

GUT-BRAIN AXIS ALTERATIONS IN A NITROGLYCERIN MODEL OF MIGRAINE: FROM MICROBIOTA DYSBIOSIS TO TRIGEMINAL SENSITIZATION

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Background. Growing evidence implicates the gut–brain axis in migraine pathophysiology; however, the mechanisms linking gut microbiota (GM) dysbiosis, microbial metabolites, intestinal inflammation, and trigeminal nociception remain poorly understood. Here, we investigated these mechanisms in a nitroglycerin (NTG)-induced chronic migraine model.

Methods. Adult male rats received five injections of NTG (5 mg/kg, i.p.) or vehicle every other day over a 9-day period. Trigeminal nociceptive sensitization was assessed 4 hours after the last administration, using the orofacial formalin test. Gut microbiota composition was analyzed in fecal samples by 16S rRNA gene sequencing. Differential abundance analysis was assessed using DESeq2, while PICRUSt2 was used to predict microbial functional profiles. Fecal and serum short-, medium-, and long-chain fatty acids were quantified by GC–MS. Inflammatory markers were evaluated in ileum, colon, and cervical spinal cord by RT-qPCR.

Results. Compared with controls, NTG-treated rats exhibited significant trigeminal hyperalgesia at the orofacial formalin test. Alpha diversity of the gut microbiota was unchanged, whereas beta diversity analysis revealed a distinct microbial community structure in NTG-treated rats. Differential abundance analysis showed a reduction in specific Firmicutes taxa and an enrichment of Bacteroidota-associated taxa, including members of the Rikenellaceae family and the Clostridia_vadinBB60_group genus. Functional prediction indicated an increased representation of microbial pathways involved in fatty acid biosynthesis. Among the measured metabolites, fecal propionic acid levels were significantly elevated in NTG-treated animals, while other fatty acids remained unchanged. Intestinal inflammation was characterized by increased expression of IL-1β and IL-6 in both the ileum and colon. At the central level, NTG induced an upregulation of IL-6 and downregulation of IL-4 expression in the cervical spinal cord.

Conclusions. Chronic NTG exposure induces trigeminal nociceptive sensitization accompanied by gut microbial dysbiosis, selective elevation of fecal propionate, intestinal inflammation, and central neuroimmune activation. These findings support the involvement of gut–brain axis-related mechanisms, whereby microbiota-associated metabolic and immune alterations may contribute to migraine-related trigeminal sensitization.