

## ANTIHYPERALGESIC EFFECTS OF THE PYRROLIDINONE DERIVATIVE NIK-13317 IN MODELS OF NEUROPATHIC PAIN

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Rashid and Ueda (1) reported that nefiracetam, a lipophilic analog of piracetam, was able to dose dependently reverse the mechanical and thermal hyperalgesia induced by partial ligation of the sciatic nerve in mice. Chemical modifications of the structure of dimiracetam, a bicyclic analog of the nootropic piracetam, afforded an array of novel derivatives among which NiK-13317 displayed a very promising antihyperalgesic profile. NiK-13317 (30 -100 mg kg<sup>-1</sup> i.p. - p.o.; 3 mg kg<sup>-1</sup> e.v.), was able to reverse the reduction of pain threshold induced by chronic constriction injury of sciatic nerve, streptozotocin or resiniferotoxin (substance P agonist) without showing any effects when administered in the absence of pre-existing painful conditions. Pain threshold was evaluated by either paw-pressure (Randall & Selitto) or by the incapitance test. In the model of hyperalgesia induced by i.pl. capsaicin and evaluated in the Von Frey test, NiK-13317 reduced the withdrawal response frequency only at the dose of 100 mg kg<sup>-1</sup> p.o.. The tested compound actually exerts its antihyperalgesic effect at a supraspinal level since it was effective also after i.c.v. administration (3-30 µg per rat i.c.v.). The activity of NiK-13317 was also confirmed in a mouse model of neuropathy induced by streptozotocin, in which a thermal painful stimulus was applied to evaluate the pain threshold (hot-plate). NiK-13317, after repeated administration to the sciatic nerve-ligated rat (100 mg kg<sup>-1</sup> p.o. for 14 days) showed a statistically significant effect up to 24 h after the last administration. The intensity of antihyperalgesic effect of NiK-13317 was comparable to that exerted by the well-known antineuropathic drug gabapentin (100 µg i.c.v., 100 mg kg<sup>-1</sup> i.p.-p.o.), and it was more effective than levetiracetam (500 µg i.c.v.). Moreover NiK-13317 (50-100 µg per mouse i.c.v.; 100 mg kg<sup>-1</sup> s.c.) was weakly active in the acetic acid abdominal constriction (chemical stimulus) test and in the hot-plate test (thermal stimulus). Furthermore, in the range of analgesic/antihyperalgesic doses, it did not produce any inhibition of motor coordination, spontaneous motility or explorative activity as evaluated by the rota-rod, hole board and Irwin tests and did not exhibit any effects on the convulsions induced by pentylentetrazole. These results suggest that NiK-13317 might represent a novel and well tolerated therapeutic agent for the relief of neuropathic pain.

1. Rashid M. H., Ueda H. (2002) J. Pharm. Exp. Ther. 303: 226-231.