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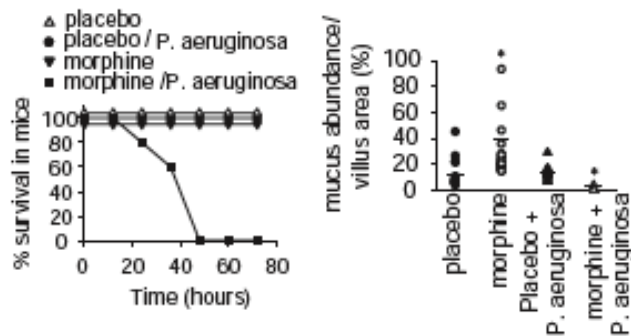
SYSTEMIC ADMINISTRATION OF MORPHINE SHIFTS THE PHENOTYPE OF *P. AERUGINOSA* TO SUPPRESS MUCUS PRODUCTION AND DISRUPT THE INTEGRITY OF THE INTESTINAL EPITHELIUM

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Introduction: Morphine use in critically ill patients has been shown to be an independent risk factor that predicts the severity of sepsis and mortality by mechanisms that remain elusive. We have previously reported that *P. aeruginosa* can directly sense the presence of morphine and become activated to express a highly motile and epithelial barrier disrupting phenotype. Here we sought to gain mechanistic insight into the process by which *P. aeruginosa* is “cued” to penetrate the intestinal epithelial barrier by examining the effect of chronic morphine administration on the ability of *Pseudomonas aeruginosa* to alter the mucus layer of the distal intestine, a key component of the epithelial barrier.

Methods: 7-week male C57BL6 mice were anesthetized and randomly assigned to subcutaneous implantation with either a 25 mg slow-release morphine or a placebo pellet and allowed access to food and water ad lib. At the time of pellet implantation, *P. aeruginosa* was injected via laparotomy into the distal ileum to fill the cecum in all mice. Animals were followed for mortality and sacrificed when moribund. Cecal tissues were examined histologically for intestinal integrity and mucus production using H & E and Alcian blue staining, respectively, with evaluation of mucus abundance using ACIS software.

Results: Subcutaneous implantation of 25 mg morphine pellet and injection of $200 \cdot L$ of 10^7 CFU *P. aeruginosa* PAO1 resulted in 100% mortality in mice at 48 hours (n= 10, p= 0.001). Animals implanted with a placebo pellet with injection of *P. aeruginosa* or mice implanted with morphine alone demonstrated 100% survival. Histological analysis of cecal sections demonstrated that morphine treatment alone increased intestinal goblet cell number and mucus production while not disturbing the integrity of the underlying intestinal epithelium. The administration of morphine followed by *P. aeruginosa* injection into the intestine resulted in a drastic decrease of goblet cells, suppression of mucus production and superficial erosion (n= 30, p= 0.0005) (see Figure).



Conclusion: These studies demonstrate that in the presence of systemic morphine, *P. aeruginosa* exhibits a distinct behavioral phenotype in the intestinal tract that suppresses goblet cell production of mucus and disrupts the integrity of the intestinal epithelium. A more complete understanding of the mechanisms by which intestinal pathogens shift their phenotype in response to the systemic administration of morphine may be critical to identify the role of morphine as an independent factor in sepsis-related outcomes in critically ill patients.