Netherlands Journal of Medicine, 41 (1992) 255–258

NJM 00642

Editorial

Rationale for the use of the $ACTH_{4-9}$ analogue ORG 2766 in the treatment of diabetic neuropathy

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Key words: Diabetic neuropathy; $ACTH_{4-9}$; Neuropeptide

Introduction

Neuropeptides were originally defined by de Wied [1] as pituitary peptides that exert their effects on either central or peripheral neural tissues. They can directly modulate nervous system function and behaviour. The pituitary hormones ACTH and α-MSH belong to this group and have been extensively studied for their effects on neurones. Neuropeptides belong to a large group of neurotrophic factors, such as nerve growth factor (NGF), laminin, neural cell adhesion molecule (N-CAM) etc. [2].

ACTH stimulates the production of steroid hormones in the adrenal glands, hormones which are involved in a number of metabolic processes associated with stress and coping. ACTH was later discovered to have neurotrophic potential. Fragments of ACTH and α-MSH have different, and sometimes stronger, effects on nervous tissue than ACTH itself. The relationship between $ACTH_{1-39}$, α-MSH and the $ACTH_{4-9}$ analogue ORG 2766 is shown in Fig. 1.

The neurotrophic effects of ACTH and MSH-like peptides were first studied in detail in the peripheral nervous system. The regenerative capacity of the peripheral nervous system is limited, but regeneration and reinnervation are possible if damage is restricted to the neuronal processes (dendrites and axons). Numerous humoral and structural factors from neuronal, glial or target cell origin appear to facilitate nerve repair. The first study on the neurotrophic effect of peptides on post-lesion repair was performed by Strand and Kung, who reported that adrenalectomized rats subjected to a sciatic nerve crush recovered faster when treated with $ACTH_{1-39}$ than when given saline solution [3]. They attributed this to a faster outgrowth of regenerating axons, although

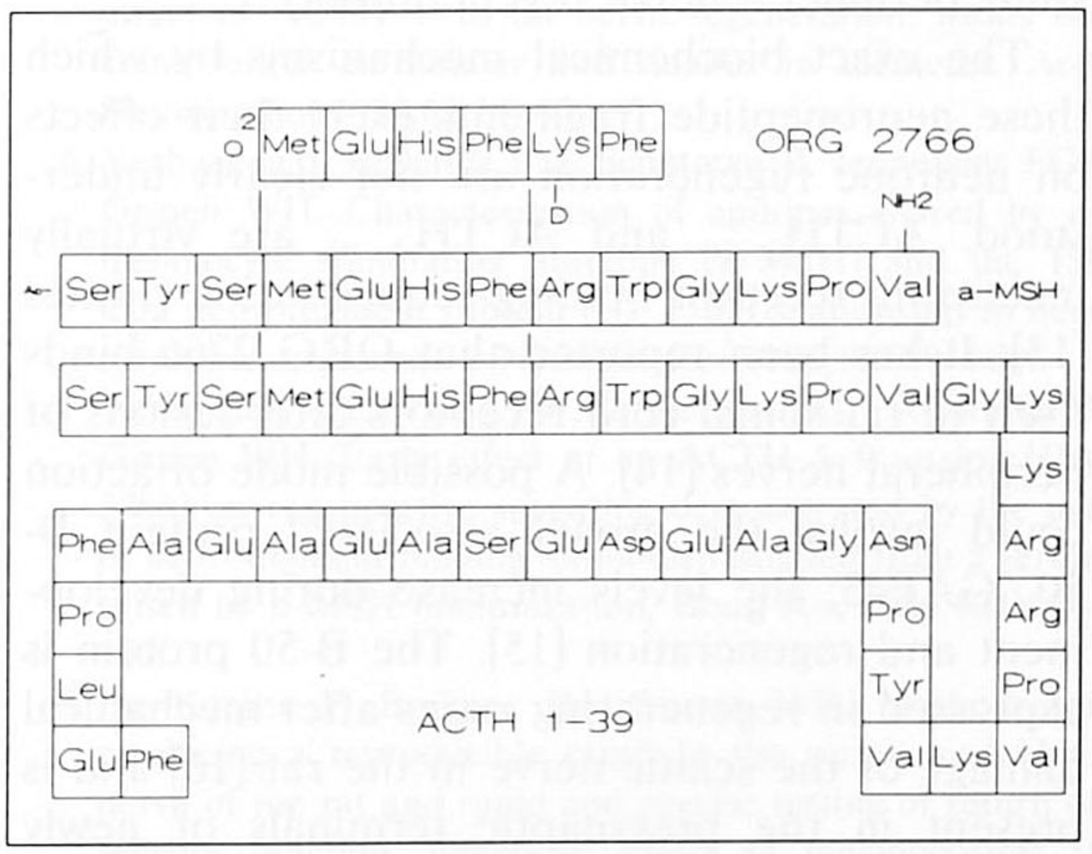

Fig. 1. Relationship between the $ACTH_{4-9}$ analogue ORG 2766, α-MSH and $ACTH_{1-39}$.

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other investigators, using various ACTH/MSH fragments, have demonstrated that the number of sprouts is increased [4–6]. A neurofilament-binding antibody technique has been used to show that ORG 2766 evokes neurite outgrowth as early as 72 h after sciatic crush [7]. However, most of the newly formed axons are of a smaller diameter than those axons from nerves of untreated animals.

Analogues of melanocortins, including ORG 2766, exhibit a U-shaped dose-response relationship and are maximally active in the dose range of 7–75 μg/kg when given daily or every 48 h s.c. [8,9]. Recovery of sensorimotor function following crush lesion of the sciatic nerve in rats was monitored in these studies with the foot reflex withdrawal test and a free-walking pattern analysis test. It was found that peptide treatment must begin within a short period after induction of the lesion as there is a "critical period" of 1 wk [10]. The beneficial effects of ORG 2766 on histological and neurophysiological parameters are still apparent after several months [4,11]. The precise amino acid sequence that confers the neurotrophic activity of neuropeptides is uncertain. It is clear, however, that as for many other effects of melanocortins on the nervous system, the critical information for stimulation of neurite outgrowth is contained in the amino acid sequence between position 4 and 10 [12]. The $ACTH_{4-9}$ analogue ORG 2766 is thus frequently used to study peripheral nerve regeneration.

The exact biochemical mechanisms by which these neuropeptide fragments exert their effects on neurone regeneration are not clearly understood. $ACTH_{1-10}$ and $ACTH_{4-10}$ are virtually inactive in receptor binding-sequestration studies [13]. It has been reported that ORG 2766 binds itself to rat spinal cord receptors after lesions of peripheral nerves [14]. A possible mode of action could involve the growth-associated protein B-50/GAP43; the levels increase during development and regeneration [15]. The B-50 protein is expressed in regenerating axons after mechanical damage of the sciatic nerve in the rat [16] and is present in the presynaptic terminals of newly formed neuromuscular junctions [17]. Furthermore, evidence is accumulating to suggest that this protein is also formed in activated Schwann cells after peripheral nerve damage [18]. However, little is known about the fate of this growth-associated protein during nerve damage other than mechanical trauma [19]. It has been suggested that the B-50 protein plays a role in calmodulin buffering and as such is involved in transmembrane signal transduction [20–22].

Treatment of peripheral neuropathies

Cisplatin-induced neuropathy

Cisplatin, an anti-tumour drug used in chemotherapy for ovarian and testicular cancer, causes a purely sensory neuropathy. It has been estimated that 40–100% of patients with ovarian cancer suffer from a sensory peripheral neuropathy [22]. Cisplatin administration causes a marked slowing of the H-reflex-related sensory nerve conduction velocity, but not of motor nerve conduction velocity [23]. Cotreatment with ORG 2766 protects against cisplatin-induced sensory neuropathy and also improves sensory nerve conduction velocity in an existing neuropathy. This was observed even during continuous cisplatin administration [23,24]. Gerritsen van der Hoop et al. [24,25] showed that there was no change in the total number of fibres, but a decrease in the number of thick myelinated fibres and a reduced degree of myelination in the sural nerves of rats given cisplatin for 12 weeks. A multi-centre, placebo-controlled trial has been carried out with 55 patients with ovarian cancer treated with cisplatin to study the possible preventive action of ORG 2766 on the development of neuropathy. Measurement of vibration perception threshold was used to monitor the development of neuropathy. The rate of tumour regression was similar in the placebo and peptide-treated groups, but after 4 and 6 cycles of chemotherapy the placebo-treated group of patients showed a dramatic increase in vibration perception threshold. In contrast, there was no alteration in vibration perception threshold of patients treated with ORG 2766 (1 mg/m^2 s.c.) before and after cisplatin treatment. These patients showed significantly fewer neurological signs and symptoms than the

TABLE 1

Effects of melanocortins on recovery from nerve damage.

Parameter	Trauma		Diabetes		Cisplatin	
	No treatment	Peptide	No treatment	Peptide	No treatment	Peptide
outgrowth	+	+ +	–	–	–	–
SNCV	↓	↑	↓	↑	↓	↑
MNCV	↓	↑	↓	↑	–	–
nerve fibre diameter	–	–	↓	↑	↓	↓
Sensorimotor function	↓	↑	↓	↑	↓	↑

+ = stimulation; – = no effect; ↓ = reduction; ↑ = restoration towards basal level. From: Gispen WH; TIPS 1990;11:221–222.

placebo-treated patients. Thus, ORG 2766 can prevent or attenuate cisplatin-induced neuropathy without adversely affecting the cytotoxic effect of the drug in humans [25].

Diabetic neuropathy

In streptozocin-induced diabetic rats with uncontrolled hyperglycaemia, sensory and motor nerve conduction velocity decline rapidly when compared to age-matched control animals [26]. Van der Zee et al. demonstrated that ORG 2766 completely prevented this worsening of nerve conduction velocity, if the ORG 2766 therapy was started at the same time as the STZ administration [26]. They showed that preventive treatment with this $ACTH_{4-9}$ analogue restored the tyramine responsiveness, causing a change in systolic and diastolic blood pressure back to normal values, whereas the phenylephrine response was not affected [9]. These data were taken to suggest that the peptide also counteracts autonomic diabetic neuropathy. The effects of ORG 2766 on different models are summarized in Table 1.

It can be concluded that the $ACTH_{4-9}$ analogue ORG 2766 has a beneficial effect on nerve recovery from mechanical lesions, cisplatin-induced neuropathy or diabetic neuropathy, although the pathogenetic mechanisms underlying these three conditions are quite different. It is possible that ORG 2766 generally enhances the endogenous repair capacity of peripheral nerves.

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