An essential role for eIF4E phosphorylation in peripherally-mediated pain plasticity

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ABSTRACT

Aim of Investigation

Translational control of gene expression is a key process for the regulation of plasticity in the nervous system. Multiple lines of evidence indicate that translation control plays a critical role in peripheral pain plasticity but precise mechanisms underlying this effect have not been elucidated. Here we have tested the hypothesis that eIF4E, which binds the 5'CAP of mRNAs, plays an important role in pain plasticity via upstream phosphorylation through the MAPK pathway, specifically ERK and MNK1/2.

Methods

We used transgenic mice harboring a Ser209Ala mutation in eIF4E to assess the role of eIF4E phosphorylation in pain plasticity. Behavioral testing was done of eIF4E^{S209A} mice and their wild-type (WT) littermates. We used biochemical techniques to assess changes in brain-derived neurotrophic factor expression in these mice. Finally, we used patch clamp electrophysiology to assess changes in excitability in nociceptors lacking eIF4E phosphorylation

Results

eIF4E^{S209A} mice showed clear deficits in behavioral hypersensitivity induced by nerve growth factor (NGF), interleukin 6 (IL6) and protease activated receptor type 2 (PAR2) agonists. Although overall protein synthesis rates (measured with sunset assay) were not lower in these mice, BDNF protein expression was markedly reduced indicating that eIF4E phosphorylation selectively targets certain mRNAs in DRG neurons. Electrophysiological characterization of DRG neurons from eIF4E^{S209A} revealed no differences in baseline properties, however, hyperexcitability induced by NGF was abrogated in transgenic mice. eIF4E^{S209A} mice also showed blunted cold allodynia following peripheral nerve injury suggesting a deficit in neuropathic pain. This effect was recapitulated in MNK1/2$^{-/-}$ mice indicating that targeting MNK1/2, the kinase for the S209A site in eIF4E, may be an effective therapeutic strategy. To that end, the MNK1/2 inhibitor, cercosporamide, reduced neuropathic cold allodynia and behavioral hypersensitivity mediated by NGF.

Conclusions

eIF4E phosphorylation plays a crucial role in sensitization of the peripheral nervous system following injury. Therefore, targeting eIF4E phosphorylation via the ERK/MNK1/2 pathway is a novel target for the manipulation of pain plasticity.

Acknowledgements

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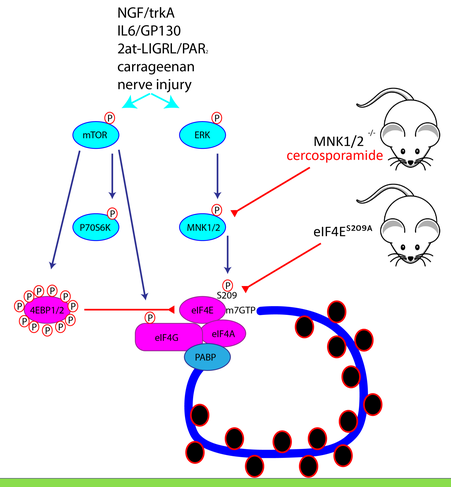
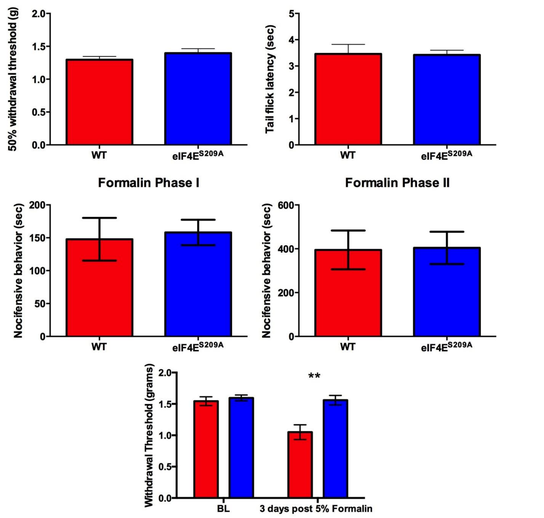


HYPOTHESIS

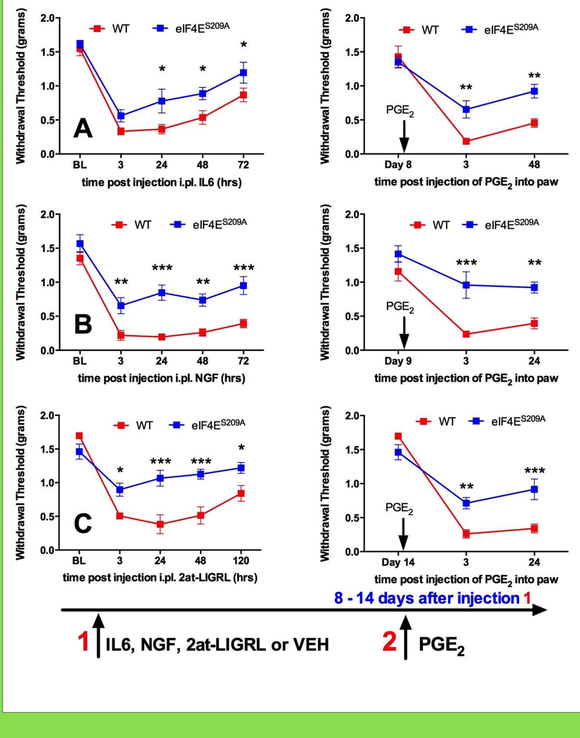
MNK/eIF4E signaling is critical for nociceptor plasticity leading to chronic pain

RESULTS

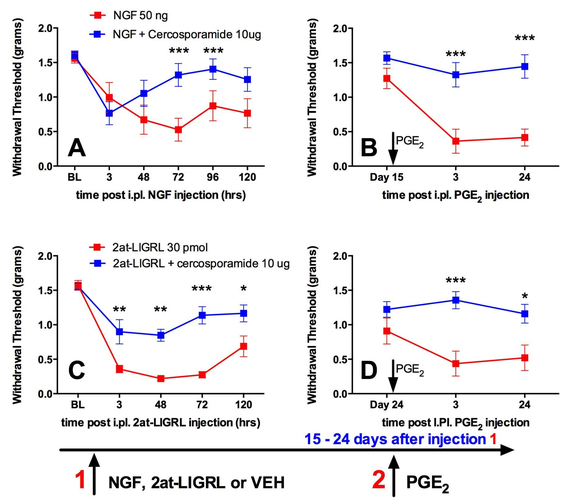
eIF4E^{S209A} mice have normal acute pain responses but fail to show mechanical hypersensitivity to formalin



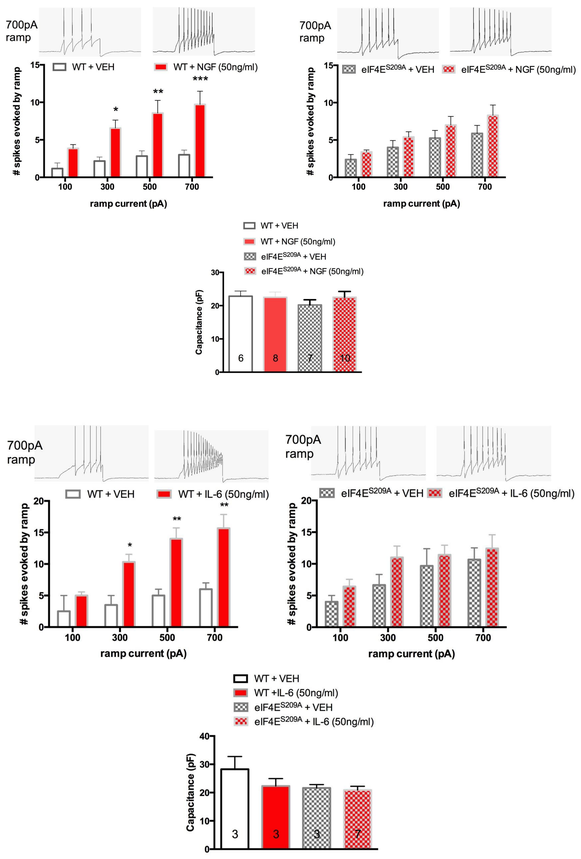
eIF4E^{S209A} mice show decreased acute mechanical hypersensitivity to algogens and fail to develop hyperalgesic priming



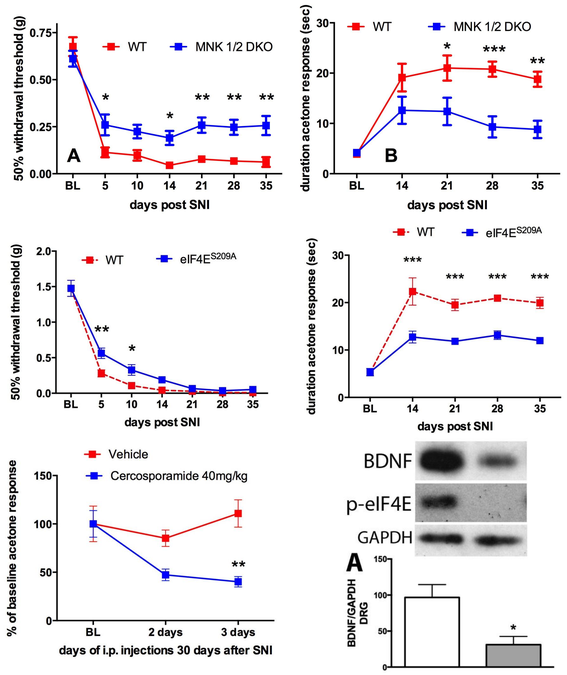
Local injection of the MNK inhibitor cercosporamide attenuates acute mechanical hypersensitivity and blocks the development of hyperalgesic priming



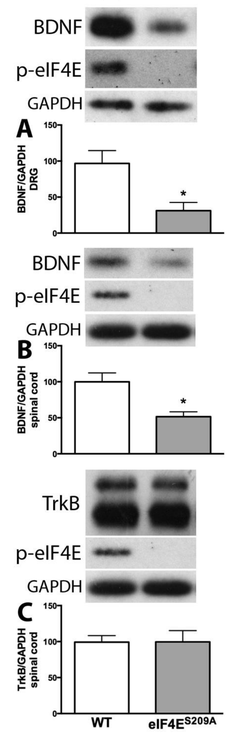
eIF4E^{S209A} mouse DRG neurons *in vitro* fail to sensitize in response to nerve growth factor or interleukin 6



MNK1/2$^{-/-}$ and eIF4E^{S209A} mice show deficits in neuropathic pain in the SNL model, an effect that is recapitulated by cercosporamide treatment



BDNF expression is decreased in the DRG and spinal cord of eIF4E^{S209A} mice whereas TrkB expression is normal



Conclusions

1. MNK/eIF4E signaling plays a crucial role in sensitization of nociceptive neurons
2. eIF4E phosphorylation may control the translation of mRNAs involved in pain plasticity, such as BDNF
3. MNK represents a new pharmacological target for the manipulation of pain plasticity
4. Future work will focus on mRNAs in the DRG that are targeted by eIF4E phosphorylation and how these proteins contribute to sensitization of nociceptors