ELSEVIER

European Journal of Pharmacology 296 (1996) 277–283

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Presynaptic deficit of sympathetic nerves: a cause for disturbed sciatic nerve blood flow responsiveness in diabetic rats

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Received 3 July 1995; revised 16 October 1995; accepted 24 October 1995

Abstract

Reduced nerve blood flow is thought to play an important role in the pathogenesis of diabetic neuropathy. This disturbance in nerve blood flow might be the consequence of either microangiopathy or an impaired autonomic innervation of the vasa nervorum. In order to differentiate between a vascular or an adrenergic-autonomic defect as the underlying cause of the disturbed nerve blood flow, we investigated the effects of the adrenocorticotropic hormone [ACTH]-(4–9) analogue Org 2766 on sciatic nerve blood flow under basal and adrenergic-stimulated conditions. Org 2766 has neuroprotective effects without cardiovascular effects. Treatment with Org 2766 was started 6 weeks after the induction of experimental diabetes mellitus. At week 12 the sciatic nerve blood flow, measured by laser-Doppler flowmetry, was reduced to 60% of the non-diabetic level; blood pressure was unchanged in diabetic rats compared to non-diabetic rats. Basal haemodynamic values were not affected by Org 2766 treatment. Vasa nervorum adrenergic responsiveness to tyramine (presynaptic) and phenylephrine (postsynaptic) was investigated. Diabetic rats showed adrenergic hyporesponsiveness. Treatment with Org 2766 restored the reduced presynaptic response to tyramine without affecting the reduced postsynaptic response to phenylephrine. It is concluded that a presynaptic-sympathetic deficit of nervi vasorum causes a disturbed flow responsiveness in diabetic rat sciatic nerve and that adrenergic autonomic disturbances in the vasa nervorum have only a small role in the reduced basal nerve blood flow of diabetic rats.

Keywords: Diabetic rat; Nerve blood flow; Vasa nervorum; Adrenergic responsiveness; ACTH-(4–9) analog, Org 2766

1. Introduction

Interruption of the nerve blood supply severely impairs nerve function (Lundborg, 1988) and is supposed to play a role in experimental diabetes (for review: Cameron and Cotter, 1994). The early reduction in peripheral nerve blood flow (Cameron et al., 1991; Kappelle et al., 1993) and consequent endoneurial hypoxia (Zatz and Brenner, 1986; Dyck, 1989; Stevens et al., 1994; Tesfaye et al., 1994) seen in experimental diabetes mellitus rapidly leads to a diminished nerve conduction velocity (Cameron et al., 1991; Bravenboer et al., 1992, 1993; Kappelle et al., 1994a). Yet, the aetiology of the reduced blood flow and the mechanisms involved remain obscure because factors which regulate nerve blood flow are poorly understood. Blood flow control mechanisms have become an important issue in diabetic neuropathy (Dhital et al., 1986; Koistinaho et al., 1990; Zochodne and Ho, 1993), and results from our group indicate that the adrenergic responsiveness of the vasa nervorum is decreased in diabetic rats. This disturbed neuronal control might result in an impairment of nerve blood flow and thus might contribute to the pathogenesis of diabetic neuropathy (Kappelle et al., 1993, 1994a). On the one hand direct damage to the autonomic innervation of the vascular supply to neurons may add to the blood flow disturbances in experimental diabetes. On the other, there is evidence that direct vascular disturbances (microangiopathy: Zatz and Brenner, 1986; King et al., 1993) resulting in reduced nerve blood flow have an important role in the development of diabetic neuropathy.

The neurotrophic effect of adrenocorticotropic hormone (ACTH)-related peptides, and the synthetic ACTH-(4–9) analogue Org 2766 has been shown to be

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SSDI 0014-2999(95)00718-0

effective in peripheral nerve disorders in both rats and humans (Gerritsen van der Hoop et al., 1988, 1990; Gispen, 1990). Van der Zee et al. (1989) and Bravenboer and colleagues (Bravenboer et al., 1992, 1993) provided evidence that Org 2766 can protect against experimentally induced peripheral diabetic neuropathy. It seems that Org 2766 exerts a protective and beneficial action on (presynaptic) sympathetic nerve fibres in the streptozotocin-induced diabetic rat (Van der Zee et al., 1990; Kappelle et al., 1994b). Recently, we reported that Org 2766 does not have a direct effect on the cardiovascular system (De Wildt et al., 1993) and is capable of improving the disturbed adrenergic responsiveness of the macrocirculation of the streptozotocin-induced diabetic rat (Van Buren et al., 1995). Given these results, Org 2766 may have neurotrophic effects on the autonomic nervous system of the rat (Vandertop et al., 1995). In order to differentiate between a direct vascular or an adrenergic autonomic defect as the underlying cause of the disturbed nerve blood flow in diabetic rats, we investigated the effects of the ACTH-(4–9) analogue Org 2766 on sciatic nerve blood flow under basal and adrenergic-stimulated conditions.

2. Materials and methods

2.1. Animals and induction of experimental diabetes

Male U:WU/CPB-Wistar rats weighing approximately 320 g were housed in Macrolon cages (two rats per cage). Diabetes mellitus was induced by a single i.v. injection of streptozotocin (Serva GmbH and Co., 40 mg/kg). Rats with blood glucose levels higher than 15 mmol/l as measured by an Ames Glucose Test Pack (Kappelle et al., 1994b) were considered diabetic. They were maintained on a 12-h light/dark cycle (light on at 7:00 h a.m.). All rats received water and standard rodent chow ad libitum. The non-diabetic control rats were given a food-restricted diet (14 g rat chow/24 h) in which the caloric intake was adjusted to keep their body weights similar to those of diabetic rats.

2.2. Drugs

Org 2766, (H-Met-(O_2)-Glu-His-Phe-D-Lys-Phe-OH), was a gift from Organon Int. BV, Oss, Netherlands. The peptide was dissolved in saline and administered s.c. at a dosage of 75 μg/kg every 48 h. L-Phenylephrine hydrochloride (Sigma, St Louis, USA; 1, 2 and 3 μg/kg) and tyramine hydrochloride, 98% (Janssen chimica, Tilburg, Netherlands, 75, 150 and 300 μg/kg) were administered i.v. at a rate of 200 μl/min by means of an infusion pump. Saline served as a vehicle.

2.3. Preparation and measurements

2.3.1. General

All experimental protocols were approved by the Ethical Committee on the use of experimental animals of the Faculty of Medicine of the Utrecht University. Surgery was performed on animals anaesthetized with urethane (10% dissolved in 0.9% NaCl solution) injected i.p. in a dose of 1.2 ml/100 g body weight. Body temperature was recorded with a rectal probe and maintained at 37°C by using a homeothermic blanket system (Harvard Apparatus).

2.3.2. Laser-Doppler flowmetry measurements

The method is described in detail by Kappelle and colleagues (Kappelle et al., 1993, 1994a). In short, blood flow in the left sciatic nerve was assessed using a laser-Doppler flowmeter (Periflux PF3, Perimed, Sweden, Perimed needle probe PF302, tip diameter of 0.45 mm) and is expressed in arbitrary units (perfusion units, PU). Basal nerve blood flow was determined by taking 14 consecutive flow measurements at different locations on the nerve (Yasuda et al., 1989; Van Buren et al., 1995).

2.3.3. Flow responsiveness

The method is described in detail by Kappelle and colleagues (Kappelle et al., 1993, 1994a). After the basal sciatic nerve blood flow was quantified, a polyethylene catheter (PE-50, Intramedic), containing 50 IU/ml sodium heparin in saline, was implanted in the right common iliac artery, its tip positioned just at the bifurcation of the abdominal aorta. The right artery was closed around the catheter with ligatures, to ensure that all vasoactive agents applied entered the left common iliac artery. Arterial blood pressure was measured and recorded on a Wekagraph WK-821 AR recorder by means of a Viggo-Spectramed DTX/plus transducer connected to a preamplifier/biotachometer system (University of Utrecht), via a Y-shaped injection system. Vasoactive agents were administered locally through this system to the left hind paw of the animal, without interrupting blood pressure recording. After a 15-min stabilization period, the responses of the sciatic nerve blood flow to an i.v. bolus injection of the α-adrenoceptor agonist, phenylephrine (1, 2 and 3 μg/kg) and the presynaptic catecholamine-releasing substance, tyramine (75, 150 and 300 μg/kg) were recorded in each animal. The response to phenylephrine was used to identify possible postsynaptic defects and that to tyramine was taken as a measure of presynaptic defects. The injection volume was 100 μl. An interval of 5 min was allowed between the administration of the different dosages of phenylephrine and tyramine so that arterial blood pressure could return to baseline. There was a 15-min interval between injec-

tion of the highest dose of phenylephrine and the lowest dose of tyramine. Mean arterial blood pressure was calculated by using the formula: MAP = (2 × diastolic blood pressure + systolic blood pressure)/3. In this system, phenylephrine and tyramine had minor effects on systemic blood pressure (Kappelle et al., 1993). Therefore, the responses to phenylephrine and tyramine are expressed as % NBF change. Sciatic nerve vascular resistances were calculated by dividing the mean blood pressure by the mean Doppler shift values and were expressed as arbitrary units (AU).

2.4. Data analysis

The data are presented as means ± standard errors of the mean (S.E.M.). Experiments were carried out in a blind fashion. Differences in baseline haemodynamic variables between the groups were assessed by analysis of variance (ANOVA), followed by Student-Newman-Keuls tests to assess differences between pairs of groups. Group differences in adrenergic responsiveness were assessed by a multivariate analysis of variance with repeated measurements (MANOVA), followed by a Student-Newman-Keuls test. Statistical significance was assumed at the 0.05 level.

2.5. Outline of the study

A group of 36 rats was randomly divided into three subgroups of 12. Group 1: non-diabetic and food-restricted control rats were fed on a food-restricted diet for 12 weeks. Group 2: diabetic rats were treated with Org 2766, 75 μg/kg in 0.5 ml saline, s.c. every 48 h. Group 3: diabetic rats were treated with placebo, 0.5 ml saline, s.c. every 48 h. Treatments (groups 2 and 3) were started 6 weeks after the induction of diabetes mellitus because at this time there is a significant impairment of nerve function in streptozotocin-induced diabetic rats (Bravenboer et al., 1993). Org 2766 treatment was continued for 6 weeks (Van Buren et al., 1995). After 12 weeks, sciatic nerve blood flow was assessed in all rats by laser-Doppler flowmetry. Thereafter the adrenergic response of sciatic nerve blood flow to local application of phenylephrine and tyramine was tested.

3. Results

3.1. Plasma glucose levels and body weights

All rats that received streptozotocin became diabetic. The blood glucose levels were more than 15 mmol/l throughout the study (Table 1). The mean body weights of the non-diabetic control rats and of the diabetic rats decreased slightly during the experiment (Table 1).

Table 1
Mean blood glucose levels and body weights

Group	Gluc (mmol/l)		
	0 wk	6 wk	12 wk
Diet	6.1 (0.9)	5.5 (1.3)	6.8 (1.2)
DMOrg	27.7 (1.3) [a]	24.3 (1.2) [a]	22.3 (1.7) [a]
DMPla	30.4 (1.1) [a]	25.3 (1.7) [a]	23.6 (2.2) [a]
	Body weight (g)		
	0 wk	6 wk	12 wk
Diet	327 (9)	297 (12)	272 (12)
DMOrg	331 (8)	282 (9)	264 (12)
DMPla	316 (12)	274 (12)	264 (12)

Mean blood glucose levels (Gluc) at week 0 (0 wk, onset of diabetes mellitus), week 6 (6 wk, start treatment) and week 12 (12 wk, end of the experiment), and body weight at 0 wk, 6 wk and 12 wk ± S.E.M. of the non-diabetic controls (Diet group), the Org 2766-treated diabetic rats (DMOrg group) and the placebo-treated diabetic rats (DMPla group). [a] Statistically significant difference from non-diabetic controls, $P < 0.001$.

3.2. Basal haemodynamic variables

The data for the basal haemodynamic variables are summarized in Table 2. The mean arterial pressure of the placebo-treated and Org 2766-treated groups was not significantly different from the mean arterial pressure of the non-diabetic control group after 12 weeks of diabetes mellitus (MAP: Diet 112 ± 12; DMPla 110 ± 5; DMOrg 103 ± 3 mm Hg). Neither systolic nor diastolic blood pressure differed significantly among the three experimental groups. The sciatic nerve blood flow and vascular resistance of the diabetic rats were significantly lower (approximately 40%, $P < 0.05$) and higher (approximately 45%, $P < 0.05$), respectively, than that of the non-diabetic control rats. After 6 weeks of treatment there was no difference between the basal haemodynamic variables of the Org 2766-treated diabetic rats and the placebo-treated diabetic rats.

Table 2
Basal haemodynamic variables

Group	P_{syst} mm Hg	P_{diast} mm Hg	NBF PU	NVR AU
Diet	134 (7)	101 (8)	54 (1)	2.2 (0.1)
DMOrg	123 (3)	93 (3)	33 (2) [a]	3.1 (0.2) [a]
DMPla	130 (5)	100 (5)	31 (1) [a]	3.3 (0.2) [a]

Basal values (means ± S.E.M.) for systolic pressure (P_{syst}), diastolic pressure (P_{diast}), sciatic nerve blood flow (NBF; PU, perfusion units) and sciatic nerve vascular resistance (NVR; AU, arbitrary units) at week 12 of the non-diabetic controls (Diet group), the Org 2766-treated diabetic rats (DMOrg group) and the placebo-treated diabetic rats (DMPla group). [a] Statistically significant difference from non-diabetic controls, $P < 0.05$.

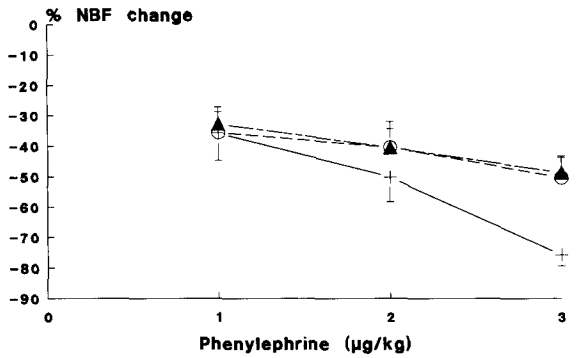

Fig. 1. Response of sciatic nerve blood flow to local phenylephrine (1, 2 and 3 μg/kg) application. The response of the sciatic nerve blood flow to local phenylephrine administration in the placebo-treated diabetic rats (▲, $n = 10$) and Org 2766-treated diabetic rats (○, $n = 9$) was significantly smaller at the dose of 3 μg/kg than in the non-diabetic control rats (+, $n = 9$), respectively, $t = 4.09$, df = 17, $P < 0.01$ and $t = 3.17$, df = 16, $P < 0.01$. The response of sciatic nerve blood flow to doses of 1 and 2 μg/kg phenylephrine was not significantly different among the three groups.

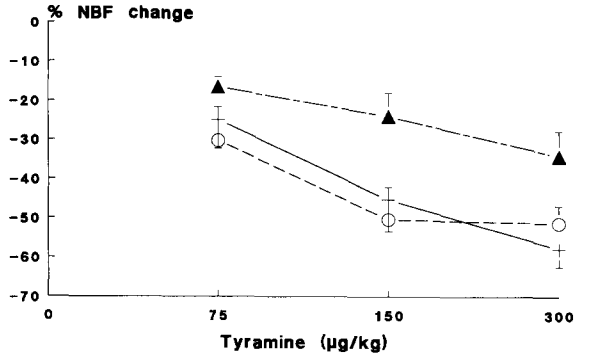

Fig. 2. Response of sciatic nerve blood flow to local tyramine (75, 150 and 300 μg/kg) application. The response of the sciatic nerve blood flow to local tyramine administration in the placebo-treated diabetic rats (▲, $n = 10$) was significantly smaller than that of the non-diabetic control rats (+, $n = 9$) ($F(1,14) = 7.13$, $P < 0.05$). The response to tyramine of the Org 2766-treated diabetic rats (○, $n = 9$) was significantly greater than that of the placebo-treated diabetic rats ($F(1,16) = 6.18$, $P < 0.05$) and not different from that of the non-diabetic controls.

3.3. Measurement of nervi vasorum sympathetic autonomic function

Sciatic nerve blood flow in diabetic rats and in non-diabetic control rats decreased dose dependently after administration of phenylephrine. The decrease was statistically significant only at the dose of 3 μg/kg (ANOVA: $F(2,27) = 8.10$, $P < 0.05$). The response of the sciatic nerve blood flow to local phenylephrine administration in the placebo-treated diabetic rats and Org 2766-treated diabetic rats was the same and significantly smaller at the dose of 3 μg/kg than in the non-diabetic control rats ($t = 4.09$, df = 17, $P < 0.01$ and $t = 3.17$, df = 16, $P < 0.01$, respectively) (Fig. 1). Sciatic nerve blood flow in diabetic rats and in non-diabetic control rats decreased dose dependently after administration of tyramine. The response of the placebo-treated diabetic rats was smaller than that of the non-diabetic control rats ($F(1,14) = 7.13$, $P < 0.05$) and that of the Org 2766-treated diabetic rats ($F(1,16) = 6.18$, $P < 0.05$). In fact, the response of the sciatic nerve blood flow to tyramine of the Org 2766-treated diabetic rats was similar to that of the non-diabetic control rats (Fig. 2).

The % change of the sciatic nerve vascular resistance to phenylephrine in the placebo-treated diabetic rats and Org 2766-treated diabetic rats was the same and significantly smaller than in the non-diabetic control rats ($F(1,17) = 6.80$, $P < 0.05$ and $F(1,16) = 6.31$, $P < 0.05$, respectively) (Table 3). The % change of the sciatic nerve vascular resistance to tyramine of the placebo-treated diabetic rats was smaller than that of the non-diabetic control rats ($F(1,14) = 9.77$, $P < 0.05$) and that of the Org 2766-treated diabetic rats ($F(1,16) = 7.18$, $P < 0.05$). In fact the % change of the sciatic nerve vascular resistance to tyramine of the Org 2766-treated diabetic rats was similar to that of the non-diabetic control rats (Table 3).

Table 3
Initial and % change of sciatic nerve blood flow and vascular resistance

Dose	DMPla			DMOrg			Diet		
	Initial		% change	Initial		% change	Initial		% change
	NBF [a]	NVR [a]	NVR [a,b]	NBF [a]	NVR [a]	NVR [c]	NBF	NVR	NVR
PHE 1	31 (1)	3.3 (0.2)	70	33 (2)	3.1 (0.2)	82	54 (1)	2.2 (0.1)	101
PHE 2	31 (1)	3.3 (0.2)	103	34 (2)	3.1 (0.2)	136	51 (1)	2.2 (0.1)	235
PHE 3	33 (1)	3.1 (0.2)	132	36 (1)	3.0 (0.2)	173	52 (2)	2.1 (0.2)	446
TYR 75	32 (1)	3.2 (0.1)	30	34 (2)	2.8 (0.3)	53	47 (3)	2.3 (0.3)	48
TYR 150	33 (1)	3.1 (0.1)	59	34 (2)	2.8 (0.2)	139	49 (2)	2.0 (0.2)	146
TYR 300	33 (1)	3.1 (0.2)	64	35 (2)	2.7 (0.2)	148	47 (3)	2.3 (0.2)	183

Sciatic nerve blood flow (NBF; PU, perfusion units) and vascular resistance (NVR; AU, arbitrary units) of the non-diabetic controls (Diet group), the Org 2766-treated diabetic rats (DMOrg group) and the placebo-treated diabetic rats (DMPla group), before (initial) and after (% change) administration of phenylephrine (PHE 1, 2 and 3 μg/kg) and tyramine (TYR 75, 150 and 300 μg/kg). Data are given as means ± S.E.M. [a] $P < 0.05$ vs. non-diabetic controls for both phenylephrine and tyramine. [b] $P < 0.05$ vs. Org 2766-treated diabetic rats for tyramine. [c] $P < 0.05$ vs. non-diabetic controls for phenylephrine.

4. Discussion

The present study using laser-Doppler blood flowmetry shows a reduction in sciatic nerve blood flow of about 40% of control values in diabetic rats, which is in accordance with earlier studies (Cameron et al., 1991; Kappelle et al., 1993, 1994a; Stevens et al., 1994; Van Buren et al., 1995). In all these investigations, including the present study, systemic arterial pressure was not different between the experimental groups, suggesting that the changes in sciatic nerve blood flow are due to local vasomotor abnormalities in diabetes. This is supported by the data of the sciatic nerve vascular resistance (Table 2).

These local disturbances could include impairment of the microvasculature affected either by microangiopathy (Zatz and Brenner, 1986; King et al., 1993) or by an impairment of blood flow control mechanisms in the vasa nervorum (Kappelle et al., 1993, 1994a). These flow control mechanisms are not yet fully understood. It seems that autoregulation is negligible (Sundqvist et al., 1985; Sugimoto and Monafo, 1987). Little information is available about the neurovascular reactivity of normal and diabetic nerves. Histochemical studies have demonstrated that noradrenergic, serotonergic and peptidergic nerve fibres terminate on the vasa nervorum, providing a mechanism of neurogenic control (Appenzeller et al., 1984; Rechthand et al., 1986). Recent reports suggest that variations in the tone of adrenergic nerves of the vasa nervorum have an important role in the regulation of nerve blood flow (Kihara and Low, 1990; Zochodne and Low, 1990; Hotta et al., 1991). An increase in perivascular adrenergic fibres in the tibial and sciatic nerves and higher levels of noradrenaline in the vagus of diabetic animals have been reported (Dhital et al., 1986; Koistinaho et al., 1990). However, the density of adrenergic innervation is the same as or below the non-diabetic level in the chronic diabetic state (Koistinaho et al., 1990) and the noradrenaline content of the sciatic nerve is reduced in diabetic rats (Ward et al., 1989). These changes may contribute to the complex microvascular abnormalities in the diabetic peripheral nerve and impair the regulation of nerve blood flow.

We studied the adrenergic responsiveness of the vasa nervorum in the sciatic nerve of diabetic rats. The vasa nervorum were hyporesponsive, with respect to sciatic nerve blood flow and vascular resistance, to both phenylephrine and tyramine in placebo-treated diabetic rats. These observations are in accordance with earlier results when we investigated the responsiveness of the vasa nervorum to sympatho-adrenergic stimuli in diabetes mellitus (Kappelle et al., 1993, 1994a). In these studies it was hardly possible to ascribe the reduced adrenergic responsiveness to phenylephrine and tyramine in diabetic rats by either a presynaptic or a postsynaptic sympathetic neuronal deficit. Indeed, since the impaired response to tyramine is dependent on both pre- and postsynaptic function and postsynaptic function is disturbed (reduced phenylephrine response), it is not possible to make a statement about a possible impairment of presynaptic function as a result of diabetes mellitus based on the tyramine response alone. Moreover, since the basal nerve blood flow in diabetic rats is lower than in non-diabetic rats, the reduced adrenergic responsiveness could also be interpreted as a functional antagonism. However, in the present study Org 2766 (vide infra) was able to restore selectively the tyramine response, with respect to sciatic nerve blood flow and vascular resistance (Fig. 2 and Table 3) without affecting the phenylephrine response (Fig. 1 and Table 3). This observation rejects the possibility of functional antagonism since basal blood flow was comparable in both the Org 2766-treated and placebo-treated diabetic animals. It can be concluded that, in diabetic rats, there is a presynaptic adrenergic deficit in nerve functioning which can be reversed by the neuroregenerative properties of Org 2766. In addition, the autonomic control of the vasa nervorum is seriously affected in experimental diabetic neuropathy.

In order to differentiate between a direct vascular or an adrenergic autonomic defect as the underlying cause of the disturbed nerve blood flow in diabetic rats, we investigated the effects of the ACTH-(4–9) analogue Org 2766 on sciatic nerve blood flow under basal and adrenergic-stimulated conditions. Org 2766 did not influence systemic blood pressure in diabetic rats, in accordance with the results of previous studies from our laboratory with diabetic (Kappelle et al., 1994b; Van Buren et al., 1995) or non-diabetic rats (De Wildt et al., 1993). After 6 weeks of treatment there was no difference between the basal haemodynamic variables, e.g. blood pressure, sciatic nerve blood flow and vascular resistance, of the Org 2766-treated diabetic rats and the placebo-treated diabetic rats (Table 2). The adrenergic flow and vascular resistance response of the vasa nervorum to phenylephrine and tyramine was reduced in the placebo-treated diabetic rats as compared to the non-diabetic controls, confirming previous results of a decreased responsiveness to noradrenaline in diabetes (Jackson and Carrier, 1983; Van der Zee et al., 1990; Kappelle et al., 1993, 1994a, b; Van Buren et al., 1995). Org 2766 treatment did not affect the response to phenylephrine, which implies that Org 2766 treatment has little, if any, affect on postsynaptic adrenergic responsiveness. However, the response to tyramine was significantly improved by Org 2766. We hypothesize that the amelioration of the tyramine flow and vascular resistance response by the neurotrophic Org 2766, which is independent of postsynaptic α-adrenergic effects, is due to a beneficial

effect of Org 2766 on presynaptic autonomic nerve fibres. That Org 2766 did not improve basal sciatic nerve blood flow and vascular resistance, but had a beneficial effect on the presynaptic function of the nervi vasorum of the sciatic nerve of diabetic rats can only be ascribed to neuroprotective effects (Gispen, 1990) and not to haemodynamic actions of Org 2766 because this ACTH-(4–9) analogue does not have a direct effect on the cardiovascular system in rats (De Wildt et al., 1993).

From our results we conclude that a presynaptic-sympathetic deficit of nervi vasorum causes a disturbed flow responsiveness in the diabetic rat sciatic nerve, which is supported by the fact that Org 2766 exerts its neurotrophic effects on the reduced adrenergic responsiveness mainly at the presynaptic level. And that adrenergic autonomic disturbances in the vasa nervorum are of little importance to the reduced sciatic nerve blood flow observed in streptozotocin-induced diabetic rats.

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