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Poster PF0263 : Enhancing KCC2 activity to counteract morphine-induced hyperalgesia

Part of Poster Session D

PF0263

Description

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Aim of Investigation
Morphine-induced hyperalgesia (MIH) is a severe adverse effect accompanying repeated morphine treatment which leads to a paradoxical decrease in nociceptive threshold. In our past work, we showed that MIH is associated with a decreased expression of the chloride extruder KCC2 in the superficial dorsal horn, which in turn weakens synaptic inhibition onto pain transmitting neurons in lamina I (Ferrini et al., Nat Neurosci, 2013). Here we tested whether the administration of small molecules enhancing KCC2 activity (Gagnon et al., Nat Med, 2013) may counteract the expression of morphine hyperalgesia.

Methods
Adult male rats (about 300 g) received subcutaneously either morphine (10 mg/Kg) or saline twice a day. Mechanical sensitivity was tested at day 1, 3, 7, 8, 9 before morphine/saline morning injection with a modified von Frey method (SUDO). In a first series of experiments to test whether MIH can be reversed, rats received a single intraperitoneal injection of either the KCC2 enhancer CLP257 (100 mg/Kg) or vehicle at day 9 (two hours before behavioral testing). In a second series of experiments, to test whether MIH can be prevented, rats were administered twice every day (from day 1 to 9) with the CLP257 carbamate prodrug (CLP290, 100 mg/Kg) or vehicle. The GABA reversal potential (EGABA) of spinal lamina I neurons was measured by imposing a chloride load through the recording pipette in slices obtained from morphine-treated and control rats.

Results
MIH was typically expressed after 7-8 days of morphine treatment. Morphine-treated rats exhibited decreased mechanical threshold and increased vocalization when subcutaneously injected. A single intraperitoneal injection of CLP257 in rats with established MIH was sufficient to restore a normal nociceptive behavior. Continuous oral administration of CLP290 starting from the first day of morphine treatment significantly mitigated MIH. EGABA of lamina I neurons in slices from morphine-treated rats was more depolarized as compared to control rats. However, pre-incubation with CLP257 (100 μM) restored a normal EGABA in lamina I neurons.

Conclusion
Our data indicate that enhancing KCC2 activity is a viable therapeutic approach for counteracting morphine-induced hyperalgesia. Co-administration of CLP257 with morphine may represent a potential co-adjuvant therapy to improve morphine analgesic effect.