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Introduction

- Opioids are known to induce tolerance, hyperalgesia, and high abuse liability with prolonged usage. Therefore, it is very important to identify novel approaches to mitigate these negative side effects.
- Morphine, a μ-opioid receptor agonist, is commonly used as an analgesic to alleviate acute and chronic pain.
- Astrocyte Elevated Gene-1 (AEG-1) is a multifunctional protein that regulates inflammation, myeloid cell activity and lipid metabolism.
- AEG-1 is expressed in tissues involved pain signaling transduction, such as the periaquaductal gray, spinal cord, and dorsal root ganglia.

Goal of Study

- Studies have shown interactions and overlaps in cellular signaling between the inflammatory/immune responses and the endogenous opioid system which could suggest a role for AEG-1 in opioids effects.
- Thus, our goal is to investigate the role of AEG-1 in morphine mediated pharmacological effects including analgesia.

Methods

Animals:

- Adult (12-32 weeks old) AEG-1 WT or global KO male and female mice on C57BL/6J background

Drugs:

- Morphine Sulphate: dissolved in 0.9% saline solution.
- Naloxone Hydrochloride: dissolved in 0.9% saline solution.

Models:

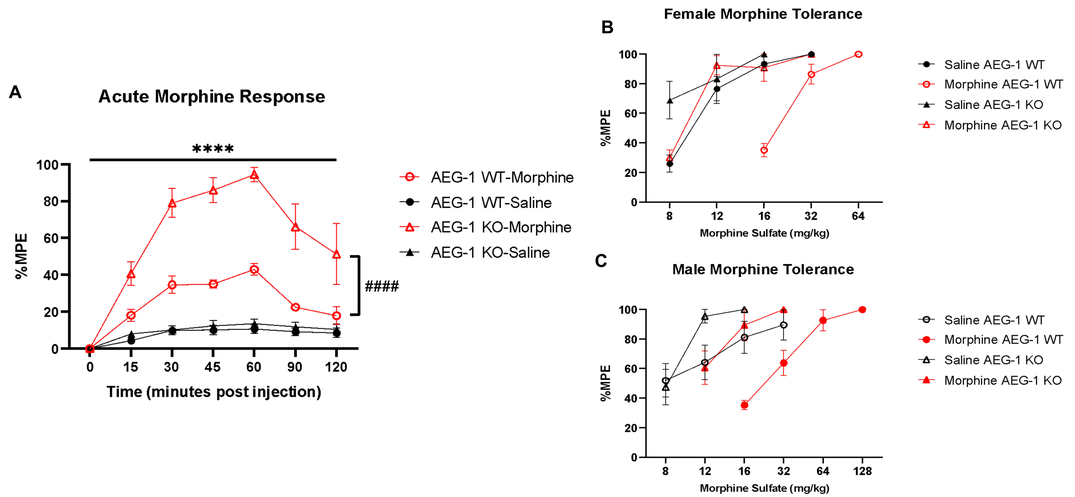
- **Acute response**: Mice injected (i.p.) w/ drug or vehicle. Tail immersion test was performed at 15-, 30-, 45-, 60-, 90-, and 120-minutes post injection.
- **Cumulative Dose Response**: Mice injected increasing doses of morphine. Tail immersion performed 20 min after each injection, and next injection administered immediately after test.
- **Chronic Treatment**: Morphine tolerance induced via a 4 day consecutive administration course (2x a day) at 20-, 40-, 40-, and 80-mg/kg doses, respectively.

Assays:

- Tail Immersion: Assess thermal nociception at 50.2° C
- Locomotor Activity Boxes: Assess spontaneous locomotion
- Charcoal Transit Assay: Assess GI transit inhibition

Results

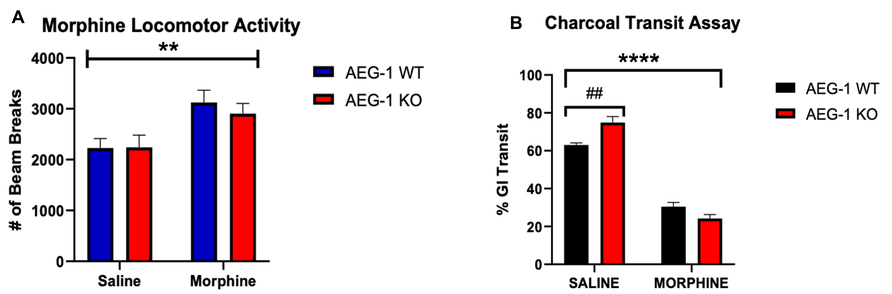
AEG-1 Deletion Enhances the Antinociceptive Effects Of Morphine



The tail immersion assay was used to assess thermal nociception. We observed an enhancement in the antinociceptive effects of morphine (10 mg/kg, i.p.) in AEG-1 KO mice in (A) an acute response time course (n=8-10/genotype/treatment for males & females) and a (B/C) chronic morphine administration (n=6/genotype/treatment) in males and females, respectively. (B/C) AEG-1 KO mice displayed reduced morphine tolerance development compared to their WT counterparts as demonstrated by the rightward shift in the WTs. Significance determined using (A) ordinary two-way ANOVA, *significant from vehicle control, #significant between transgenic mice in similar treatment group, $\alpha = p < 0.05$. * Significant difference from vehicle controls, # Significant difference from WT controls.

Results

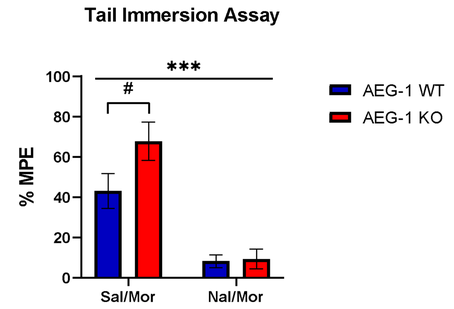
AEG-1 Deletion Has No Effect on Hyperlocomotion or GI Transit Inhibition Induced by Morphine



To assess the impact of AEG-1 deletion on morphine-induced hyperlocomotion and GI transit inhibition, (A) AEG-1 KO and WT mice were injected with morphine (10 mg/kg; i.p.) and allowed to roam freely in locomotor chambers for 60 min (n=8/genotype/treatment, males and females) and (B) AEG-1 KO and WT mice were injected with morphine and analyzed for % GI transit (n=16/genotype/treatment, males & females). There was no significant difference in locomotor activity or % GI transit between AEG-1 WT and KO mice treated with morphine. Significance determined using (A/B) ordinary two-way ANOVA, $\alpha = p < 0.05$. * Significant difference from vehicle controls, # Significant difference from WT controls.

Results

AEG-1 KO Enhancement is OPR-Dependent



To determine if the role of AEG-1 in morphine-induced antinociception is mediated by opioid receptor (OPR) activation, AEG-1 WT and KO mice (n=8-11/genotype/treatment, males & females) were pre-treated with naloxone (2 mg/kg, s.c.) prior to morphine (5 mg/kg) administration. The tail immersion assay was used to assess acute antinociception. Pretreatment with naloxone was shown to block the enhancement of morphine thermal antinociception in AEG-1 KO mice Significance determined using (A/B) ordinary two-way ANOVA, $\alpha = p < 0.05$.* Significant difference from vehicle controls, # Significant difference from WT controls.

Conclusion / Future

Conclusions:

- AEG-1 deletion enhances the antinociceptive effects of morphine and reduces tolerance following chronic morphine treatment.
- AEG-1 deletion does not impact morphine-induced locomotor activity or GI transit inhibition.
- AEG-1 deletion enhances morphine antinociception in an OPR-dependent manner
- AEG-1 may function as a modulator of the endogenous opioid system.

Future Directions:

- Determine if other opioid drugs produce a similar enhancement in antinociception in the AEG-1 KO mice.
- Assess the impact of AEG-1 deletion on morphine-induced hyperalgesia.
- Determine if chronic administration of morphine alters AEG-1 expression and function of OPR in neurological tissues involved in pain signaling transmission.

Acknowledgements

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