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PROTECTION FROM CISPLATIN INDUCED NEUROPATHY IN RATS BY THE ACTH(4-9) ANALOGUE ORG. 2766

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INTRODUCTION

Cisplatin (DDP) is an effective anti-tumor agent, widely used in the treatment of ovarian, testicular and bladder cancer. Though a number of other side effects, like nausea, vomitus, ototoxicity and nephrotoxicity, frequently occur in the course of treatment, at present a peripheral, purely sensory neuropathy is dose limiting. This neuropathy is clearly dose dependent and often only partly reversible after cessation of treatment (Thompson et al., 1984). The onset is characterized by a decrease of vibratory and fine touch perception, both thick fiber qualities. At higher cumulative doses also propriocepsis is diminished and a sensory ataxia can result in wheelchair dependency (Ozols et al., 1985). Perception of pain and temperature (thin fiber qualities) is not affected and motor function remains intact.

Only a few data are available at present with regard to histological changes in nervous tissue of patients treated with cisplatin. In a series of sural nerve biopsies (the sural nerve is purely sensory) a decrease in the number of thick myelinated fibers was observed. Whether this was due to a loss of these fibers or to a shift towards smaller

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Abbreviations: Cisplatin: Cis-diaminedichloroplatinum(II); HSNCV: H-reflex related sensory nerve conduction velocity; SNCV: Sensory nerve conduction velocity; MNCV: Motor nerve conduction velocity; Org. 2766: ACTH(4-9), H-Met(O_2)-Glu-His-Phe-D-Lys-Phe-OH.

fibers could not be elucidated (Gastaut and Pellisier, 1985). Levels of cisplatin in sensory, dorsal root ganglia (obtained post-mortem) are equal to those found in tumor tissue, whereas levels in brain and spinal cord are twenty times lower, suggesting an effect of the drug at the level of the ganglion (Thompson et al., 1984).

TREATMENT WITH ORG. 2766

ACTH, α-MSH and a number of analogues have been shown to exert a neurotrophic action both in the central and in the peripheral nervous system. This neurotrophic effect could be demonstrated at the histological, neurophysiological and behavioral level and involves both sensory and motor modalities in young, adult and aging rats. There is evidence to suggest that exogenous administered peptides mimick or amplify endogenous signals that play a role in the onset of the neuronal response to injury. It was postulated that also neural damage other than mechanical injury could benefit from peptide treatment as the regenerative repertoire per se may be independent of the cause of damage, being an intrinsic property of the nervous system. Hence, it was tested whether Org. 2766 treatment might counteract the onset or the severity of neuropathies induced by drugs, such as cisplatin, or by metabolic conditions, such as diabetes, as well (Gispen et al., 1987).

An animal model for cisplatin neurotoxicity was developed in rats. At cumulative doses of 13 mg/kg and higher the SNCV decreased, as in the human situation (De Koning et al., 1987a). Concomitant subcutaneous treatment with Org. 2766, an ACTH(4-9) analogue, devoid of corticotrope and melanotrope effects, (dose: 10 μg/rat, four times a week) prevented the decrease in SNCV, that was found in animals treated with cisplatin only (De Koning et al., 1987b).

When treatment with Org. 2766 was started once a neuropathy had already been established, an improvement was also seen, although normal values were not reached. Furthermore, rats were less susceptible to a second treatment period with cisplatin, when co-treated with Org. 2766 during the first period (Gerritsen van der Hoop et al., 1988a). In a high-dose cisplatin treatment regimen the sensory deficit developed more rapidly. Administration of the peptide proved to be similarly effective in preventing the onset of the neuropathy during the complete, albeit shorter treatment period of 5 weeks (Gerritsen van der Hoop et al., 1988b).

Histomorphological examination of sural nerves revealed that the total number of fibers was not affected by cisplatin treatment. No signs of axonal degeneration of secondary demyelination were present in teased fiber preparations. A change, however, was observed in the distribution of myelinated fibers. The number of thick fibers was decreased in rats treated with cisplatin (Fig. 1). Since the total number of fibers was unchanged, this indicates that a shift had occurred towards less thick myelinated fibers. This shift in fiber distribution was absent in animals that received Org. 2766 as co-treatment (Gerritsen van der Hoop et al., 1988b).

These results are in line with the findings in the only available series of patients studied (Gastaut and Pellisier, 1985) and could explain the observed decrease in SNCV, since nerve conduction is faster in thick myelinated fibers. The anti-tumor activity of

cisplatin is not hampered by Org. 2766 as was shown both in a plasmacytoma model in rats (De Koning et al., 1987) and in a model with a gynaecological tumor in mice (Gerritsen van der Hoop et al., 1988a).

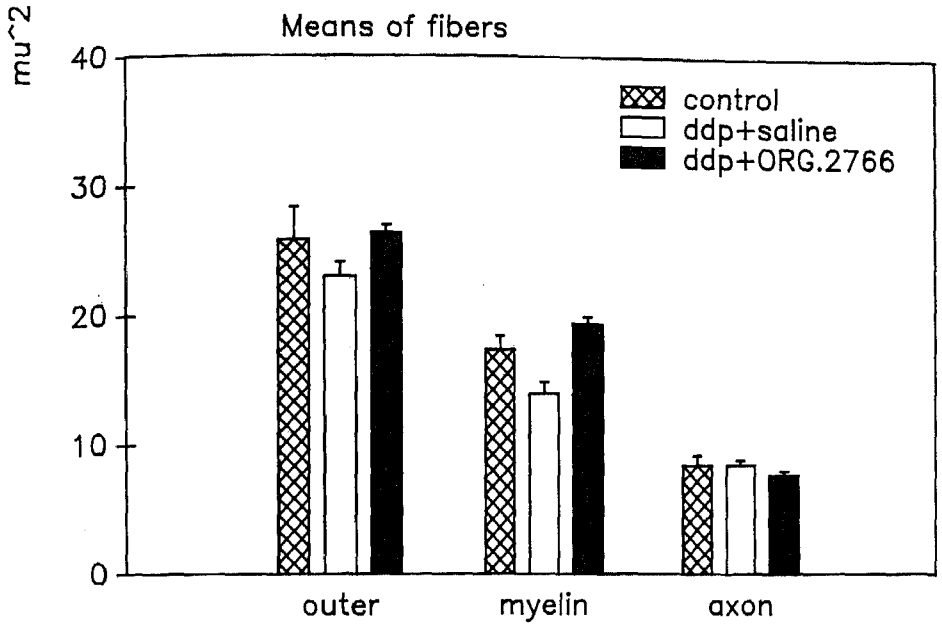

Figure 1. Means of areas of individual nerve fibers (over 600/rat) in the sural nerve (each group n=6). Outer area (the total fiber), inner area (axonal area) and the myelin area are all depicted (DDP = cisplatin treatment, cum. dosis 22 mg/kg).

CONCLUSIONS

Cisplatin treatment induces a purely sensory neuropathy both in humans and in rats. The ACTH(4-9) analogue Org. 2766 protects from cisplatin induced neurotoxicity in rats, as can be observed both with the use of electrophysiological and histological techniques.

In view of these promising results a placebo controlled, double blind study was started in patients with ovarian cancer, treated with cisplatin. Possible beneficial effects of Org. 2766 in this trial could result in an improved quality of life, whereas higher cumulative doses of cisplatin might be administered without neurotoxic side effects.

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