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Gut Dysbiosis was Inevitable, but Tolerance was not: Temporal Responses of the Murine Microbiota that Maintain its Capacity for Butyrate Production Correlate with Sustained Antinociception to Chronic Voluntary Morphine

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Prolonged opioid use can produce tolerance to the analgesic effects, necessitating dose escalation for continued pain management, thereby increasing liability for opioid use disorder (OUD). In rodents, as with humans, not all individuals develop the same degree of tolerance and OUD even when receiving the same drug dose. Alterations in the gut microbiota have been shown to both ameliorate and exacerbate analgesic tolerance. We hypothesized that microbiota composition might explain the variability in degree of tolerance. To examine this hypothesis, we used a murine model of chronic oral morphine self-administration that preserved and leveraged natural variation in both degree of analgesic tolerance and the microbiota and performed a comprehensive examination of microbiota associations with degree of tolerance. Whereas mice developed variable degrees of tolerance, they all shared global morphine-induced microbiota changes, particularly a depletion of beneficial community members and an expansion of pathobionts. Though these global changes were informative, they obscured more nuanced microbiota signatures that differentiate tolerant from non-tolerant mice. High-resolution temporal analyses revealed a divergence in the progression of dysbiosis and the response of the microbiota to morphine disturbance between tolerant and non-tolerant mice. Specifically, non-tolerant mice maintained a higher abundance of butyrate-producing bacteria. We also found that butyrate supplementation significantly reduced the development of tolerance. This study highlights the role of butyrate as a potent protective tool to counter adverse effects of morphine-induced dysbiosis and points to a potential therapeutic target to curtail the treatment-limiting side effects of prolonged opioid use.

Hyperlink to relevant publication: https://pubmed.ncbi.nlm.nih.gov/38659831/