# MMPIP, an mGluR7-selective negative allosteric modulator, alleviates pain and normalizes affective and cognitive behavior in neuropathic mice

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This study investigated the effects of a single administration of 6-(4-methoxyphenyl)-5-methyl-3-pyridinyl-4-isoxazolo[4,5-c]pyridin-4(5H)-one (MMPIP), a negative allosteric modulator (NAM) of metabotropic glutamate receptor 7 (mGluR7), on pain and on affective and cognitive behavior in neuropathic mice. The activity of pyramidal neurons in the prelimbic cortex (PLC), which respond to stimulation of the basolateral amygdala (BLA) with either excitation or inhibition, was also investigated. The spared nerve injury (SNI) of the sciatic nerve induced according to the method of Decosterd and Woolf.(Decostered and Woolf., 2000), 14 days after surgery, thermal hyperalgesia and mechanical allodynia, reduced open-arm choice in the elevated plus-maze, increased time of immobility in the tail suspension, and increased digging and burying in the marble burying test. Cognitive performance was also significantly compromised in the SNI mice. Spared nerve injury induced phenotypic changes on pyramidal neurons of the PLC; excitatory responses increased, whereas inhibitory responses decreased after BLA stimulation. mGluR7 expression, mainly associated with vesicular glutamate transporter, increased in the hippocampus and decreased in the BLA, PLC, and dorsal raphe in SNI mice. MMPIP increased thermal and mechanical thresholds and open-arm choice. It reduced the immobility in the tail suspension test and the number of marbles buried and of digging events in the marble burying test. MMPIP also improved cognitive performance and restored the balance between excitatory and inhibitory responses of PLC neurons in SNI mice. 7-hydroxy-3-(4-iodophenoxy)-4H-chromen-4-one, XAP044, another selective mGluR7 NAM, reproduced the effects of MMPIP on thermal hyperalgesia, mechanical allodynia, tail suspension, and marble burying test. Altogether, these findings show that mGluR7 NAMs reduce pain responses and affective/cognitive impairments in neuropathic pain conditions.

*Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. PAIN 2000;87:149–58.*