Peripheral nerve development and regeneration: recent advances and clinical applications
E. Scarpini, M.G. Fiori, D. Pleasure, G. Scarlato (eds)
Fidia Research Series, vol. 19
Liviana Press, Padova © 1989

BENEFICIAL EFFECTS OF MELANOCORTINS ON AXONAL REGENERATION AND DIABETIC-INDUCED PERIPHERAL NEUROPATHY

Catharina E.E.M. Van der Zee, Roland Gerritsen van der Hoop, Marjolein Van der Velde, Willem H. Gispen

Division of Molecular Neurobiology, Rudolf Magnus Institute
and Institute of Molecular Biology and Medical Biotechnology,
University of Utrecht, Vondellaan 6,
3521 GD Utrecht, The Netherlands

INTRODUCTION

Several groups reported the effectiveness of ACTH- and MSH-peptides in peripheral nerve regeneration. The beneficial effect of the melanocortins has been demonstrated at the functional, electrophysiological and histological level (see for reviews Strand and Smith, 1986; Gispen et al., 1987; De Koning and Gispen, 1988).

In the recovery of function, subcutaneous constant release of the peptide from an osmotic mini-pump or from biodegradable polymer microcapsules was as effective as repeated subcutaneous injections. Oral administration proved to be ineffective. Local application to the damaged nerve via microporous Accurel^{R} polypropylene tubes, or via a biodegradable matrix also resulted in an enhanced recovery following nerve damage (Dekker et al., 1987; Van der Zee et al., 1988).

The mechanism by which the peptides exert their neurotrophic influence is still largely unknown. It has been suggested that the exogenous administered peptides possibly mimick or amplify endogenous signals that trigger the neuronal response to injury (Edwards et al., 1984). Should the regenerative response be independent of the cause of damage, then not only mechanical damage, like the crush lesion or transection, but also peripheral neuropathies caused by neurotoxic agents or diabetes mellitus, might benefit from peptide treatment.

Abbreviations: NCV: Nerve conduction velocity; Org. 2766: ACTH(4-9 analogue), H-Met(O_2)-Glu-His-Phe-D-Lys-Phe-OH; ACTH: Adreno corticotrophic hormone; MSH: Melanophore stimulating hormone.

DIABETIC NEUROPATHY

A major complication in diabetes mellitus pathology is the distal symmetric polyneuropathy (Greene, 1987). Commonly peripheral motor and sensory nerve conduction velocities (NCV) are greatly decreased in patients with clinical polyneuropathies (Thomas and Eliasson, 1975). In experimental models of acute diabetes mellitus in rats, there is a well documented slowing of NCVs in peripheral nerves, albeit that the underlying metabolic mechanism is still not fully understood (Greene, 1987).

A disturbance in the glucose metabolism, nerve sorbitol accumulation, increase in fructose and decrease in myoinositol level have been considered to induce diabetic peripheral neuropathy.

Over the years, numerous studies both in experimental models of the disease and in patients have been carried out to assess the efficacy of putative pharmacotherapy in the treatment of diabetic polyneuropathies (Harati, 1987). The rationale of such therapy was either based on the presumed mechanism underlying the diabetic neuropathy (a role for aldose reductase inhibitors has been suggested) or on presumed efficacy of a compound to enhance peripheral nerve function (like gangliosides).

ORG. 2766 PEPTIDE TREATMENT

Recently our group reported that Org. 2766 (ACTH4-9 analogue) is effective in protecting from cisplatin induced sensory neuropathy in the rat and that the peptide even improves nerve function when a neuropathy already exists (De Koning et al., 1987; Gerritsen van der Hoop et al., 1988).

In this report an animal model for the streptozocin-induced diabetic neuropathy was used. Streptozocin diabetic rats developed high blood glucose levels within one week and subsequently lost weight during the experiment. The method used for determination of nerve conduction velocities were described by De Koning and Gispen (1987). Whereas non-diabetic control rats showed an age-related increase in nerve conduction velocities, in diabetic rats a delayed motor and, even more severe, a delayed sensory nerve conduction velocity was seen. At seven weeks, the non-diabetic control rats showed an age-related increase in H-reflex related sensory nerve conduction velocity (from 55 ± 1 to 69 ± 5 m/s); the saline treated diabetic rats demonstrated a decrease (from 55 ± 1 to 41 ± 3 m/s) and the Org. 2766 treated diabetic rats showed a slight increase (from 55 ± 1 to 59 ± 2 m/s) in sensory conduction velocity (Fig. 1). Eventually the treatment with Org. 2766 restored the impaired motor and sensory nerve conduction velocity to normal values (Van der Zee et al., 1989).

Histological analysis of the sural nerve of control and diabetic rats revealed that the total number of nerve fibers was not affected in diabetic rats. In teased fiber preparation no demyelination or axonal degeneration was registrated. However, a shift in the distribution of the different classes of myelinated nerve fibers towards fewer thick myelinated fibers was observed in diabetic rats, which was also reported, earlier, by Jakobsen (1978). Peptide treatment with Org. 2766 resulted in a normal distribution of

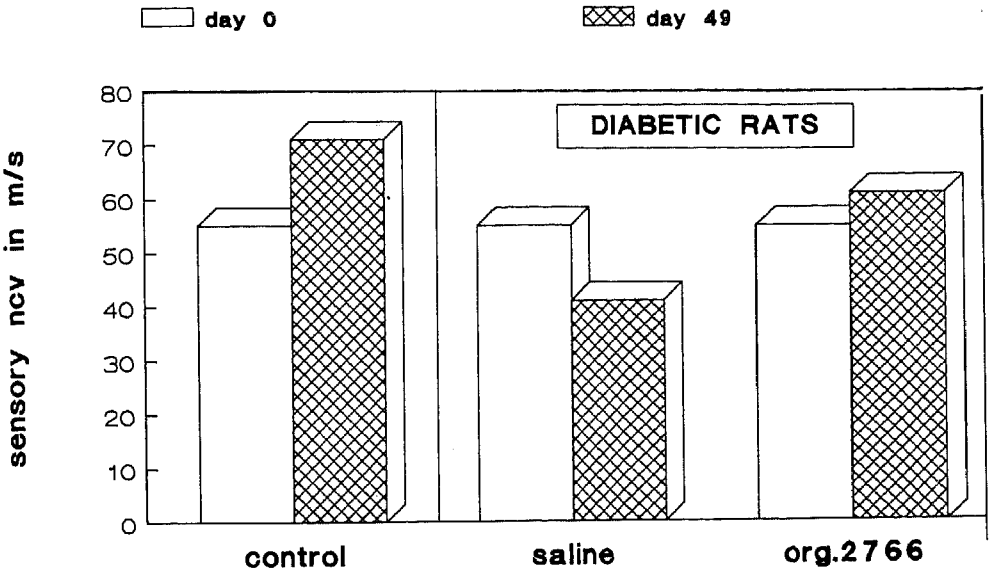

Figure 1. Sensory nerve conduction velocity in female non-diabetic control rats (200-220 g, n = 10), showing an age-related increase at day 49 compared to day 0. The difference between Org. 2766 treatment (10 μg/3x p.w., n = 12) and saline treatment (n = 9) on the sensory nerve conduction velocity at day 49 in streptozocin-induced diabetic rats was significant ($p < 0.05$, Student's *t*-test). Values are expressed as means ± S.E.M.

myelinated nerve fibers. The decrease in nerve conduction velocities in diabetic rats might be related to the reduction of thick myelinated nerve fibers in the peripheral nerve, while the nerve conduction velocity is determined predominantly by these nerve fibers. The peptide Org. 2766 apparently exerted a protective action on the nerve fibers, without affecting the increase in blood glucose level.

CONCLUSIONS

In streptozocin-induced diabetes neuropathy both the motor and sensory nerve conduction velocities are impaired. The peptide Org. 2766, an ACTH4-9 analogue, protects from streptozocin induced diabetic peripheral neuropathy, as has been demonstrated electrophysiologically and histologically.

Possible application for clinical use is under further investigation.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Prinses Beatrix Fonds.

REFERENCES

Dekker A, Princen MM, de Nijs H, de Leede LGJ, Broekkamp CLE (1987) Acceleration of recovery from sciatic nerve damage by the ACTH(4-9) analog Org. 2766: Different routes of administration. Peptides 8: 1057-1059.

De Koning P, Gispen WH (1987) Org. 2766 improves functional and electrophysiological aspects of regenerating sciatic nerve in the rat. Peptides 8: 415-422.

De Koning P, Gispen WH (1988) A rationale for the use of melanocortins in neural damage. In: Stein DG, Sabel B (eds): Pharmacological Approaches to the treatment of Brain and Spinal cord Injuries, Plenum Press, New York, pp. 233-258.

Edwards PM, Van der Zee CEEM, Verhaagen J, Schotman P, Jennekens FGI, Gispen WH (1984) Evidence that the neurotrophic actions of α-MSH may derive from its ability to mimic the actions of a peptide formed in degenerating nerve stumps. J Neurol Sci 64: 333-341.

Gerritsen van der Hoop R, De Koning P, Boven E, Neijt JP, Jennekens FGI, Gispen WH (1988) Efficacy of the neuropeptide Org. 2766 in the prevention and treatment of cisplatin-induced neurotoxicity in rats. Eur J Cancer Clin Oncol 24: 637-642.

Gispen WH, De Koning P, Kuiters RRF, Van der Zee CEEM, Verhaagen J (1987) On the neurotrophic properties of melanocortins. In: De Kloet ER, Wiegant V, de Wied D (eds): Neuropeptides and brain function. Progr Brain Res 72: 319-331.

Greene DA, Lattimer SA, Sima AAF (1987) Sorbitol, phosphoinositides, and sodium-potassium-ATPase in the pathogenesis of diabetic complications. N Engl J Med 316: 599-606.

Harati Y (1987) Diabetic peripheral neuropathies. Annals of Internal Medicine 107: 546-559.

Jakobsen J (1978) Morphometry of peripheral nerves in streptozotocin diabetic rats. In: Canal N, Pozza G (eds): Peripheral Neuropathies. North-Holland, Elsevier, pp. 269-274.

Strand FL, Smith CM (1986) LPH, ACTH, MSH and motor systems. In: De Wied D, Gispen WH, Greidanus TjB (eds): Neuropeptides and Behavior (1). Oxford, Pergamon Press, 1986, pp. 245-272.

Thomas PK, Eliasson SG (1975) Diabetic neuropathy. In: Dyck PJ, Thomas PK, Lambert EM (eds): Peripheral Neuropathy. PA Saunders, Philadelphia, pp. 956-981.

Van der Zee CEEM, Brakkee JH, Gispen WH (1988) α-MSH and Org. 2766 in peripheral nerve regeneration: different routes of delivery. Eur J Pharmacol 147: 351-357.

Van der Zee CEEM, Gerritsen van der Hoop R, Gispen WH (1989) Beneficial effect of the peptide Org. 2766 (ACTH-(4-9)-analog) in the treatment of peripheral neuropathy in streptozocin-diabetic rats. Diabetes 38: 225-230.