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POSTER
KK18

Society for Neuroscience

SfN's 44th Annual Meeting

Washington, DC : November 15-19, 2014



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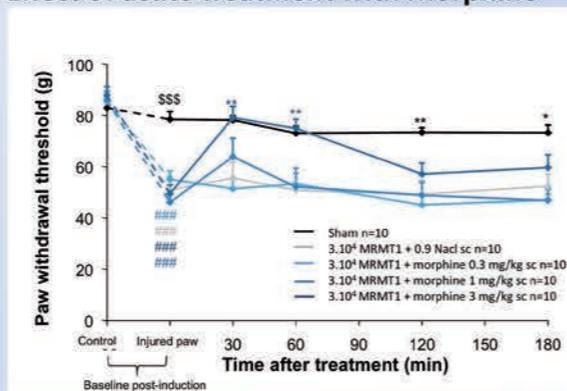
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Introduction: Bone is a privileged site of metastasis for primary tumors such as lung, prostate and breast. Generally, bone metastases are associated with severe pain, including movement-evoked pain and spontaneous pain. The development of new analgesics effective in relieving cancer-induced bone pain requires relevant animal models. A rat model based on a local injection of syngenic MRMT-1 rat mammary gland carcinoma cells into the bone cavity mimics relevant features of the clinical pain experienced by patients with bone metastases.

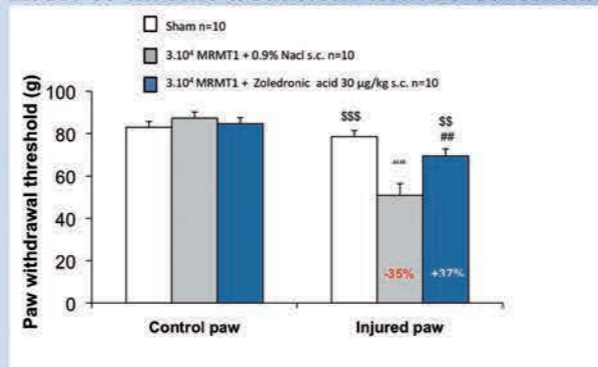
Aim of investigation : The aim of this study was to characterize the MRMT-1-induced bone cancer pain model using classical validated tools used to evaluate new lead compounds on behavioral pain responses and correlate these responses with medical imaging methods.

Material and Methods : Bone cancer pain was induced by unilateral implantation of 3.10⁴ MRMT-1 tumor cells into the medullary cavity of the tibia in anaesthetized rats. Fourteen days after cell inoculation, behavioral responses of different types of MoA-based analgesics were assessed on mechanical allodynia. At the end of the time course, Micro-computed tomography analyses, X-ray radiography and histological analyses were performed on tumor-bearing rats.

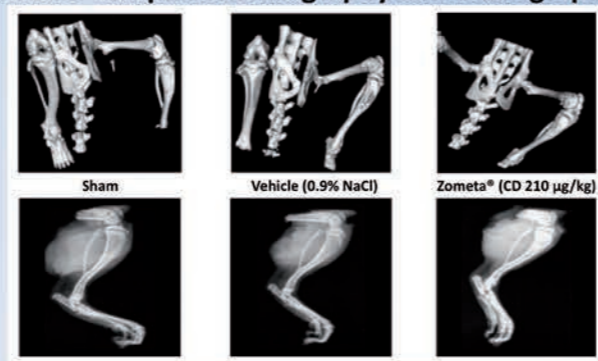
1. Effect of acute treatment with Morphine



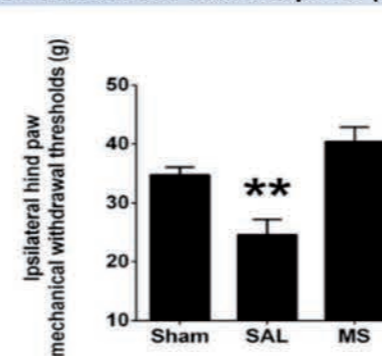
2. Effect of chronic treatment with Zoledronic acid



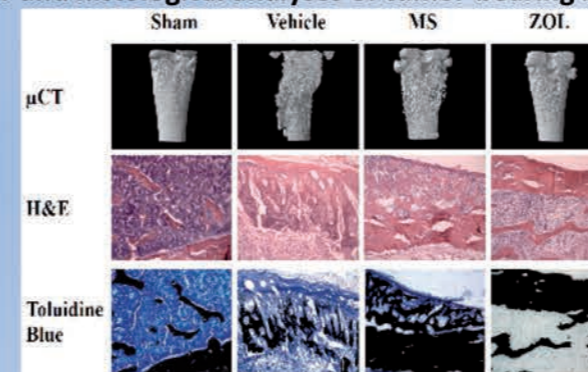
3. Micro-computed tomography and Radiography



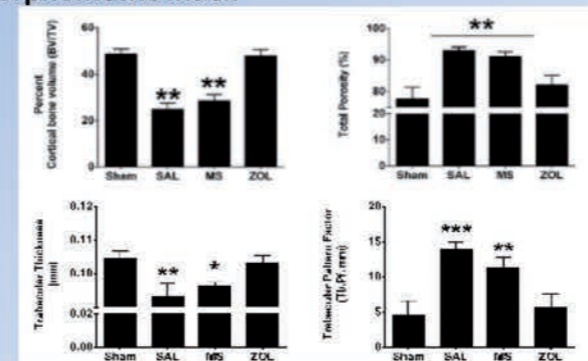
4. Effect of chronic treatment with morphine (6 mg/kg/day)



5. µCT and histological analyses of tumor-bearing bone



6. Morphometric index



Results :

1. Fourteen days after cancer cell implantation, tumor-bearing rats exhibited mechanical allodynia and ambulatory-evoked pain.

2. After acute treatment, Morphine (0.3; 1; 3 mg/kg, s.c.) reversed in a dose-related manner the mechanical hypersensitivity in the tumor-inoculated hind paw as well as the repeated treatment at the highest tested dose (3 mg/kg; twice-daily over seven days).

3. Rats receiving chronically systemic zoledronate (30 µg/kg, 7 administrations over the 14 day-period) showed significant reduction in pain-related behaviors, compared to saline-treated tumor-bearing rats.

4. Cancer-bearing rats exhibited severe bone lesions, as represented by bone parameter changes in volume density (BV/TV), porosity, trabecular pattern factor and trabecular thickness

Conclusion : MRMT-1-induced bone cancer pain model exhibits same features than those observed in clinic and constitutes thus, a good tool for the assessment of new therapeutic approaches in the treatment of breast cancer cells metastasizing to bone.

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PRECLINICAL PHARMACOLOGY OF PAIN**



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