

# Stress co-opts the gut to affect epileptogenesis. Commentary on “Facilitation of kindling epileptogenesis by chronic stress may be mediated by intestinal microbiome”

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There is now a consensus that a gut microbiome-brain axis exists that can profoundly affect neurological function.<sup>1</sup> Alterations in the gut bacterial composition have been shown to alter a number of neurological diseases in animal models, ranging from Parkinson's disease<sup>2</sup> to various neuropsychiatric conditions.<sup>3</sup> Gut microbiome composition can be altered in various ways; in fact, it is increasingly likely that the effects of the ketogenic diet may involve alterations in the gut microbiome.<sup>4</sup> Chronic stress also alters the gut microbiome<sup>5</sup> and this is now considered a likely mechanism for the well-known effects of stress on behavior and neurological function. Stress is also known to alter brain excitability, with chronic stress being pro-epileptic.<sup>6</sup> In this short communication, Medel-Matus and colleagues<sup>7</sup> have asked if the effects of stress on kindling may be mediated by alterations in the gut microbiome. To test this, they depleted gut bacteria in rats with an antibiotic regimen and reconstituted the microbiome with fecal transplants from either chronically stressed or unstressed donors. When the recipient rats were subsequently subjected to a 7d kindling protocol, rats that had received the stressed fecal microbiome progressed more quickly to stage 4/5 seizures and seizures were of longer duration than in recipients of the unstressed microbiota. In fact, the respective microbiota-transplanted rats kindled in a manner that was identical to that seen in rats that were either chronically stressed or unstressed—that is, stressed microbiota transplantation mimicked the effects of stress on non-transplanted, kindled rats. Even more remarkable, transplantation

of unstressed microbiota was able to reverse the effects of stress in recipient rats.

This study, as admitted by the authors, is preliminary and lacks mechanistic insight. However, it complements a study that appeared almost concurrently showing that the effects of the ketogenic diet on seizures in mice were mediated by changes in the gut microbiome.<sup>8</sup> It is interesting that the current study did not reveal any alteration in brain excitability (revealed by after-discharge threshold) as a function of the transplantation of the “stress” microbiota. Previous studies have reported that rodent models with colitis-induced gut dysbiosis do show increased brain excitability.<sup>9</sup> Perhaps stress and experimental colitis have different effects on the gut.

This study raises many questions and opens the door to a host of experiments. How is the gut dysbiosis communicated to the brain? Is it via the vagus,<sup>10</sup> or are circulating pro-inflammatory molecules or immune cells trafficked to the brain<sup>11</sup>? How does the stress alter the composition and diversity of the microbiome and what are the bacterial or digestive products that are causal for the subsequent kindling changes? Stress is known to increase levels of pro-inflammatory molecules in the brain; as some of these molecules facilitate seizures and epilepsy,<sup>12</sup> are the different fecal transplants associated with different inflammatory states in the brain? Finally, does kindling itself alter the gut microbiome and is part of the development of the kindled state due to changes in gut microbiome? This could possibly be tested in germ-free animals.

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It is important to recognize that while a “stressed” microbiome is pro-epileptic, it does not itself cause epilepsy, although to the best of my knowledge this has never been tested in long-term stressed animals. However, as the authors suggest, the presence of a dysbiotic microbiome in conditions as varied as autism spectrum disorder and colitis may underlie the increased incidence of co-morbid epilepsy in these conditions.<sup>13</sup>

The findings from this study also raise important issues concerning our experimental protocols. As rodents are coprophagic, experimental and control animals must be kept separate to ensure that the gut microbiome is not “normalized” by this behavior. Furthermore, since “stress” can be socially transmitted,<sup>14</sup> similar care must be exercised to avoid interactions between stressed and unstressed animals in experimental epilepsy studies.

In summary, this article is worthy of recognition in the journal because it is ground breaking in the epilepsy field, with exciting data that will undoubtedly lead to a better understanding of the mechanistic underpinnings for co-morbidity in epilepsy and other medical conditions. One looks forward to follow-up studies to explore these matters from the authors’ laboratories. In addition, we hope that a study will be forthcoming examining the gut microbiota in patients with epilepsy under varying stressful conditions.

## CONFLICT OF INTEREST

The author has no conflict of interest to disclose.

I confirm that I have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Read the winning article: “Facilitation of kindling epileptogenesis by chronic stress may be mediated by intestinal microbiome”

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