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# The ACTH-(4–9) analog, ORG 2766, prevents taxol-induced neuropathy in rats

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Taxol is a novel and promising oncolytic agent the use of which is hampered by its neurotoxicity. We now describe a taxol-induced neuropathy in rats and its prevention by the adrenocorticotropic hormone-(4–9) (ACTH-(4–9)) analog, ORG 2766. A decrease in sensory nerve conduction velocity was seen in taxol-treated rats, both with daily injections of small amounts (6 mg/kg per week) and with weekly injections of higher amounts (9 mg/kg per week) of taxol. Concomitant administration of ORG 2766 completely prevented the occurrence of a neuropathy.

Taxol neuropathy; Neuroprotection; ORG 2766

Taxol is a novel oncolytic drug of clinical importance (Rowinsky et al., 1990). Its oncolytic activity is due to extreme stabilization of tubulin polymers (Schiff et al., 1979). Currently its major indication is cisplatin refractory ovarian carcinoma (McGuire et al., 1989). An important side-effect is the induction of a sensory neuropathy with symptoms of distal numbness, paresthesias and pain. Deep tendon reflexes, propriocepsis, vibration and temperature sense and pin prick sensation are lost to some extent. Motor signs and symptoms are mostly mild or absent, as is autonomic dysfunction (Lipton et al., 1989). Because of the great clinical interest in taxol and the debilitating neuropathy, we investigated this neuropathy in an animal model.

Experiments were performed in young adult male Wistar rats weighing between 190 and 220 g at the start of the experiments. The animals were housed in groups of three animals in Macrolon® cages. Commercial rat chow and water were available ad libitum. Taxol (dissolved in Cremophor EL/dehydrated ethanol 50:50, 6 mg/ml) was obtained from Bristol-Myers. This stock was further diluted with 0.9% NaCl (saline) immediately before use. Taxol was either injected i.p. 5 times a week (6 mg/kg per week during the first 7 weeks and 12 mg/kg per week during weeks 8 and 9, first experiment) or once a week (9 mg/kg per week, second experiment). ORG 2766 (H-Met($O_2$)-Glu-His-Phe-D-Lys-Phe-OH, Organon International B.V., Oss, The Netherlands) was dissolved in saline and injected s.c. every 48 h in a dose of 75 $\mu$g/kg.

In the first experiment three groups of seven animals each were treated with vehicle/saline (age-matched controls), taxol/saline and taxol/ORG 2766, respectively. Body weight was measured daily and the taxol dose was adjusted according to the actual weight. The animals were injected with taxol 1.2 mg/kg per day (concentration 0.3 mg/ml) 5 days a week for 7 weeks; during week 8 and 9 the daily dose was doubled (cumulative dose: 66 mg/kg). The second experiment was similar to the first, with the exception that the taxol dose was higher and was given once a week (9 mg/kg, concentration 0.45 mg/ml) for 6 weeks (cumulative dose: 54 mg/kg). The neuropathy was quantified by electrophysiologic measurement of the motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) in the sciatic nerve, as described elsewhere (De Koning et al., 1987). Statistical evaluation of the experimental data was performed by an analysis of variance for repeated measurements (ANOVAR) followed by supplemental t-tests. The treatment code was opened only after this analysis was completed.

Apart from two animals from the second experiment that died following anaesthesia in the first week of treatment, all animals survived until the end of the experiments. In both experiments, the MNCV developed similarly in all experimental groups and no motor

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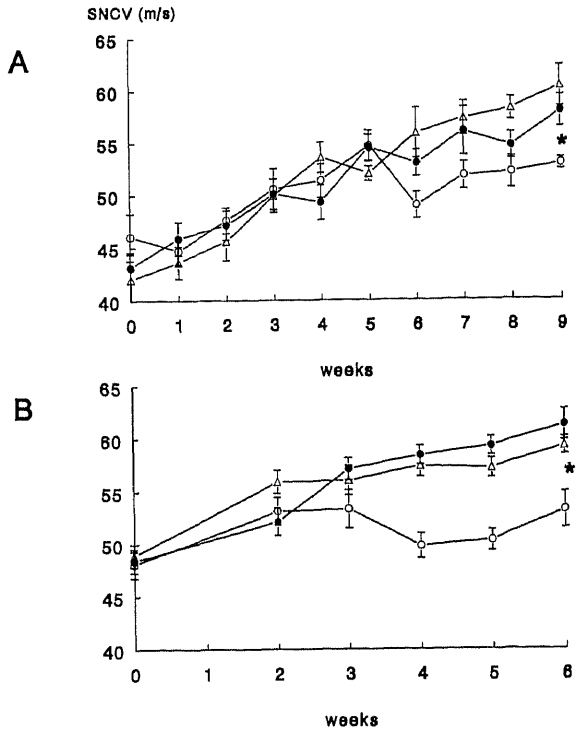


Fig. 1. Effects of taxol treatment on sensory nerve conduction velocity. (△) Age controls, (○) taxol/saline (●) taxol/ORG 2766. Values are given as means ± S.E.M. (A) First experiment. Taxol was injected daily in a dose of 1.2 mg/kg for 7 weeks, and 2.4 mg/kg for the next 2 weeks. (B) Second experiment. Taxol was injected in a dose of 9 mg/kg weekly for 6 weeks (* $P < 0.02$; age and taxol/ORG 2766 vs. taxol/saline).

neuropathy was encountered. In the first experiment a sensory neuropathy, as evidenced by a significant decrease of the SNCV, developed in the taxol/saline-treated animals from week 5 onwards (ANOVAR week 5 to 9: $F(2,17) = 4.65$, $P < 0.024$, t-test at week 9; age-controls vs. taxol/saline $t = 3.30$, $df = 11$, $P < 0.007$ taxol/peptide vs. taxol/saline $t = 2.77$, $df = 11$, $P < 0.018$) (fig. 1A). The SNCV of taxol/peptide-treated animals did not differ significantly from that of the age-matched controls. In the second experiment, a significant decrease in SNCV developed from week 3 onwards in the taxol/saline-treated animals (ANOVAR week 3 to 6: $F(2,31) = 29.08$, $P < 0.0001$, t-test at week 6; age controls vs. taxol/saline $t = 3.14$, $df = 20$, $P < 0.005$; taxol/peptide vs. taxol/saline $t = 3.55$, $df = 21$, $P < 0.002$) (fig. 1B). As in the first experiment, the taxol/ORG 2766-treated group did not significantly differ from the age-matched control group.

We conclude that taxol induces a sensory neuropathy in the rat. Concomitant administration of ORG 2766 prevents this neuropathy. This is in line with similar observations with this peptide in other models for peripheral nerve disease including cisplatin neuropathy in animals and humans (Gerritsen van der Hoop et al., 1990; Gispen et al., 1992). Although the mechanism of action of ORG 2766 is still under study, it has been suggested that neurotrophic peptides tip the damage-repair balance in favour of repair (Gispen, 1990).

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