

Propionic Acid-Producing Bacteria as Provocateurs of Anxiety and Depression? [Letter]

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Dear editor

In a recent study published by Zhao et al, the authors made an important contribution to the complex discourse surrounding the comorbidity of irritable bowel syndrome (IBS) and mental disorders.¹ In particular, the authors discovered significant and positive relationships between Patient Health Questionnaire-9 (PHQ-9) scores and an abundance of *Monoglobus* and *Lachnospirillum* spp. They also linked *Subdoligranulum* and *Holdemanella* genera to abundances to Generalized Anxiety Disorder 7-Item (GAD-7) scores. Given that *Lachnospirillum* spp. are generally recognized as pro-inflammatory gut microbiota, the authors focused their mechanistic discussions on *Lachnospirillum*, and concluded their study by pointing toward the species as a potential marker of IBS.

We agree with the arguments made by Zhao et al and are hopeful that their efforts will be widely disseminated and used as a roadmap for investigators to follow. Here, we would like to add one mechanistic pathway that was not considered by the authors. Notably, *Lachnospirillum*, and *Subdoligranulum* have one important feature in common—they are associated with a more abundant pool of propionic acid. Elevations in propionic acid, in turn, contribute to the growth of *Monoglobus*, the genera that Zhao et al linked to depression. Although short-chain fatty acids are often painted with same universally-beneficial brush, there is ample evidence to demonstrate an undesirable side of propionic acid, an aspect that can potentially explain the findings of Zhao et al.

First, elevated levels of fecal and blood propionic acid have been noted in IBS, especially IBS-D,² the subjects under scrutiny by Zhao et al. Second, multiple preclinical studies demonstrate that propionic acid is a potential neurotoxin. Propionic acid can cross the blood-brain barrier and induce inflammation, oxidative stress, mitochondrial dysfunction, while influencing and neurotransmission and gene expression.³ Indeed, propionic acid has been linked to increased anxiety and impairments in typical social behavior among animals.^{4,5} When paired with emerging research on the neuropsychiatric aspects of propionic acid, and IBS-D, we suggest that Zhao et al have opened up an important area of research, one that might provide a vital link in the complex chain of IBS.

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