Artemin: a novel target for treatment of interstitial cystitis/bladder pain syndrome

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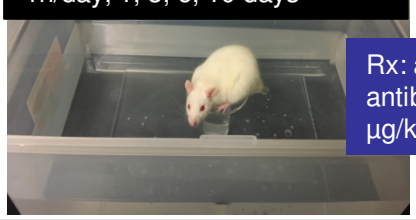
Introduction

Chronic stress plays a role in the development, maintenance and enhancement of painful bladder syndrome/interstitial cystitis (PBS/IC). The mechanisms that link stress to bladder hypersensitivity are not well understood. Altered levels of neurotrophins have been correlated with bladder hyperexcitability and pain. Artemin is a glia derived neurotrophic factor that supports the survival and development of a group of primary sensory neurons expressing TRPA1. Artemin can modulate pain responses. Thus, our overall hypothesis is that *the levels of artemin and/or its receptor are altered in PBS/IC bladder, which leads to sensory afferent hyperexcitability, changes in nociceptive channel expression or function and resultant bladder pain.* **Here, we examined the influence of psychological stress on artemin levels, bladder hyperalgesia and properties of the primary afferent neurons in a rodent model.**

Bladder function
Bladder hyperalgesia
Primary afferent neuron function

Methods

Adult female Wistar Kyoto rats
WAS : water avoidance stress
1h/day, 1, 3, 6, 10 days

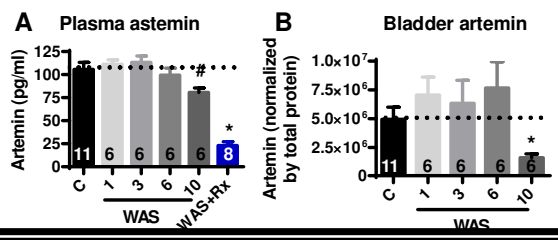


Rx: anti-artemin antibodies 100 µg/kg, i.p.), 6days

Results

a) WAS alters artemin levels in a time-dependent manner:

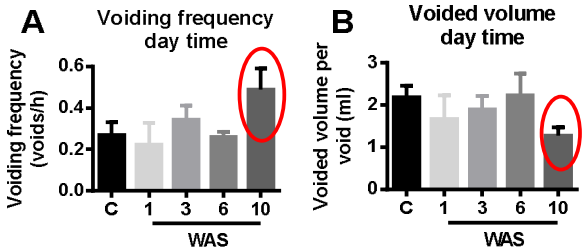
- no significant changes with acute WAS (1-3d)
- significant decrease with chronic 10d WAS
- anti-artemin antibodies during the acute phase (6d WAS) significantly decrease plasma levels



Results

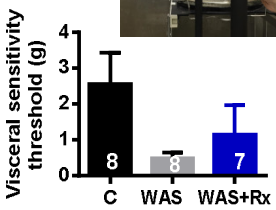
b) Chronic WAS alters bladder function - *metabolism cage studies and cystometry*

- ↑micturition frequency and ↓voided volume in 10d WAS
- no changes at earlier time points
- cystometry: ~25% ↑voiding frequency in 10d WAS



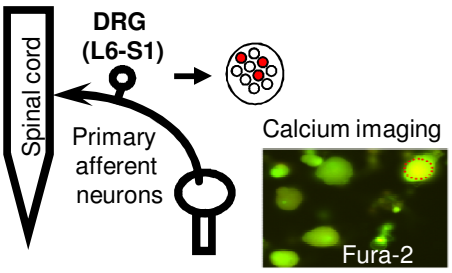
c) WAS and artemin levels modulate visceral sensitivity - *Von Frey filaments*

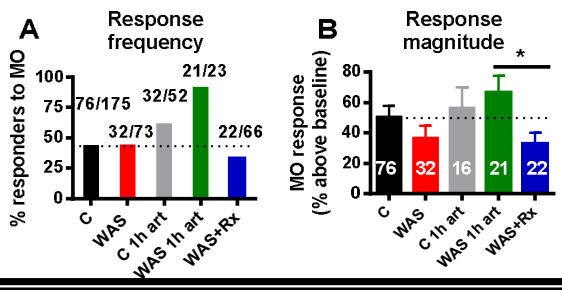
- ~70% decrease in the threshold for visceral sensitivity in 3-6d WAS rats
- partially prevented by anti-artemin treatment.



d) WAS and artemin levels modulate TRPA1 responsiveness in DRG neurons

- DRG neurons from WAS and anti-artemin treated WAS rats exhibited decreased responses to mustard oil (MO)
- DRG neurons exposed to acute in vitro artemin treatment (100ng/ml for 1h) exhibited increased responses to MO





Conclusions

- Stress can alter levels of the neurotrophic factor artemin, which can impact the expression and/or function of nociceptive TRPA1 channels and contribute to visceral sensitivity and pain.
- Acute increase in artemin could sensitize nociceptive afferents, contributing to acute pain - a potential mechanism for exacerbation of IC pain during symptom flares?
- Chronic decrease in artemin may impact recovery and survival of DRG neurons - a potential mechanism for chronic pain?
- Window for treatment: anti-artemin treatment during the acute state may prevent neuronal damage. For chronic state, increasing artemin levels and/or activating artemin intracellular pathways may be beneficial.

Manipulation of artemin expression and/or signalling pathways may offer a new pain treatment strategy for PBS/IC patients.

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