TLR4-dependent pain depends on different cell types in males and females.

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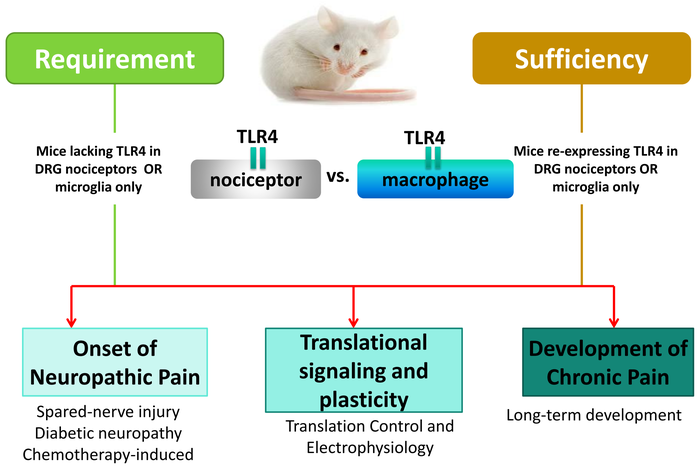
Abstract

Understanding how different cell types recognize and respond to danger-associated molecular patterns (DAMPs) could lead to a better understanding of basic mechanisms of pain plasticity and lead to new therapeutic insights. DAMPs are produced in a broad variety of tissue injury paradigms and are linked to the generation of pain and pain plasticity underlying chronic pain. High-mobility group-box1 (HMGB1) is a major DAMP that regulates pain states, it is produced after injury, and activates toll-like receptor-4 (TLR4). Here we have employed a novel transgenic model that allows for cre-mediated deletion of a floxed TLR4 allele, utilizing NaV1.8 and LysozymeM to drive cre expression in peripheral nociceptors or macrophages, respectively. We observed a robust sexual dimorphic behavioral effect in mechanical hypersensitivity and hyperalgesic priming when TLR4 is removed from peripheral macrophages in males versus nociceptors in females. After intraplantar administration of HMGB1, wild-type (WT) littermates of both sexes show a mechanical hypersensitivity that is blocked in males when TLR4 is removed from macrophages while it is blocked in females when TLR4 is removed from nociceptors. Conversely, macrophage TLR4 KO females and nociceptor TLR4 KO males develop mechanical hypersensitivity similar to their WT littermates. Moreover, these cell-specific TLR4 KO's were also associated with decreased hyperalgesic priming precipitated by PGE_2 injection in respective groups (macrophages in males and nociceptors in females). We then assessed whether intrathecal administration of LPS, another TLR4 agonist, is capable of likewise mediating a sex- and cell-specific behavioral response. These experiments show a similar trend toward cell-specific TLR4-mediated modulation of pain in a sex-dependent manner. Collectively our work demonstrates a cell-specific effect of TLR4 in acute pain plasticity and in the transition to a chronic pain state, pointing to a clear sex-difference in how DAMPs promote pain.

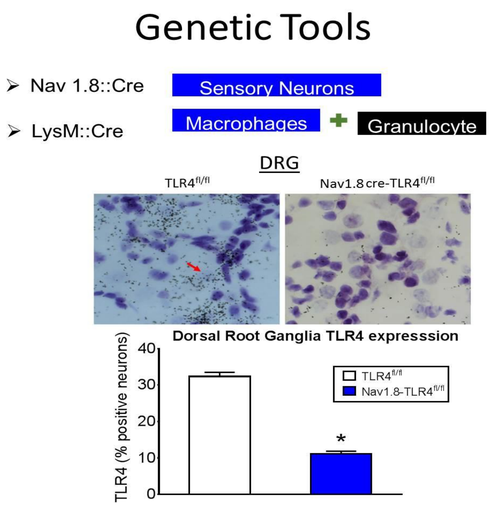
HYPOTHESIS

Neuroimmune interactions mediate pain states in a cell-type and sex-specific fashion.

Working Hypothesis



Genetic tools and validation of the model



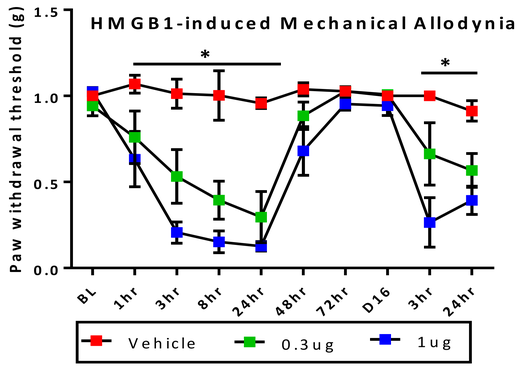
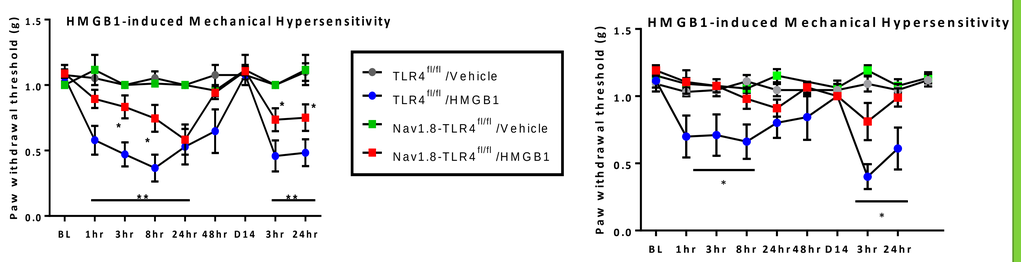


FIGURE 1. Proof-of-concept genetic & drug experiment.

Cell-Specific Toll-like Receptor 4 Modulation

MALES **FEMALES**

Nociceptor-specific ablation



Macrophage-specific ablation

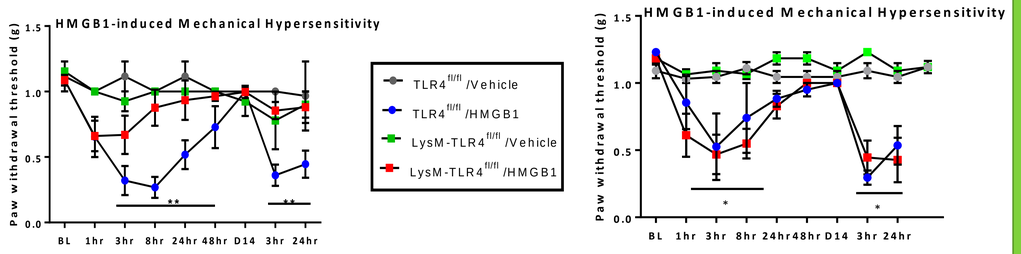
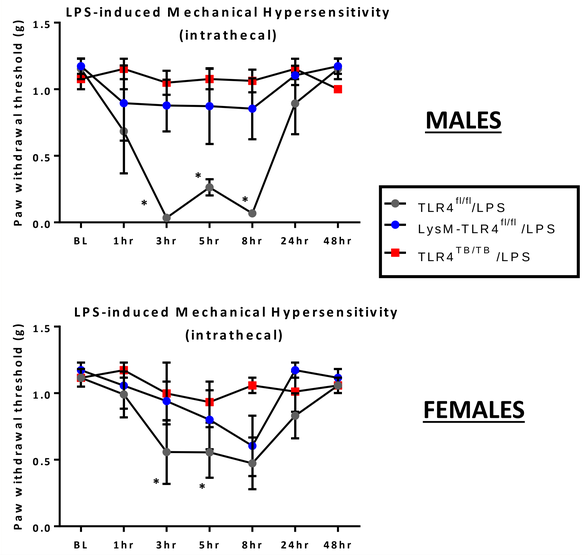


FIGURE 2. Sex- and cell-specific ablation of TLR4.

Sex Differences in Spinal Toll-like receptor 4



CONCLUSIONS

- Utilizing genetic tools to specifically remove TLR4 from nociceptors or macrophages yields a female and male, dependency, respectively in acute mechanical hypersensitivity and the transition to a chronic pain state as measured with hyperalgesic priming.
- Collectively our work demonstrates a cell-specific TLR4 effect in acute pain plasticity and in the transition to a chronic pain state.

REFRENCES

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