Therapeutic potential for melanocortins in peripheral nerve disease

Melanocortins are peptides related to the pituitary hormones ACTH and MSH and as hormones they mediate a variety of adaptive responses. The pioneering studies of De Wied[1] suggested that pituitary peptides may directly modulate nervous system function and behavior. In considering whether neural tissue is a target for circulating peptides, various investigators have studied the possibility that melanocortins may exert effects on the nervous system analogous to their known trophic effects on their target organs[2]. Early studies on the effect of melanocortins on recovery from brain lesions gave conflicting results. Peptides with full endocrine activity were used, since the rationale behind the treatment was that the corticosteroids released by ACTH would reduce the formation of reactive scar tissue, which was believed to limit proper neural tissue regeneration. However, it is now known that corticosteroids often exert catabolic rather than anabolic effects in neural tissue; indeed studies on the peripheral nervous system have shown that the corticotrophic activities of melanocortins are not involved in the trophic response and these features may have disturbed the final outcome in previous studies[3].

Postlesion repair

The regenerative capacity of the peripheral nervous system is limited, but regeneration and reinnervation are possible if the damage is restricted to the neuronal processes (dendrites and axons). Numerous humoral and structural factors of neuronal, glial or target origin appear to facilitate nerve repair[4]. The first study on the neurotrophic effect of peptides on postlesion repair in the peripheral nervous system was that by Strand and Kung[5] who reported that adrenalectomized rats subjected to sciatic nerve denervation recovered sooner when treated with $ACTH_{1-39}$ than when given saline solution.

Using a foot reflex withdrawal test and a free-walking pattern analysis test to monitor return of sensorimotor function following crush lesion of the sciatic nerve in rats, we have found that neurotropic fragments and analogues of melanocortins, including the $ACTH_{4-9}$ analogue ORG2766 (Fig. 1), exhibit a U-shaped dose–response relationship and are maximally active in a dose range of 7.0–75 μg kg^{-1} when given daily or every other day s.c.[6,7]. Oral doses of 125 mg kg^{-1} are ineffective[7,8], but it is possible to facilitate recovery of function by delivery of the peptide by slow release from osmotic minipumps implanted s.c., or from biodegradable microspheres[9].

Peptide treatment must begin within a short period of induction of the lesion – there is a 'critical period' of one week[10] – but its beneficial effects on histological and neurophysiological parameters are still apparent after several months[11,12]. The precise location of the amino acid sequence that confers neurotropic activity on the peptides is uncertain. It is clear however that, as for many of the other effects of melanocortins on the nervous system, the critical information for stimulating neurite outgrowth is contained in the amino acid sequence between positions 4 and 10; the peptide ORG2766 is frequently used in studies of these effects[13].

Histological and functional studies strongly support the notion that the melanocortins do not enhance the rate of outgrowth but rather increase the number of newly formed sprouts at the site of lesion[3]. It has been suggested that the peptides mimic or amplify an endogenous signal that operates early in the regenerative response of the damaged neuron (reactivation of expression of proopiomelanocortin or neurofilament breakdown)[3]. If this is indeed so, it may be speculated that the melanocortins will have a broader therapeutic role than enhancing postlesion repair alone: it may be possible to exploit the regenerative repertoire of neurons compromised by toxicants or metabolic disturbances to counteract the harmful effects of these conditions.

Treatment of peripheral neuropathies

Symmetric polyneuropathy is a major complication of diabetes mellitus, resulting in reduced peripheral motor and sensory nerve conduction velocities[14]. In experimental models of acute diabetes mellitus in rats (e.g. streptozocin-induced diabetes), nerve conduction velocities are reduced and fiber-size distribution in peripheral nerves is

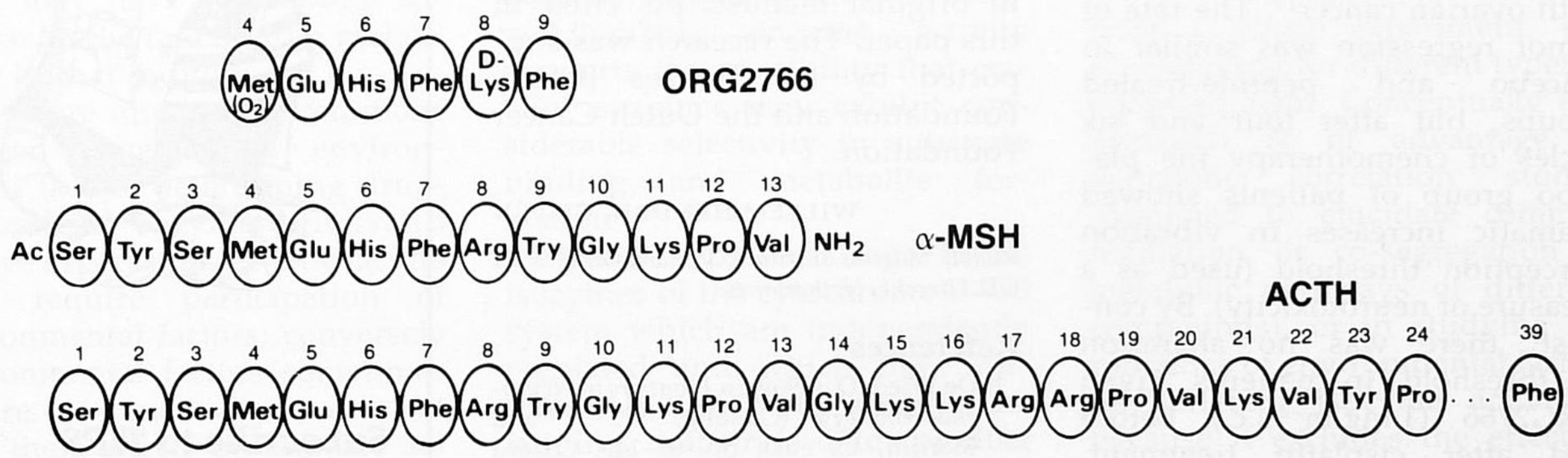

Fig. 1. Structures of some peptides of the melanocortin family.

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TABLE I. Effects of melanocortins on recovery from nerve damage

Parameter	Trauma		Diabetes		Cisplatin	
	no treatment	peptide	no treatment	peptide	no treatment	peptide
Outgrowth	+	++	–	–	–	–
Sensory nerve conduction velocity	↓	↑	↓	↑	↓	↑
Motor nerve conduction velocity	↓	↑	↓	↑	–	–
Nerve fiber diameter	–	–	↓	↑	↓	↓
Sensorimotor function	↓	↑	↓	↑	↓	↑

+, stimulation; –, no effect; ↓, reduction; ↑, restoration towards basal level.

altered; the underlying mechanism is, however, still not fully understood[14,15]. Rats treated chronically with ORG2766 (75 μg kg^{-1} s.c. three times per week) showed nearly normal nerve conduction velocities and fiber-size distribution five to seven weeks after the initial streptozocin injection. ORG2766 has no known toxic effects in humans, and a clinical study on its efficacy in insulin-dependent patients with clinical neuropathy is now being carried out.

Neuropathy is one of the major side-effects of treatment with the anticancer drug cisplatin, which is widely used, particularly for the treatment of testicular and ovarian cancers. 40–100% of ovarian cancer patients suffer from a sensory peripheral neuropathy[16]. In rats, cisplatin intoxication leads to a marked slowing of the H-reflex-related sensory, but not motor, conduction velocity[17,18]. Concurrent treatment with ORG2766 prevents this sensory nerve defect (and even cures existing signs of cisplatin-induced peripheral neuropathy), without affecting the antitumor efficacy of cisplatin[18].

The ability of ORG2766 to prevent cisplatin-induced neuropathy was subsequently tested in a multicenter, randomized, double-blind trial involving 55 women with ovarian cancer[19]. The rate of tumor regression was similar in placebo and peptide-treated groups, but after four and six cycles of chemotherapy the placebo group of patients showed dramatic increases in vibration perception threshold (used as a measure of neurotoxicity). By contrast, there was no alteration in threshold in patients given ORG2766 (1 mg m^{-2} s.c.) before and after cisplatin treatment. These patients showed significantly fewer neurological signs and symptoms than the placebo group. Thus, ORG2766 can prevent or attenuate cisplatin-induced neuropathy without adversely affecting the cytotoxic effect of the drug in humans.

□ □ □

The initial damage and the profile of abnormalities seen in cisplatin intoxication, diabetic neuropathy and following mechanical trauma are quite different, but in all cases melanocortins have a beneficial effect (Table I). This suggests that these peptides enhance the repair capacity of peripheral nerves in general. Indeed, preliminary evidence suggests that melanocortins also improve repair resulting from intoxication with acrylamide[20] or pyridoxine (R. Gerritsen van der Hoop, unpublished). The clinical usefulness of ORG2766 has already been demonstrated for cisplatin neuropathy and we are optimistic that such peptides may be useful in a variety of peripheral nerve diseases by tipping the damage–repair balance in favor of repair.

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WILLEM HENDRIK GISPEN

Rudolf Magnus Institute, Vondellaan 6, 3521 GD Utrecht, Netherlands.

References

1 De Wied, D. (1969) in *Frontiers in Neuroendocrinology* (Ganong, W. F. and Martini, L., eds), pp. 97–140, Oxford University Press
2 Strand, F. L., Rose, K. J., King, J. A., Segarra, A. C. and Zucarelli, L. A. (1989) *Prog. Neurobiol.* 33, 45–85
3 Bär, P. R., Schrama, L. H. and Gispen, W. H. (1990) in *Neuropeptides: Basics and Perspectives*, pp. 175–211, Elsevier Science Publishers
4 Varon, S. (1985) *Discussions in Neurosciences*, Fondation pour l'Etude du Système Nerveux II (3)
5 Strand, F. L. and Kung, T. T. (1980) *Peptides* 1, 135–138
6 De Koning, P., Brakkee, J. H. and Gispen, W. H. (1986) *J. Neurol. Sci.* 74, 237–246
7 Van der Zee, C. E. E. M., Brakkee, J. H. and Gispen, W. H. (1988) *Eur. J. Pharmacol.* 147, 351–357
8 Dekker, A. J. A. M., Princen, M. M., De Nijs, H., De Leede, L. G. J. and Broekkamp, C. L. E. (1987) *Peptides* 8, 1057–1059
9 Gispen, W. H. and Wiegant, V. M. *J. Control. Release* (in press)
10 Edwards, P. M. *et al.* (1984) *J. Neurol. Sci.* 64, 333–341
11 De Koning, P. and Gispen, W. H. (1987) *Peptides* 8, 415–422
12 Bijlsma, W. A., Jennekens, F. G. I., Schotman, P. and Gispen, W. H. (1983) *Muscle Nerve* 6, 104–112
13 De Wied, D. and Jolles, J. (1982) *Physiol. Rev.* 62, 976–1059
14 Greene, D. A., Lattimer, S. A. and Sima, A. A. F. (1987) *N. Engl. J. Med.* 316, 599–606
15 Van der Zee, C. E. E. M., Gerritsen van der Hoop, R. and Gispen, W. H. (1989) *Diabetes* 38, 225–230
16 Thompson, S. W., Davis, L. E., Kornfeld, M., Hilgers, R. D. and Standeter, J. C. (1984) *Cancer* 54, 1269–1275
17 De Koning, P., Neijt, J. P., Jennekens, F. G. I. and Gispen, W. H. (1987) *Toxicol. Appl. Pharmacol.* 89, 81–87
18 Gerritsen van der Hoop, R. *et al.* (1988) *Eur. J. Cancer Clin. Oncol.* 24, 637–642
19 Gerritsen van der Hoop, R. *et al.* (1990) *New Engl. J. Med.* 322, 89–94
20 Edwards, P. M., Sporel, E., Gerritsen van der Hoop, R. and Gispen, W. H. (1989) *Human Toxciol.* 8, 159 (Abstr.)