MedicalXpress

Anti-inflammatory drug and gut bacteria have a dynamic interplay, according to study

January 5 2016, by Karen Kreeger

A nonsteroidal anti-inflammatory drug (NSAID) changed the composition and diversity of gut microbes, which in turn shaped how the drug is broken down and ultimately, cut its effectiveness, according to an animal study from the Perelman School of Medicine at the University of Pennsylvania. Gut bacteria that make up the gastrointestinal microbiome play an important role in the metabolism of most chemicals humans ingest, motivating studies of microbe-driven breakdown of clinically important drugs. In fact, gut bacteria are involved in the digestion of over 30 U.S. Food and Drug Administration (FDA)-approved drugs.

In findings published this month in eLife, first author Xue Liang, PhD, a postdoctoral researcher in the lab of senior author Garret A FitzGerald, MD, chair of the department of Systems Pharmacology and Translational Therapeutics and director of the Institute for Translational Medicine and Therapeutics, found that interactions between gut bugs in mice and the NSAID indomethacin (similar to ibuprofen and naproxen) inhibit the action of cyclooxygenases (COX) -1 and -2. NSAIDs block these COX enzymes and reduce fatty acids called prostaglandins in the body. Because of this, NSAIDs reduce inflammation, pain, and fever. However, since prostaglandins that protect stomach lining cells and promote blood clotting are also reduced, NSAIDs can promote ulcers and bleeding in the stomach.

The team tested indomethacin in mice at clinically relevant doses during both acute and chronic exposure. Both doses suppressed production of prostaglandins and caused damage to the small intestine of the mice,

reminiscent of the upper and lower gastrointestinal complications induced by NSAIDs in humans. This damage included increased permeability, ulceration, bleeding, and perforation in the intestinal tract.

Deep gene sequencing of gut microbiota showed that exposure to both doses of indomethacin in animal experiments shifted the composition of intestinal bacteria towards a pro-inflammatory structure, including the expansion of Peptococcaceae species and Erysipelotrichaceae species in the gut microbiota, as well as the underrepresentation of the S24-7 species in fecal microbiota.

To test the impact of intestinal microbes on the metabolism of indomethacin, the team used antibiotics to deplete the microbiota, then compared metabolism in treated and control mice. The antibiotic suppression of intestinal bacteria significantly reduced activity by the bacteria enzyme β-glucuronidase. In the absence of the enzyme, indomethacin reabsorption into the circulation was reduced, resulting in increased elimination, a shortened half-life, and reduced exposure to the drug. Consequently, the ability of the drug to suppress pro-inflammatory prostaglandins was impaired.

"Humans show considerable individual differences in the composition of their gut bacteria due to genetics, age, diet, time of day, and pets, among other factors, and therefore likely their responses to indomethacin," Liang said. "The drug-microbe interactions in this study provide clear-cut candidate mediators of individualized drug responses to be studied in the future."

The researchers suggest that the findings open up many new questions for future studies. For example, they aim to investigate whether gut microbiota composition would be differently influenced by COX-1- or COX-2-specific inhibition, given that COX-2 inhibitors show less gastrointestinal complications. The team also plans to explore if

alterations in gut microbiota composition are a driver or a passenger in gastrointestinal ailments, following ingestion of indomethacin. Given that the investigators have previously shown the influence of the host molecular clock on the gut microbiota, they will also ask if taking this NSAID at different times of day might lead to higher efficacy and less side effects in animal models and eventually in humans.

More information: Xue Liang et al. Bidirectional interactions between indomethacin and the murine intestinal microbiota, *eLife* (2015). DOI: 10.7554/eLife.08973

Provided by University of Pennsylvania