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Investigating The Role of AEG-1 in Mouse Models of Pain

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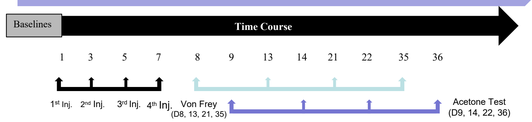
Introduction

- Astrocyte Elevated Gene 1 (AEG-1) was first identified as an upregulated gene in primary human fetal astrocytes infected with HIV-1 and has since been observed to have elevated expression levels in various CNS diseases[1].
- AEG-1 acts as a scaffolding protein and mediates inflammation via direct protein-protein interaction with p65 (NF-κB) [1].
- AEG-1 global knockout mice have been shown to be more resistant to inflammation compared to wild type littermates[1].
- Chemotherapy Induced Peripheral Neuropathy (CIPN) may develop in cancer patients undergoing treatment and may result in them having to switch to less effective drug regiments or ceasing treatment entirely[2].
- Current FDA approved drugs for chronic pain and neuropathy show modest efficacy and have severe side effects such as drug misuse and addiction[3].

Hypothesis

- AEG-1 acts as a mediator of inflammation via a NF-κB-dependent molecular mechanism. Therefore, making it a potential target for treatment in inflammatory pain.
- Therefore, we decided explore the role of AEG-1 in mouse models of Chronic Inflammatory pain and Chemotherapy Induced Peripheral Neuropathy (CIPN).
- We hypothesized that deletion of AEG-1 gene would result in protection from nociception in our chosen mouse models of pain

Methods



Animals:

- C57BL6/J male and female mice, 8-14 weeks old (n = 5).
- AEG-1 WT or global knockout male and female mice on C57BL6/J background, 8-14 weeks old (n = 6).

Models:

- Chronic Inflammatory Pain was induced via Freund's Complete Adjuvant (CFA). Mice received 20 µL, i.pl, injections of 50% CFA or vehicle.
- Chemotherapy Induced Peripheral Neuropathy was induced via **Paclitaxel** (Taxol®). Mice received 8 mg/kg, i.p, injections of paclitaxel or vehicle. (Previously described by Toma, *et. al* [4])

Assays:

- Von Frey: Assess mechanical hypersensitivity.
- Acetone Test: Assess cold sensitivity.
- qRT-PCR: Assess quantity of specific mRNA transcripts.

Results

AEG-1 in Chronic Inflammatory Pain

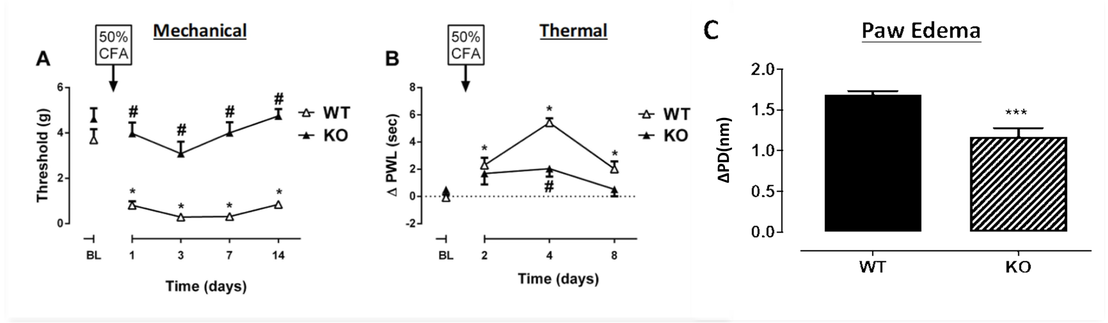
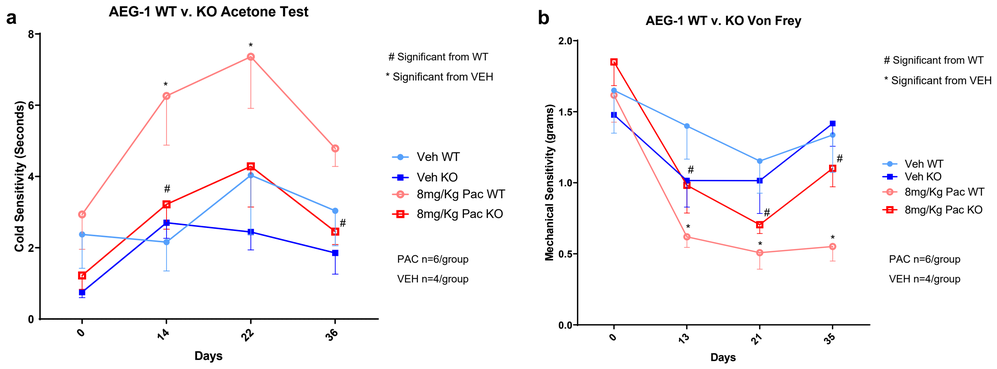


Figure 1: AEG-1 WT and global KO mice were given a single intraplantar injection of 50% CFA in mineral oil to model chronic inflammation. (a) AEG-1 WT mice displayed a higher degree of mechanical hypersensitivity at all time points, post injection, compared to AEG-1 KO mice. (b) AEG-1 WT mice displayed a higher degree of thermal sensitivity on day 4, post injection, compared to AEG-1 KO. (c) AEG-1 WT mice appear to show higher paw edema, measured 3 days following CFA injection, compared to AEG-1 KO mice.

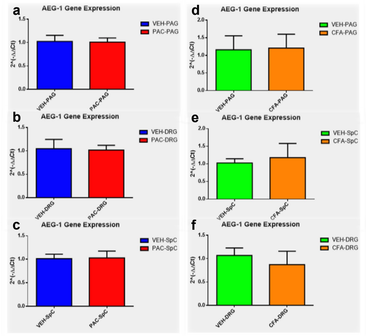
Results

AEG-1 in CIPN



AEG-1 WT and global KO mice were given 4 periodic intraperitoneal injections of Paclitaxel in a Kolliphore solution (8 mg/kg) to model chemotherapy-induced peripheral neuropathy. AEG-1 KO mice displayed enhanced recovery from Paclitaxel-induced (a) mechanical hypersensitivity and (b) cold sensitivity at later time points compared to WT littermates.

Results



AEG-1 mrRNA expression was measured in the Peri Aquaductal Gray (PAG), L4-6 spinal cord (SpC), and corresponding Dorsal Root Ganglia (DRG). These tissues are involved in neural pain processing pathways. C57Bl6/J mice were injected with either 4 x 8 mg/kg Paclitaxel (a-c) or 50% CFA (d-f), sacrificed 3 day post final injection, and tissues collected. No difference detected between drug treated mice compared to vehicle.

Conclusion / Future

- Transgenic global knockout of AEG-1 appears to provide protection from CFA induced mechanical hypersensitivity, thermal sensitivity, and paw edema.
- AEG-1 expression levels do not differ between C57BL6/J mice treated with CFA or Control at 3 days post injection.
- Transgenic global knockout of AEG-1 appears to provide enhanced recovery from paclitaxel induced mechanical hypersensitivity and cold sensitivity.
- AEG-1 expression levels do not differ between C57BL6/J mice treated with 8mg/Kg paclitaxel or Control at 3 days post injection cycle.

Future:

- Optimized IHC studies to assess AEG-1 and NF-κB protein localization in mice PAG, SpC, and DRG of various pain models.
- Performing a time course and collecting tissues at earlier time points to assess potential changes in AEG-1 expression in neuronal tissues.
- Assess the effects of analgesic drugs (such as morphine and gabapentin) on the anti-nociceptive phenotype displayed by AEG-1 KO mice.

Acknowledgements

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