levels were similar, at about 5 mmol/l in the two studies. After 3 h of hyperglycaemic clamping, plasma-glucose was 15.3 ± 0.2 mmol/l, while it remained at the basal level in study 2 (5.8 ± 1.5 mmol/l).

Basal levels of serum-insulin, C-peptide and growth hormone were similar. As intended, somatostatin infusion prevented breakthrough of insulin secretion during hyperglycaemia, whereas during euglycaemia a definite suppression of insulin secretion followed upon somatostatin infusion, leading to relative hypoinsulinaemia in both studies.

Basal levels of serum-osmolality, -creatinine, -urea, -bicarbonate, -protein, -sodium, -potassium, -calcium, -magnesium, -chloride and -phosphate were

similar in the two groups. In Study 1, serum-osmolality increased by 4 mosmol during hyperglycaemia, whereas it was unaltered at basal level in Study 2.

In both studies serum-sodium decreased and -potassium increased. The changes were more pronounced in Study 1.

Changes were seen in the levels of some of the other inorganic ions as well, but none of these were similar in the two studies (Table 1).

Nerve function (Table 2). The thresholds of nerve stimulation showed no consistent changes. During hyperglycaemia NCV decreased by 2.5 m/s, though only the change of velocity in the proximal part of the median nerve obtained statistical significance. Correspondingly distal motor latency increased significantly and the amplitude of compound action potential decreased.

However, in the euglycaemic study comparable although less pronounced changes in NCV and action potential amplitude were seen.

Employing a bivariate regression analysis, a highly significant correlation was found between serum-sodium and NCV ($r = 0.78$, 2p-value < 0.01, $n = 13$) in the basal state, and a weaker, but still significant correlation ($r = 0.66$, 2p-value < 0.05, $n = 13$) was found between the final NCV measurement and the serum-sodium during the same period.

Table 2. Threshold, nervous conduction velocity, and amplitude of the action potential in different segments of the median nerve before and after 3 h glycaemic clamping (Study 1 $\approx$ 15 mmol/l, Study 2 $\approx$ 5 mmol/l)

Group No.	Unit	Study 1				Study 2			
		Eight subjects				Five subjects			
		Before	After	Change	2 <i>p</i> -value	Before	After	Change	2 <i>p</i> -value
<i>Threshold</i>									
Sensory	μV	3.23 ± 1.50	3.11 ± 1.26	-0.11 ± 1.23	N.S.	2.76 ± 0.90	2.23 ± 0.56	-0.53 ± 1.23	N.S.
Motor	μV	0.56 ± 0.14	0.65 ± 0.07	0.09 ± 0.10	0.047	0.55 ± 0.11	0.60 ± 0.08	0.05 ± 0.06	N.S.
<i>Conduction velocity</i>									
Sens Dist	m/s	51.5 ± 2.5	49.1 ± 4.8	-2.4 ± 3.1	(0.064)	52.7 ± 2.6	51.5 ± 2.3	-1.2 ± 4.5	N.S.
Sens Prox	m/s	62.9 ± 3.0	60.1 ± 3.5	-2.8 ± 3.0	0.033	64.5 ± 3.9	62.8 ± 3.4	-1.7 ± 1.3	0.043
Motor	m/s	60.0 ± 2.0	57.8 ± 3.1	-2.3 ± 3.8	N.S.	61.2 ± 6.2	59.4 ± 3.3	-1.8 ± 3.5	N.S.
<i>Distal motor</i>									
Latency	ms	3.3 ± 0.2	3.5 ± 0.3	0.13 ± 0.14	0.038	3.4 ± 0.2	3.5 ± 0.2	0.14 ± 0.11	(0.052)
<i>Amplitude</i>									
Sens Dist	μV	24.8 ± 6.7	22.5 ± 7.2	-2.3 ± 3.7	N.S.	28.7 ± 8.8	26.6 ± 7.6	-2.1 ± 1.5	0.034
Sens Prox	μV	9.5 ± 3.7	7.6 ± 2.1	-1.9 ± 2.3	(0.053)	10.0 ± 1.8	8.5 ± 1.9	-1.5 ± 0.7	0.011
Motor	mV	21.8 ± 4.6	17.6 ± 5.6	-4.2 ± 4.5	0.034	19.1 ± 6.8	18.0 ± 3.3	-1.1 ± 3.8	N.S.

Values are mean $\pm$ SD

The changes in plasma-glucose, serum-sodium, -calcium, -phosphate, -carbamide and -protein correlated closely ($r = \pm 0.76$ – 0.91 , $2p$ -value < 0.001), but no direct correlation to the change in nerve conduction was found. Neither was there any correlation between changes in serum-insulin and C-peptide vs changes in NCV, but a relative hypoinsulinism prevailed in both studies.

Discussion

In the present study NCV was found to be reduced during short-term hyperglycaemic clamping (3 h) in healthy men. In a recent study on newly-diagnosed diabetic patients, NCV was found to correlate with glycated haemoglobin [9], whereas no correlation was found between acute blood glucose levels and NCV's. This was taken to indicate that electrophysiological disturbances are associated with sustained rather than transitory hyperglycaemia. No other parameters of metabolic disturbances were measured.

An association between nerve function and transient hyperglycaemia has previously been found in insulin-dependent diabetic patients [10, 11] as well as in animals [12]. Factors such as the level of glucose, insulin and increased osmolality have been speculated to be responsible, but the influence of other factors of known importance for nerve function, such as levels of serum-sodium and -potassium, has not previously been focused on.

In a study on healthy subjects, hyperglycaemia and concomitant hyperinsulinemia (2 h) was found to be associated with an increase in NCV [13]. Serum-electrolytes were essentially unchanged and it was hypothesized that either the increased serum-insulin level or the increased serum-osmolality were respon-

sible for the increase NCV. In a follow-up study [11] on insulin-dependent diabetic subjects, 15 min of hyperglycaemia (+ 15 mmol/l) was also found to augment NCV, whereas NCV decreased after 2 h of sustained hyperglycaemia. The immediate increase was ascribed to increased serum-osmolality, whereas the reduction following sustained hyperglycaemia was suggested to be due to the combination of hyperglycaemia, relative insulin depletion and increased serum-osmolality. The possible influence of changes in electrolytes was not evaluated.

In the present study, however, a reduced NCV was also found following 3 h of euglycaemic clamping with infusion of somatostatin alone. In both parts of the study blood chemistry was closely monitored. In the hyperglycaemic study the elevated plasma glucose level was accompanied by increased serum-osmolality and -potassium. Insulin was stable at basal, while serum-carbamide, -protein, -calcium and -sodium decreased. In the euglycaemic study serum-sodium and -carbamide decreased, whereas serum-potassium increased and serum-osmolality was unchanged.

The basal level of sodium was found to correlate closely with basal NCV, but although sodium decreased and potassium increased in both studies no correlation was found between the decrease in NCV and the changes in blood chemistry. This may be due to a possible delay in transmission of changes in blood chemistry to the endoneurium, so the blood levels do not accurately reflect the levels in the endoneurium. Because movement of sodium ions into the axon is responsible for the generation of the action potential, it is not surprising that changes in extracellular sodium can modify nerve conduction. Nevertheless, the finding of an association between serum-sodium and nerve conduction velocity still needs confirmation from further studies, but corroborate the hy-

pothesis that short-term changes in nerve conduction associated with hyperglycaemia may be due to changes in metabolic state.

Another explanation may be that the changes in serum-electrolytes were not connected to the changes the reduction in NCV. As somatostatin was infused in both studies, it cannot be excluded that somatostatin per se may affect NCV. Somatostatin levels have previously been found to be elevated in diabetes [14], and a direct depressive action of somatostatin on nervous modalities has been described before [15]. However, such an effect of somatostatin on NCV remains hypothetical.

Likewise, insulin in itself cannot be ruled out as the causal factor. In the present study, relative hypoinsulinaemia was present in both protocols, as was the case in the study by Sindrup et al. [11] dealing with insulin-dependent diabetes and NCV. Diabetes has been suggested to induce disturbances by a reduction in nerve membrane Na^+ - K^+ -ATPase activity [16]. A reduced (true or relative to glycaemic level) insulin level may reduce NCV by reducing Na^+ - K^+ -ATPase activity [17]. Other, but undisclosed, metabolic effects of glycaemic clamps such as changes in non-esterified fatty acids, ketones, amino acids etc. might also have had an effect on NCV.

A standard requisite in drug trials of the effect on diabetic neuropathy include measurements of nerve conduction, and small changes (few m/s) have been interpreted as an improvement of the neuropathy. The results of the present study suggest that small changes can be due to changes in the metabolic state rather than changes in the degree of neuropathy. Thus, NCV is not a sufficient measure of the degree of neuropathy necessitating cautious interpretation of studies where nerve conduction velocity is used to assess degree of neuropathy.

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