# [PR2-123] Effect of common opioids and methylnaltrexone on pediatric tumor growth: Differential expression of mu-opioid receptors in tumor lines

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Background–Although debate exists regarding the effects of anesthesia and opioids on tumor growth and metastasis, retrospective studies suggest a protective role of regional anesthesia with decreased opioid administration in melanoma and breast, prostate and colon cancers [1]. Overexpression of the mu-opioid receptor (MOR) appears to increase proliferation of bronchioalveolar carcinoma [2]. There is no literature to date addressing the effects of opioids on pediatric tumor lines. We screened 16 pediatric and 3 non-small cell lung cancer (NSCLC) lines for the presence of MORs and their response to common opioids.
Methods–Sixteen pediatric tumors including 5 malignant peripheral nerve sheath tumors (MPNSTs), 6 osteosarcomas, 3 neuroblastomas, 1 glioblastoma and 1 Ewing's sarcoma and 3 NSCLCs were screened for the presence of MORs using an immunohistochemistry assay. Cell cultures were used to evaluate the effect of opioid exposure on tumor growth. Nine lines were treated with 5-fold dilutions of morphine and fentanyl; 5 were also screened with supra-therapeutic concentrations of opioids. Several lines were treated with opioid plus chemotherapy (GSK1120212) and opioid plus methylnaltrexone (MNTX).
Results–Immunohistochemistry revealed 4 unique MOR staining patterns. Ten lines showed intense membrane expression of MORs, including 4 osteosarcomas, 1 neuroblastoma, the glioblastoma and the Ewing's sarcoma and the 3 adult lines (Figure 1A). Two MPNST lines showed discrete areas of localized MOR immunostaining at sites of cell contact (Figure 1B) and a neuroblastoma and MPNST showed purely endosomal expression of MORs with very low levels of membrane expression (Figure 1C). Lastly, 1 neuroblastoma, 2 osteosarcomas and 2 MPNST lines showed only minimal levels of MOR staining (Figure 1D). Of those with intense membrane expression, the NSCLCs, CHP-212 neuroblastoma, U87 glioblastoma and SK-N-MC Ewing's sarcoma showed no differential growth when exposed to opioids; the CHP-212 cells were also exposed to high-dose morphine and a combination of GSK1120212 plus morphine or MNTX with no significant effect on growth. MPNST lines with cell contact up-regulated expression of MORs and a neuroblastoma with endosomal expression of MORs showed no differential growth response to opioid exposure.
Conclusion–Among common pediatric tumor lines including neuroblastomas and osteosarcomas, there is differential expression of MORs. The presence of MORs or location of receptor expression did not influence tumor growth despite exposure to high concentrations of commonly used opioids, morphine and fentanyl, and MNTX. The presence of intra- and extracellular receptors may have implications explaining the analgesic versus side effects of opioids and further study is necessary to explore the implications of MOR expression in both normal as well as cancer cells and animal tumor models.
1. Anesthesia and analgesia. 2011;112(3):558-67.
2. Anesthesiology. 2012;116(4):857-67.

Figure 1. Immunohistochemistry of opioid receptors. Intense membrane expression (A), localized expression at sites of cell contact (B), endosomal expression (C) and minimal levels of MOR immunostaining (D).