RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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Controlling Acute Peripheral Pain with Modified Gut Bacteria: An fMRI Study

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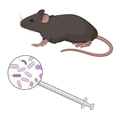
Abstract

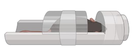
This study assessed the pain-alleviating potential of human gut microflora using functional MRI in a mouse model of acute pain. Three analgesic bacterial strains were tested (HB-32, HB-345, and HB-1074) against an analgesic control (meloxicam) and a bacterial control (LGG). Mice were gavaged with test articles and imaged while fully awake in response to noxious stimulation via Complete Freund's Adjuvant (CFA) injection into the hind paw. The pain was associated with a robust increase in negative BOLD signal that was alleviated by meloxicam in males but not females. The most robust reduction of negative BOLD signal was provided by HB-1074 in females. The study suggests sex differences in bacterial analgesic responsiveness, emphasizing sex-specific considerations in microbiome-based pain therapeutics.

Experimental Design

Days 1-6



Treatment via Oral Gavage
- *Procedural Control:* Saline
- *Analgesic Control:* Meloxicam
- *Bacterial Control:* LGG
- *Test Analgesic Bacteria:* HB-32, HB-345, HB-1074



Acclimation
- Training for conscious fMRI scanning

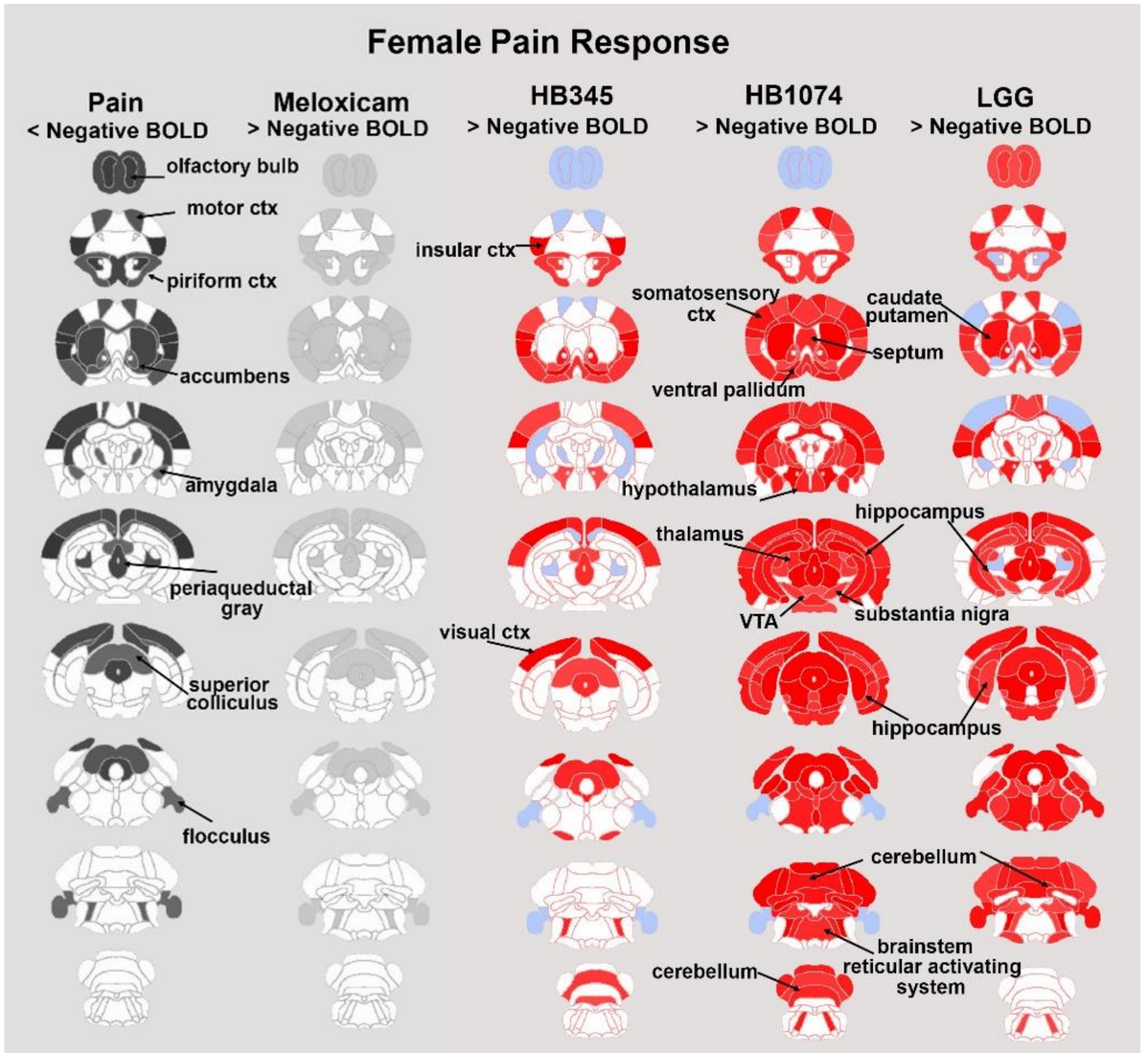
Day 7

Noxious Stimulus
- Complete Freund's Adjuvant injection

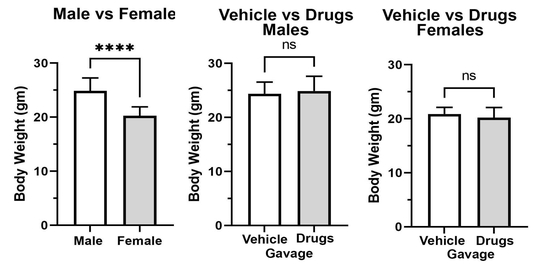
7T Magnetic Resonance Imaging
- Functional MRI measures alterations in blood oxygen level-dependent (BOLD) signal in response to CFA and test articles

Hot Plate Test
- Peripheral sensitization phenotypes

Reduction of Pain-Induced Negative BOLD Signal



The pain induced by CFA was characterized by an increase in negative BOLD 30 min post injection in brain areas associated with pain processing. Changes in positive BOLD were minimal in this model. The analgesic meloxicam used as a positive control blocked the increase in negative BOLD in males but not females. HB-32 had little to no effect on pain-induced negative BOLD signal. HB-345 showed modest activity in female and male mice to reduce pain-induced negative BOLD. HB-1074 had a robust effect in females reducing negative BOLD in the pain circuitry and globally over much of the brain. HB-1074 had a modest effect in males reducing BOLD signal; however, the reduction was unrelated to pain neural circuitry. The commercially available probiotic LGG also had a robust effect in females reducing negative BOLD in pain circuitry and globally while having little effect in males.



Body weights taken before imaging were significantly different between male and females but not between gavage treatments. The behavioural assay for pain was inconclusive.

Discussion

The increased negative BOLD signal characteristic of CFA induced pain was significantly reduced by meloxicam in male animals, serving as a partial positive control for evaluating the activity of test articles. HB-1074 had a highly significant global effect on reducing negative BOLD in females but not males. This drug effect was also true of LGG in females but not males. The CFA model of peripheral pain combined with functional MRI can be used to evaluate brain neural circuitry affected by novel analgesics; however, the MRI data suggest a significant sex difference in responsivity to traditional and novel therapeutics. As well, assessment of behavioural and peripheral sensitization phenotypes should be tested in a separate study, and likely requires different time points

Acknowledgements

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EKAM
THE IMAGE OF DRUG DISCOVERY