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EDITORIAL

Aluminum Meddles With Visceral Pain Perception

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder that afflicts 10%–25% of the population in developed countries. Human ingestion of aluminum has increased in these countries as a result of its use as a food additive and unintended exposures because of groundwater contamination. Mimicking estimated average human ingestion of aluminum via administering it orally to rats increases their perception of visceral pain. These results suggest a possible role for increased exposure to aluminum in driving the post-mid-20th-century increased incidence of IBS.

Symptoms of IBS vary between patients but include diarrhea, constipation, and visceral pain. Despite histologically normal intestinal biopsy specimens, biological signatures of IBS include alterations in intestinal gene expression, increased gut permeability, and changes in gut microbiota composition. Thus, although the cause(s) of IBS are not defined, these and other data highlight the enormous breadth of factors that might play a role in this disorder.[1] Similar alterations also are associated with inflammatory bowel disease (IBD), although the magnitude of changes is typically greater in IBD. Nevertheless, these data suggest that IBS and IBD may share triggers and pathogenetic mechanisms. That prevalence of both IBS and IBD have shown marked increases in incidence, roughly paralleling the modernization of society that accelerated in the mid-20th century, raising the possibility that environmental factors associated with human activity may be a driver of both diseases. A study by Esquerre et al[2] in this issue of *Cellular and Molecular Gastroenterology and Hepatology* suggests that aluminum may be one such trigger.[2]

Although human beings have always had some degree of exposure to aluminum, the most abundant metal on earth, industrialization has increased the magnitude of exposure owing to the use of aluminum salts as stabilizers in processed foods and the concentration of ground water aluminum in agricultural products. This has led to the hypothesis that aluminum may contribute to intestinal disease.[3] Consistent with this, aluminum has been shown to exacerbate experimental IBD in mice.[4] Esquerre et al[2] now have shown that aluminum ingestion can augment visceral pain perception in rats, suggesting it also might play a role in IBS.

No animal models perfectly recapitulate IBS. Nevertheless, sensitivity to visceral pain has become a commonly used proxy for IBS development. Esquerre et al[2] assessed the impact of aluminum ingestion on the threshold pressure needed to induce visceral pain, as shown by abdominal contraction in rats. They observed that as little as 1 week of aluminum ingestion at doses thought to mimic typical exposure of human beings to aluminum in developed countries resulted in significant decreases in threshold pressures needed to induce visceral pain. The reduced pain thresholds persisted as long as aluminum exposure continued, but faded when exposure was discontinued. These rats were hypersensitive to aluminum upon re-exposure. Further analyses indicated intertwined roles for mast cells and protease-activated receptors in aluminum-induced sensitization to visceral pain.

Although the observations by Esquerre at al[2] support the plausibility that aluminum ingestion might contribute to the incidence of IBS, determining the extent to which it might actually be doing so remains an important challenge. Their hypothesis predicts that individuals exposed to high levels of aluminum would have increased the incidence of IBS and that IBS incidence might vary regionally in accordance with aluminum ingestion. Unfortunately, only broad societal estimates of aluminum exposure are available, and aluminum levels are difficult to measure in individuals. One also might question the relevance of this rat model because human and rodent sensitivity to toxins can vary markedly, thereby making it difficult to estimate human risk based on rodent studies. Another limitation of the current study was that constipation and diarrhea were not present in the model used. Nevertheless, it is interesting to note that sensitivity to aluminum was greater in female rats, relative to male rats, mirroring the gender bias of human IBS. Overall, this work, along with previous studies, suggests that aluminum ingestion may contribute to modern diseases of the gastrointestinal tract, including IBS, and, consequently, that human aluminum ingestion deserves careful scrutiny.

ALEXIS BRETIN, PhD
ANDREW T. GEWIRTZ, PhD
Center for Inflammation, Immunity and Infection
Institute for Biomedical Sciences
Georgia State University
Atlanta, Georgia

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Correspondence
Address correspondence to: Andrew T. Gewirtz, PhD, Center for Inflammation, Immunity, and Infection, Institute for Biomedical Sciences, Georgia State University, Atlanta, Georgia 30303. e-mail: agewirtz@gsu.edu.

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