MMPIP, a mGluR7 selective negative allosteric modulator, alleviates pain and normalizes affective and cognitive behaviour in neuropathic mice

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This study has investigated the effect of a single subcutaneous administration of MMPIP, a negative allosteric modulator of metabotropic glutamate receptor 7 (mGluR7) [1], on pain responses and on affective and cognitive behaviour in a neuropathic pain model induced by the spared nerve injury (SNI) of the sciatic nerve in mice [2,3]. The electrophysiological activity of pyramidal neurons of the prelimbic/infralimbic (PL-IL) division of the prefrontal cortex which respond with an excitation or inhibition to the basolateral amygdala (BLA) or pressoceptive stimulation was also investigated in sham and SNI mice. SNI produced, 14 days after surgery, thermal hyperalgesia and mechanical allodynia, reduced the open-arm choices in the elevated plus maze (EPM) while increased the time of immobility in the tail suspension and the digging and burying in the marble burying test. Cognitive performance in the object recognition and y maze tests were significantly compromised 14 day after SNI. SNI also induced phenotypical changes on pyramidal neurons of the PL-IL cortex in a way that the excitatory responses increased whereas the inhibitory ones decreased after BLA or mechanical stimuli. A single subcutaneous administration of MMPIP increased thermal and mechanical thresholds, the open arm choice and reduced the time of immobility in the tail suspension and the number of buried marbles. MMPIP also improved the cognitive performance. MMPIP restored also the balance between excitatory and inhibitory responses in the SNI mice. Finally, the mGluR7 expression proved to be altered 14 days after SNI in a way that it was increased in the periaqueductal grey, PL/IL cortex and hippocampus and decreased in the amygdala and dorsal raphe.

References

1. Ferraguti F, Shigemoto R. Metabotropic glutamate receptors. Cell Tissue Res. **2006** 326(2):483-504.
2. Palucha A, Pilc A. Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. Pharmacol Ther. **2007** Jul;115(1):116-47.
3. Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain. **2000**; 87(2):149-58.