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RESEARCH ARTICLE

Rosuvastatin positively changes nerve electrophysiology in diabetic rats

K. Tarhzaoui[1]
P. Valensi[1]*
G. Leger[1]
F. Cohen-Boulakia[2]
R. Lestrade[2]
A. Behar[2]

[1]*Laboratory of Nutrition, Metabolic Diseases and Cardiovascular Prevention, Paris Nord University, CRNH-IdF, Bobigny, France*

[2]*Pierre et Marie Curie University (Paris 6), Paris, France*

*Correspondence to:
Prof. P. Valensi, Laboratoire de Nutrition, Maladies Métaboliques et Prévention, Cardiovasculaire, Hôpital Jean Verdier, Avenue du 14 Juillet, 93140 Bondy, France.
E-mail: paul.valensi@jvr.aphp.fr

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Abstract

Objective To examine the effect of rosuvastatin on peripheral nerve function in diabetic rats using electrophysiological measurements.

Background Diabetes was induced in 5-day-old male Wistar rats by intraperitoneal (i.p.) injection of streptozotocin (STZ). As many as 45 diabetic rats were randomized to three groups: one treated with rosuvastatin (group R), another with rosuvastatin and mevalonate (group MR) and the other was untreated (group U). The data were compared with a group of normal age-matched rats i.e. control rats (group C).

Methods Neurophysiological measurements were performed at the age of 3 months (T1) and again at the age of 8 months (T2), after 3 months of treatment.

Results At T1, there was a trend to lower amplitude of compound motor action potential (CMAP) in the three diabetic groups as compared to controls, and no difference for motor nerve conduction velocity (MNCV), amplitude of sensory nerve action potential (SNAP), sensory nerve conduction velocity (SNCV) between diabetic groups and controls. At T2, the amplitude of CMAP was significantly lower in groups R and MR *versus* group U and control rats. MNCV was significantly and similarly decreased in the three diabetic groups; the latency of the first sensory peak (fastest sensory fibres) was significantly increased in group U but was normal in groups R and MR.

Conclusions This study shows that :

1. rosuvastatin exerts a beneficial effect on the conduction of the fastest sensory fibres;
2. these effects are independent of blood pressure and lipid changes.

Keywords nerve function; electrophysiology; diabetes; statins and rats

Introduction

Neuropathy is one of the most common complications of diabetes mellitus in humans [1,2]. In rats with streptozotocin (STZ)-induced diabetes, nerve changes consist of fibre loss, axonal degeneration and segmental demyelinization [3]. Biological changes to nerves include impaired resistance to

oxidative stress and increased free radicals [4], accumulation of advanced glycated end products [5], enhancement of polyol pathway activity [6], and defects in axonal transport [7]. Vascular alterations consist of hypoperfusion of the vasa nervorum [8,9] and an increase in capillary permeability to proteins [10]. Several articles have also highlighted the role of C-peptide deficiency, nitrosative stress, and poly adinosinediphosphate ribose polymerase (PARP) and Cox-2 activation in diabetic neuropathy [11].

Several studies suggest beneficial effects of statins on endothelial dysfunction [12–14]. In this respect, we have recently shown that cerivastatin and rosuvastatin may prevent the increase in peripheral Capillary Filtration of Albumin (CFA) in rats with early STZ-induced diabetes [15,16]. This effect appeared to be independent of blood pressure and lipid changes [16]. The beneficial effect on microcirculation may reduce endoneurium swelling and thus contribute to the prevention of diabetes-induced peripheral nerve function impairment.

We have recently described in detail the neurophysiological changes in rats with early induced diabetes (STZ administration at 5 days of age) [17,18]. These rats with early induced diabetes exhibited marked but not severe hyperglycaemia, a severe insulinopenia and insulin resistance [19]. The decrease in compound motor action potential (CMAP) amplitude (at 3 months) and the lengthening of the difference between latencies of the first and second sensory peaks (4 months) appeared as the earliest neurophysiological changes in diabetic rats. These changes are consistent with alterations to the growth and maturation of axon size and myelin thickness, but the decrease in CMAP amplitude may result from impaired function of muscle cells. However, the fact that significant correlations between sensory parameters seen in normal rats during maturation (3–4 months) are not found in diabetic rats indicates early electrophysiological changes, at least for sensory nerve function, in diabetes. Nerve conduction velocities are markedly reduced only later, at 6 months, in agreement with the protection of neural growth during maturation [20,21].

Rosuvastatin has been tested for 2 weeks in rats over 3 months of age, with diabetes induced by STZ, and shown to prevent the impairment in motor nerve conduction by improving nerve blood flow [22]. Similarly, in rats with early STZ-induced diabetes, short-term treatment by cerivastatin partly prevents impairment of peripheral nerve conduction [15]. Some recent data also suggest that the beneficial effects of statins might result from restoration of vasa nervorum [8].

Therefore, the aim of the present study was to test the beneficial effect of long-term treatment by rosuvastatin on both motor and sensory nerve function changes in rats with early induced diabetes, and to determine whether this effect may be independent from blood pressure and lipid changes. In order to check whether these statin effects act through the cholesterol biosynthesis pathway, we co-treated a subset of diabetic rats with the cholesterol precursor mevalonate. A group receiving mevalonate in addition to rosuvastatin was included to address whether any therapeutic effect of the statin was dependent upon or independent of the inhibition of HMG-CoA reductase. Reversal of a statin-effect under these conditions would indicate that this effect results from the inhibition of this rate-limiting enzyme, and implicate a role for mevalonate-derived isoprenoid metabolites. This required extensive neurophysiological examination as previously described [17].

Materials and methods

Animals

Diabetes was induced in 5-day old male Wistar rats by intraperitoneal (i.p.) injection of STZ at a dose of 70 mg/kg in citrate buffer (pH = 4.5). As previously shown, [19] these rats [7] may be followed up for several months without any anti-diabetic treatment. The animals did not receive any hypoglycaemic agents during the study, which commenced when the rats reached a mean age of 3 months and ended when they were aged 8 months.

All our procedures were conducted in accordance with our regional veterinary department and French national regulations (N° 93-041, 93-038). This study was carried out according to the guide for the care and use of laboratory animals published by the United States National Institute of Health (publications N° 85-23, revised 1996).

Experimental protocol

At 3 months, 45 male diabetic rats were randomized into three groups of 15 rats and received either rosuvastatin 20 mg/kg/d (group R) in drinking water and a co-treatment of rosuvastatin 20 mg/kg/d and mevalonate 20 mg/kg/d (group MR) in drinking water or no treatment (untreated, group U). A total of 15 normal Wistar rats without any treatment served as controls (group C). Neurophysiological measurements were performed on the rats aged 3 months and before any treatment (T1) was given.

For groups R and MR, treatment started 2 months later at 5 months of age and was administered for 3 months until T2. Neurophysiological measurements were performed at T1 (age 3 months) and at T2 (age 8 months), in rats with a core temperature of $37 \pm 0.5\,^{\circ}C$, maintained using a homothermic operating table. A temperature sensory probe was inserted rectally maintaining a constant temperature during investigations.

Systolic blood pressure (SBP), serum lipid levels and creatine phosphokinase (CPK) were measured at T2.

Blood glucose was periodically monitored with a strip (One Touch II, Johnson Johnson, Milpitas, CA) at T1 and T2.

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Neurophysiological measurements

Compound motor action potential (CMAP)
Motor action potential was recorded in the muscles of the first interosseous space (reference electrode near the fourth toe) after proximal monopolar cathodic stimulation at the sciatic notch and distal posterior tibialis nerve stimulation behind the internal malleolus with the anodic electrode behind the external malleolus. The ground electrode was situated between the proximal and distal stimulating electrodes. Supra-maximal stimuli (0.1 ms, 13 mA) were delivered from an ESAOTE stimulator. The CMAP was suitably amplified and registered. Two or three consecutive action potentials from the two stimulating points were superimposed and latencies of the potential were measured. The amplitude between the beginning and the peak of the potential was also measured.

Motor nerve conduction velocity (MNCV)
From CMAP measurements, motor nerve conduction velocity (MNCV) was calculated from the onset of the motor action potential using the estimated length of the nerve between the two stimulating electrodes measured on the skin. The limb was extended so as to measure nerve path length between stimulating cathodes on the skin. The latency difference of the onset of motor potential was used for the calculation of MNCV according to Hort-Legrand [18].

Sensory nerve measurements
Recordings of the nerve potentials were obtained from the sciatic notch with the previous cathodic motor electrode after bipolar stimulation of the external saphenous nerve. The stimulating electrodes were inserted below the external malleolus. Supramaximal stimuli were delivered at a rate of 1.7/s. The average of 100 responses was triphasic, positive, negative and positive. Latency (L1), the amplitude of the sensory nerve action potential (SNAP) was measured for the first positive peak and the latency of the second positive peak (L2), as a marker of slower-conducting fibres than L1.

Reproducibility
The reproducibility of neurophysiological measurements was tested by performing them twice on 12 control rats with a 30-min interval. After the first measurement, the rats remained in the same position on the homothermic operating table. The electrodes were removed from the lower limbs and fixed on the back for the second measurement. The correlation coefficients between the two measurements were high: 0.90, 0.93, 0.95, 0.87 and 0.87 ($p < 0.001$ for all) for peak latencies, SNAP amplitude, SNAP duration, CMAP amplitude and MNCV, respectively.

Blood pressure and lipid parameters measurements

SBP was measured by a plethysmographic method, similar to sphygmomanometry in humans and based on the Riva-Rocci technique. SBP is defined as the cuff pressure necessary to interrupt blood flow through an underlying artery. A small cuff was fitted around the tail and inflated. Interruption of flow through the tail artery was detected by a transducer applied to the tail distal to the cuff. SBP was measured three times at 2-min intervals and the three measurements were averaged. Three blood pressure measurements were performed not only for better reproducibility but also because of a possible variation of arterial compliance during this experiment. SBP was determined at month 8 in all the diabetic rats and in control rats using the same anaesthesia as for the CFA test.

Serum lipid levels (total, high-density lipoprotein (HDL)cholesterol and low-density lipoprotein (LDL) cholesterol, triglycerides) were measured or calculated with automated enzymatic methods (Randox, Crumlin, UK), and CPK using a blood chemistry test auto analyser.

Statistical analyses

Data are given as mean ± Standard Error Mean (SEM) values. Comparisons between groups were carried out by ANOVA or Kruskal–Wallis tests as appropriate according to the Gaussian or non-Gaussian distribution of the data. Comparisons between paired data were also calculated by ANOVA. All statistical tests were performed using SPSS software (SPSS, Chicago, IL).

Results

Body weight, biochemical measurements, and blood pressure (Table 1)

There were 15 STZ-diabetic rats in each group. At T1, mean body weight and blood glucose were not significantly different in the three diabetic groups but differed significantly from the control group ($p < 0.005$ and $p < 0.001$, respectively).

At T2, mean body weight and blood glucose were not significantly different between the three diabetic groups (U, R and MR) but differed significantly from the control group ($p < 0.05$ and $p < 0.001$, respectively).

At T2, serum triglycerides were 0.59 ± 0.04 mmol/L, 0.61 ± 0.05 mmol/L and 0.85 ± 0.07 mmol/L respectively, for groups R, MR and U. These values were significantly lower in groups R and MR than in group U ($p < 0.01$). Total cholesterol, did not differ significantly in the three groups: in group R, 2.45 ± 0.13 g/L; group MR, 2.52 ± 0.15 g/L; group U, 2.53 ± 0.13 g/L.

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Table 1. Age, body weight and blood glucose at T 1 and T2

	T1			
Group	U	R	MR	Control
Number	15	15	14	15
Age (d)	101 ± 2	106 ± 1	105 ± 1	103 ± 3
Body weight (g)	367 ± 12	387 ± 12	365 ± 10	427 ± 4**
Blood glucose (mmol/L)	17.5 ± 3.0	13.7 ± 1.2	15.3 ± 1.2	4.9 ± 0.5***

	T2			
Group	U	R	MR	Control
Number	15	15	14	15
Age (d)	249 ± 2	249 ± 2	248 ± 2	250 ± 5
Body weight (g)	518 ± 17	523 ± 20	482 ± 16	594 ± 11*
Blood glucose (mmol/L)	16.9 ± 1.0	16.9 ± 0.8	18.2 ± 1.1	5.0 ± 0.1***

*, ** and ***, $p < 0.05$, <0.005 and <0.001 *versus* groups U, R and MR.

Similarly there was no significant difference for high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (data not shown). CPK levels were 263 ± 32 IU/L, 476 ± 120 IU/L and 493 ± 168 IU/L in U, R and MR groups, respectively, with no significant difference between the three groups.

SBP was increased in group U (156 ± 11 mmHg) compared to the control group (128 ± 2 mmHg, $p < 0.03$). In group R, SBP was significantly reduced (116 ± 8 mmHg) compared to group U ($p < 0.02$). Mevalonate prevented this decrease in SBP (173 ± 15 mmHg), and SBP did not differ in group U and MR.

Electrophysiological measurements

Motor nerve conduction velocity (Figure 1)
At T1, MNCV was not significantly different in the three diabetic groups and in control rats. From T1 to T2, MNCV increased significantly in the three diabetic groups and in control rats ($p < 0.001$) as a maturation effect [18]. At T2, MNCV was significantly lower in the three diabetic groups than in control rats ($p < 0.05$), but there was no significant difference between treated and untreated diabetic groups.

Compound motor action potential amplitude (Figure 2)
At T1, there was a trend to CMAP amplitude being lower in the three diabetic groups as compared to control rats. From T1 to T2, CMAP amplitude decreased significantly in groups R and MR but not in group U. At T2, compared to control rats, there was a trend to lower values in group U. CMAP amplitude was markedly lower in groups R and MR than in control rats ($p < 0.001$ for both).

Peak 1 latency and sensory nerve conduction velocity (Figure 3)
At T1, L1 was not significantly different in the three diabetic groups and did not differ significantly between diabetic rats and control rats. At T2, L1 was significantly shorter in groups R and MR than in group U ($p < 0.01$). L1 did not differ significantly in groups R and MR from non-diabetic control rats, but was significantly longer in group U than in control rats ($p < 0.01$).

Peak 2 latency (Figure 4)
At T1 and T2, L2 was not significantly different in the three diabetic groups. L2 was significantly longer in the diabetic groups than in control rats, both at T1 and T2 ($p < 0.001$).

SNAP amplitude (Figure 5)
At T1 and T2, SNAP amplitude was not significantly different in the three diabetic groups and in non-diabetic control rats.

Discussion

In the present article, the effect of long-term (3 months) treatment by rosuvastatin on neurophysiological parameters has been studied extensively in rats with early

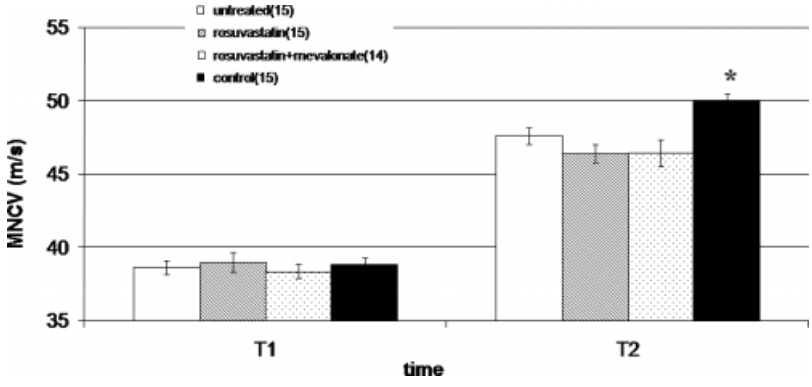

Figure 1. Motor nerve conduction velocity (MNCV). At T1, no significant difference between the four groups. At T2, *$p < 0.05$ for control *versus* diabetic groups. Numbers of rats: untreated group: 15; rosuvastatin group: 15; rosuvastatin and mevalonate co-treatment: 14; control group: 15

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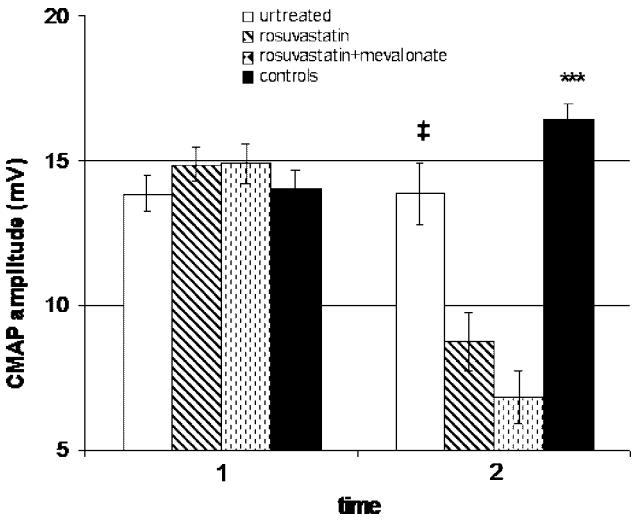

Figure 2. Amplitude of the compound motor action potential (CMAP). At T1, no significant difference between the four groups. At T2, ***$p < 0.001$ for controls *versus* both treated groups and ‡ $p < 0.001$ for untreated *versus* both treated groups. Same numbers of rats as in Figure 1

induced diabetes. In untreated rats, there was a trend to lower values of CMAP amplitude as compared to control rats and CMAP amplitude was decreased by rosuvastatin. MNCV was decreased in diabetic rats and unchanged by rosuvastatin, and the latency of the first sensory peak was significantly lengthened in diabetic rats and normalized by rosuvastatin. These data suggest that rosuvastatin exerts a beneficial effect on the conduction of the fastest sensory fibres but might induce some negative effect on muscle fibre function These effects were not influenced by changes in blood pressure nor blood lipid parameters.

In the same model of rats with early induced diabetes, we have previously shown that the decrease in CMAP amplitude and the lengthening of the difference between latencies of the first and second sensory peaks appeared at the same time as the earliest neurophysiological changes, which suggests that the earliest effect of diabetes is on sensory myelin function and muscle cell function [17,18]. The present findings are consistent with an effect of rosuvastatin on both disorders, consisting of a beneficial effect on sensory conduction but may indicate a level of muscle dysfunction.

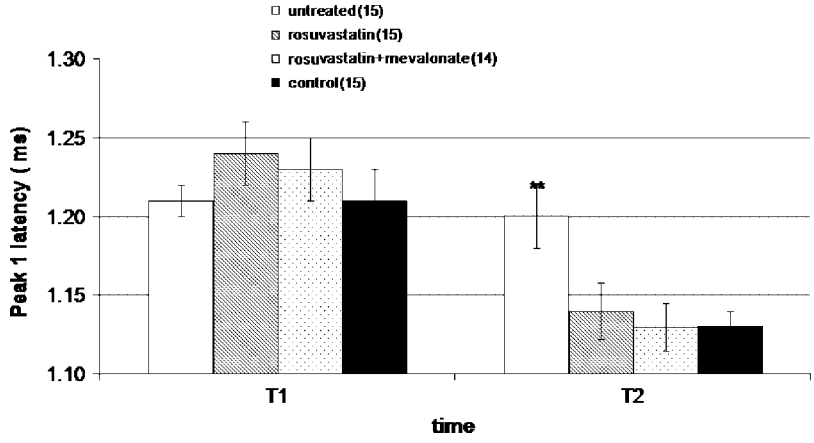

Figure 3. Peak 1 latency. At T1, no significant difference between the four groups. At T2, **$p < 0.01$ for untreated group *versus* treated groups and controls. Same numbers of rats as in Figure 1

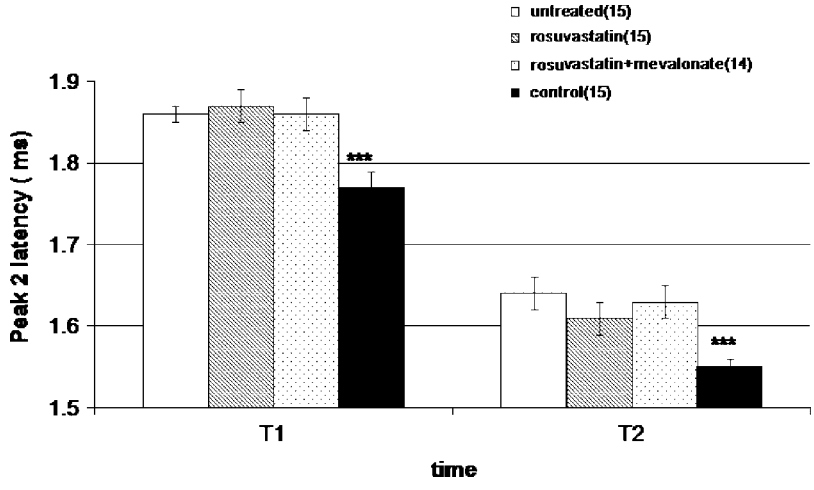

Figure 4. Peak 2 latency. At T1 and T2, ***$p < 0.001$ for controls *versus* the three diabetic groups. Same numbers of rats as in Figure 1

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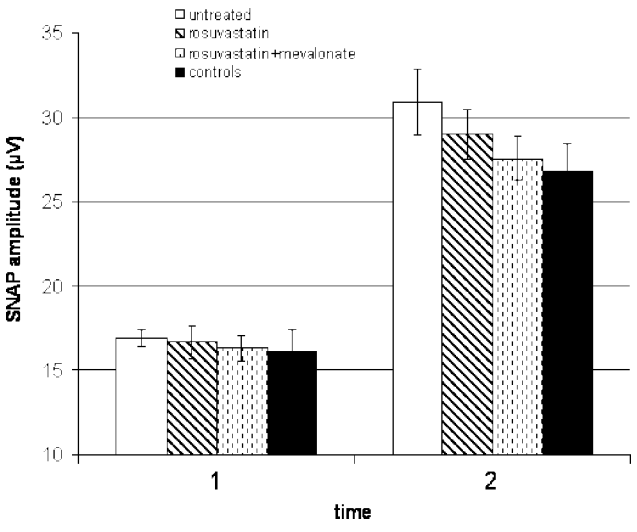

Figure 5. Amplitude of the sensory nerve action potential (SNAP). No significant difference between the 4 groups at T1 and T2. Same numbers of rats as in Figure 1

Cameron *et al*. have shown that in post-pubertal rats with STZ-induced diabetes of 6 weeks duration, 2-week treatment by rosuvastatin normalized motor and sensory nerve conduction [22]. Those rats are characterized by high hyperglycaemia and markedly increased axonal and myelin thickness impairment, whereas in our model hyperglycaemia is more moderate and this makes it possible to test treatments over several months. In addition, in our model, nerve conduction velocities became markedly reduced only after 6 months of diabetes, due to the protection of neural growth during maturation [20,21]. This was shown using the same model in which we previously reported a trend towards an improvement in peripheral nerve conduction after short-term treatment with cerivastatin [15].

After rosuvastatin treatment, CMAP amplitude is significantly lower than in untreated animals. This occurs in a model of rats characterized by a depression of this parameter as compared with non-diabetic controls. CMAP amplitude is further depressed after rosuvastatin treatment, but the mechanistic explanation of this with regard to nerve function remains unclear at this time. However, there may be an underlying deficit in muscle function, which is initiated by the induction of diabetes at an early age, which is not reversible or might be exacerbated by statin treatment. Moreover, in electrophysiological technique, CMAP amplitude is recorded only on the muscle (18) painful myopathy and muscle weakness have been described during statin treatment in the presence or absence of associated neuropathy [23,24]. In our previous study, diabetic rats treated by high doses of cerivastatin were affected by muscle weakness [15]. In addition, attention has already been drawn to the occurrence of muscle toxicity without an increase in CPK levels [25]. Neither mitochondrial injury nor a decrease in muscle ubiquinone levels seemed to be the primary cause of skeletal muscle toxicity in the cerivastatin-dosed rats [26]. The role of exercise in the toxic effects of statins has been suggested [27], while diabetes is not known as an enhancing factor for such adverse effects. However, metabolic changes or immune-mediated mechanisms associated with diabetes might induce negative effects on the detoxifying role of the liver. Our present findings suggest that the decrease in CMAP amplitude may occur before a more severe adverse muscle effect of statins. This could be expressed by an increase in CPK levels but does not exclude a statin-effect on motor nerve conduction, which might occur after longer treatment as reported in rare cases in humans [24] The positive effect of statins on sensory nerve conduction appear to be independent of blood pressure changes since this effect was unchanged by combined treatment with mevalonate. Moreover, it was not dependent on lipid changes since serum total cholesterol was not different in groups R, MR and U and serum triglyceride levels were similarly decreased in groups R and MR as compared to untreated diabetic rats.

As to SBP, it was increased in the untreated diabetic rats as previously reported [28]. This increase was prevented by rosuvastatin, but not by co-treatment with mevalonate. However, mevalonate can alter vascular tone and cause hypertension [29]. This suggests that the hypotensive effect of rosuvastatin is mainly related to inhibition of HMG-CoA reductase [30].

The improvement in sensory nerve conduction during rosuvastatin treatment has been shown to be associated with an improvement in nerve blood flow [22] and restoration of vasa nervorum [8] In our model of rats with early induced diabetes, rosuvastatin prevents the increase in peripheral capillary filtration of albumin independently from blood pressure and lipid changes [16]. We have already reported a significant association between an increase in capillary filtration and peripheral neuropathy in diabetic patients [12], which is consistent with the role of endoneurial swelling in the decrease in peripheral nerve conduction [15]. The beneficial effect of rosuvastatin on the latency of only the fastest sensory fibres suggests that these fibres are more prone to endoneurial swelling and may be influenced favourably by treatment that is able to normalize capillary permeability. In accordance with Bae JS *et al*. [31], we think that latency measurements should be available in clinical practice to detect any changes that take place before the onset of neuropathy. and possibly to used statin treatment in this issue [31].

Conclusion

Rosuvastatin exerts a beneficial effect on the conduction of the fastest sensory fibres but does not reverse an underlying impairment in muscle function independently of blood pressure and lipid changes. The consequence of reduced CMAP in response to statin treatment is not clearly understood. The positive effect on sensory nerve conduction is likely to result from both an improvement in vasa nervorum blood flow and a decrease in endoneurial swelling resulting from a decrease in capillary filtration.

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Our data suggest that patients with early, impaired electrophysiological measurements could benefit from statin treatment. However, whether statins may alter the progression of human diabetic neuropathy, needs to be tested in controlled trials.

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Conflict of interest

None declared.

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