



Oxytocin and the microbiome

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ABSTRACT

The mammalian host microbiome affects many targets throughout the body, at least in part through an integrated gut-brain-immune axis and neuropeptide hormone oxytocin. It was discovered in animal models that microbial symbionts, such as *Lactobacillus reuteri*, leverage perinatal niches to promote multigenerational good health and reproductive fitness. While roles for oxytocin were once limited to women, such as giving birth and nurturing offspring, oxytocin is now also proposed to have important roles linking microbial symbionts with overall host fitness and survival throughout the evolutionary journey.

Trillions of cells in the human body work together in complex regulatory and immune mechanisms to maintain homeostasis and achieve good health. Over the course of human evolution, thousands of microbial species have colonized the human host and now comprise more than half of the cells in our bodies. These organisms are primarily found on the major barriers between the human body and its environment: the skin, the mouth, airways, and most extensively the gastrointestinal tract [1]. While hominids have evolved to have a gut microbiome, every individual's gut microbiome is unique. The architecture of a person's gut microbiome develops alongside its host and is influenced by elements of its environment like diet, exposure to pathogens, and host genetics [2]. However, everyone's gut microbiome is initially influenced by their mother's; pioneer microbes inhabit the gut microbiome perinatally and derive from the mother's vaginal and fecal microbiota (Fig. 1) [3,4]. The gut microbiome has a significant impact by influencing metabolic pathways and the maturation of the immune system [5–7]. This is accomplished via a paradigm known as the gut-brain-axis wherein gut microbiota can communicate with the rest of the human body through the vagus nerve, thus controlling many elements of human growth and development (Fig. 1) [8,9]. The gut microbiome similarly communicates directly and indirectly with the host's immune system and can signal the release of various immune cells and factors as needed to mitigate risk for disease and infection [10]. A part of this response is controlled via the hypothalamic-adrenal-pituitary axis, which releases hormones particularly important in a host's stress response [11].

Including these immune factors, the gut microbiome influences many targets throughout the body by means of the gut-immune-brain axis. One contributor that has drawn significant research interest over

the last few decades is oxytocin, a neuropeptide hormone primarily synthesized in the hypothalamus. Oxytocin's importance to human health and survival begins with social bonds prior to conception and continues as oxytocin is essential for stimulating contractions inducing labor in pregnant mothers [12]. Once their offspring are born, mothers rely on oxytocin to bond with their babies and to stimulate lactation, making it easier for the offspring to breastfeed [13]. For a while, the scope of knowledge about oxytocin was limited to women and giving birth. However, a growing body of research suggests that oxytocin is exceedingly important to human health [14] and development, and may even be a driving force of human evolution [15,16]. Humans are an exceptionally social species and rely on communities for all facets of our lives, including sharing knowledge, child rearing, and partnership. Oxytocin is fundamental to the mechanisms that allow humans to form relationships, both social and intimate, which inevitably leads to building strong communities and the prospect of reproduction across generations [12,17–19].

Like the gut microbiome, oxytocin plays a role in maintaining homeostasis by modulating the immune system [10,11,20–23]. In 2013, fundamental discoveries involving interactions between oxytocin and the gut microbiome and the immune system paved the way for further exploring these mechanisms in whole body health [10]. To study these pathways, several studies have examined a subject's ability to heal skin wounds efficiently. Wound healing is accomplished through a balance of pro- and anti-inflammatory factors working in tandem with each other. The importance of the immune system in this process suggests that a host's ability to recover after injury could be a reasonable indicator to the health of the organism [10,11,24]. Like wound healing, the process

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of sustained good health also involves a complex balance and interplay of pro-inflammatory and anti-inflammatory responses and immune interplay throughout the body. In the 2013 study, Poutahidis et al. used an isolate of *Lactobacillus reuteri*, a beneficial probiotic microbe that was originally isolated from human breast milk, and administered the microbial treatment to mice as a supplement in regular drinking water in order to measure its effect on tissue injury repairs [10]. Amazingly, the mice that were treated with *L. reuteri* exhibited not only accelerated wound healing and displays of reproductive fitness, but also demonstrated increased circulating levels of oxytocin [10,24,25]. These studies also revealed that treatment with *L. reuteri* and the accompanying boost in endogenous oxytocin levels accelerated the wound infiltrating pro-inflammatory neutrophils, for example, and at the same time enhanced the potency of anti-inflammatory T_{REG} cells in immune cell titration assays [10]. These results exhibited that microbiota were interacting with host mechanisms to control oxytocin production and improve wound repair in some capacity.

To further investigate the pathways of communication between the gut microbiome and brain mechanisms that regulate oxytocin levels and release, vagotomies were performed to interrupt the vagus nerve transmissions between brain and gut in a cohort of mice as previously done in Bravo et al. 2011 [26]. Even when treated with *L. reuteri*, mice with vagotomy surgery did not show any of the previous signs of accelerated wound healing nor upregulated oxytocin. This revealed that the microbial mechanism involved the gut-brain-axis via the vagus nerve to communicate and influence oxytocin circulation to favor mammalian host and microbial survival (Fig. 2) [10]. Interestingly, the study found that wounds healed faster in vagus-intact mice. *L. reuteri* supplementation accelerated the timing of immune cells reaching the skin wound, but did not alter the types of immune cells involved. Thus, both beneficial pro-inflammatory and anti-inflammatory immune cells were normally represented in the robust wound repair process albeit more rapidly in probiotic-treated animals. Elegant adoptive immune cell

transfer experiments demonstrated that oxytocin was required for that effect. Taken together, findings in the 2013 study showed that a human breast milk-derived microbe boosted host injury repair via a vagus nerve-dependent gut-brain-immune axis mechanism, leading to unifying hypotheses of microbial symbionts boosting oxytocin in ways pivotal in mammalian health and survival [10]. These results further support that this symbiotic relationship between microbe and human yields beneficial immunological effects like physically healing wounds and restoring an individual's healthy phenotype (Fig. 1).

The physical manifestation of this beneficial immune paradigm extends beyond cutaneous barriers. Various studies investigated mouse weanlings that inherited a dysbiotic gut microbiome from their mothers who either had an infection or were fed a high-fat and low-fiber diet during pregnancy and eventually developed ASD-like phenotypes [27–29]. The prevalence of autism spectrum disorder (ASD) has been steadily climbing over the last few decades [30]. Social deficits and metabolic comorbidities, like constipation and diarrhea [31], caused by an unbalanced gut microbiome are two common symptoms that people with ASD experience [32]. While the occurrence of ASD is influenced by both environmental and genetic factors, researchers have discovered that oxytocin upregulation could be leveraged as a treatment for social deficits in individuals with ASD. Indeed, there is abundant evidence for a gut microbe-brain connection in this paradigm. Researchers discovered that germ-free mice, or mice that were treated with an abundance of antibiotics to wipe out the gut's microbiota, exhibited abnormal behaviors and some phenotypic characteristics of ASD [33,34], similar to those fed the high-fat and low-fiber diet [27,28]. Expanding on the research conducted by Poutahidis et al. (2013), these mice that were fed a poor diet were then treated with the same strain of *L. reuteri* (ATCC-PTA-6475) which upregulated endogenous oxytocin [10,27,28,39]. These mice exhibited fewer sociability deficits compared to their untreated counterparts.

The pregnant females that were fed a fast-food-style diet had lower

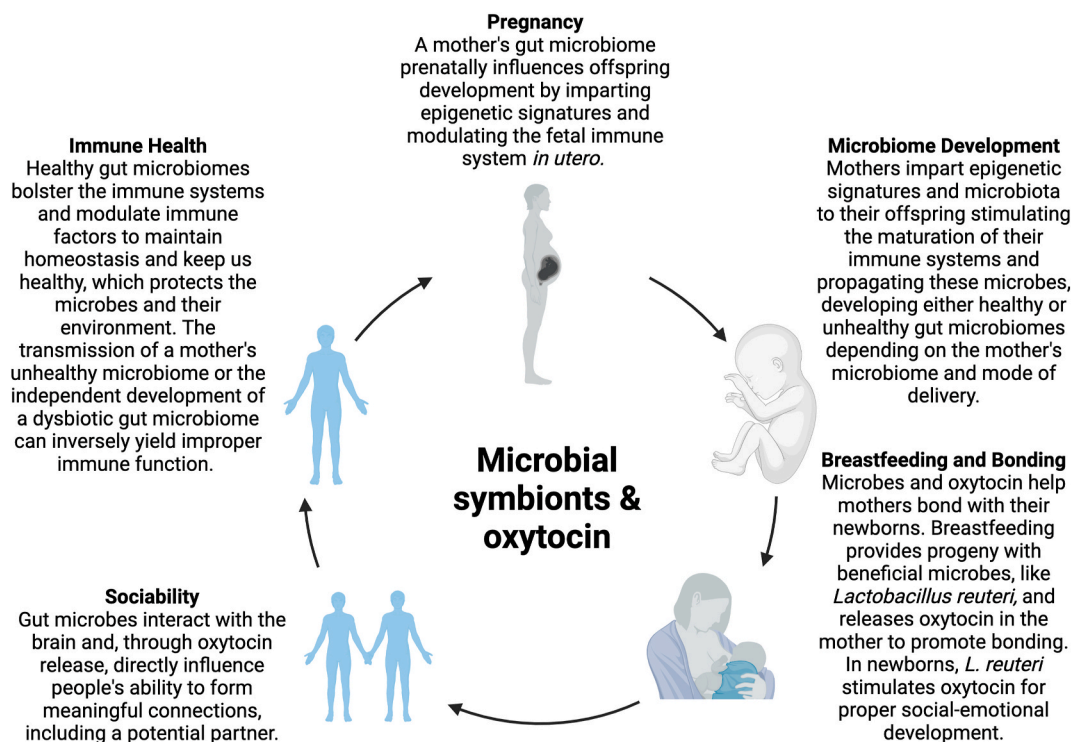


Fig. 1. Humans and the microbes that colonize their guts have developed a symbiotic relationship over the course of evolution. Microbes live on the surfaces where humans interface with their environments. This causes factors like diet, pathogens, the environment, and genetic predispositions to influence our relationship with our gut microbiomes and its outputs. Oxytocin and the gut microbiome are at the center of many of the human body's functions. Both oxytocin and the gut microbes are integral in various capacities to the stages of human life like pregnancy and breastfeeding, immune health and microbiome development, and bonding and sociability. Taken together with parallel evidence from animal models this paradigm supports multigenerational health for both the microbes and their hosts.

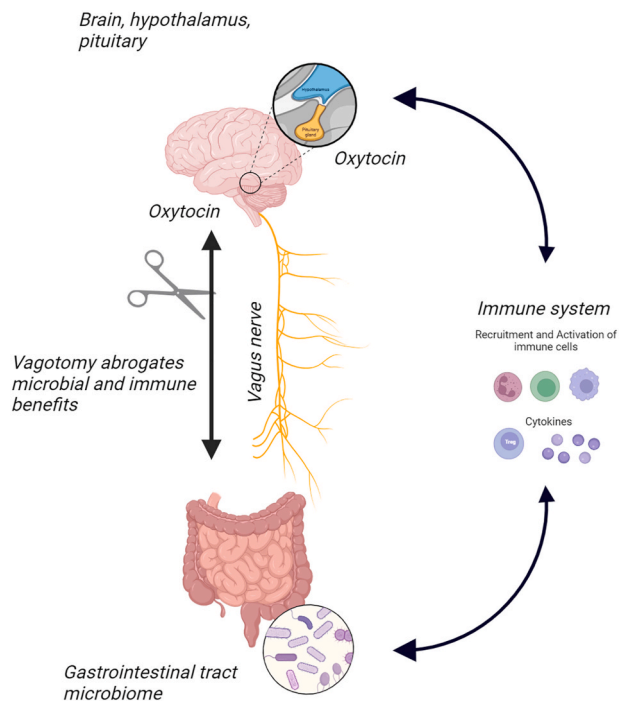


Fig. 2. The gut microbiome modulates host immune responses via the gut-brain-immune axis through a variety of mechanisms including microbial community dynamics and circulating microbial products and immune factors. Among these mechanisms, the vagus nerve allows gut microbes to communicate with the brain and modulate the immune system and maintain homeostasis in the host's body. As demonstrated in Poutahidis et al., 2013, vagotomies, which sever this line of communication, block gut-mediated immune modulation affecting the circulation, distribution, activation and potency of various immune cells [10].

counts of *L. reuteri*. As a result, their weanlings' gut microbiomes also had an altered ratio of good bacteria, specifically from *Bacteroidetes* and *Firmicutes* families, in their gastrointestinal tract [27,28,35]. A battery of sociability behavioral tests on these animals demonstrated that the mice with dysbiotic guts also had stunted social capacities. It's not conclusive how the relative abundance of microbes from the *Lactobacillus* family affects social capabilities in humans. Further testing needs to be done to determine whether microbiota stimulating endogenous oxytocin for therapeutics would be effective and safe for human subjects. However, specific microbes and pathways that are responsible for altering social behavior in individuals with ASD have not yet been extensively tested in this regard. Several other treatments are being tested for their efficacy in ameliorating typical ASD symptoms. Administration of exogenous oxytocin treated sociability deficits in patients with ASD or other psychiatric disorders are underway in various clinical trials [32,36]. Studies using fecal microbiome transplants to treat the social symptoms in ASD have also shown promise when tested in human subjects [37,38].

Difficulties with sociability is one of the major symptoms of ASD, but it is also a component of several other neurological and psychological disorders [1,35]. Separately, building upon a previous study implicating fast food-style diets and microbial dysbiosis with multigenerational effects of obesity, infertility, cancer and progeria [27,28,39], it was discovered that offspring had higher risk of hyperactivity, hyper-aggression, and antisocial tendencies, similar to symptoms of Fragile X Syndrome, a neurodevelopmental disorder mechanistically related to ASD. When mothers of these male offspring were administered *L. reuteri*, the severity of their symptoms were ameliorated [40,41]. Studies investigating anxiety, depression, and other psychological disorders demonstrated that boosting levels of oxytocin, whether administered exogenously or upregulated endogenously using microbe

interventions, improved symptoms of deficient or low sociability [36, 42–44].

There is no universal approach for leveraging the gut microbiome and oxytocin for prevention and treatment of these and other human diseases. In some instances, pre-emptive administration of probiotics like *L. reuteri* or synthetic oxytocin could reduce the possibility of developing these disorders from an early age, even *in utero* [39,41,45]. In others, oxytocin administration is coupled with probiotics to alleviate symptoms of neurological disorders, like ASD [46]. It was discovered that sterile lysates of *L. reuteri* alone could be used in place of whole organisms in order to stimulate endogenous oxytocin production in the hypothalamus and avoid concerns over live microbes entering the bloodstream in rodents [11]. Oxytocin-boosting therapy using microbiota like *L. reuteri* could be harnessed to prevent and treat obesity [14, 47,48]. *L. reuteri* is one of several recognized microbiota that interact with the immune system and the brain during wound repair. Other *Lactobacillus* strains including *L. plantarum* are successful microbial species for improving wound healing [46,49,50]. The microbe *Bacteroides fragilis* is particularly effective at inhibiting infections from other microbes, bolstering the immune system against foreign bodies [51].

Humans and their microbes are inextricably linked. The gut-brain-immune axis is integral to our health, both physical and mental. The entire extent to which our gut microbiome interplay with oxytocin influences our lives, however, is still unknown. Humans are complex beings that strive for holistic health, meaning they aspire to maintain mental, physical, emotional, and spiritual health, and gut microbes and oxytocin undoubtedly impact all spheres of human lives (Fig. 1). If our microbes impact our ability to form connections and be social with others, then perhaps they also influence the groups that we join, how we spend our time, and the people with whom we acquaint ourselves. While this is a burgeoning field of research that encompasses many biological and philosophical aspects of human life, researchers have started asking these questions [52]. Further research into the pathways of communication between the gut microbiome, the brain, and the immune system could yield better therapies and interventions for individuals diagnosed with dysbiotic guts and the neurological disorders associated with them. A reasonable place to start may be mapping the microbial species most often associated with a healthy gut to understand how to heal an unhealthy one. Some researchers have already started this work [53,54]. Slowly unraveling the mysteries of these microbial symbionts continues to bring us closer to answers and continues to shed light on the complex mechanisms that keep us healthy, build societies, and make us what we are.

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CRediT authorship contribution statement

Bernard J. Varian: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Katherine T. Weber:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Susan E. Erdman:** Conceptualization, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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