Received: 31 May 2019 | Revised: 2 September 2019 | Accepted: 3 September 2019

DOI: 10.1002/ajp.23053

COMMENTARY

AMERICAN JOURNAL OF PRIMATOLOGY WILEY

Primate microbial endocrinology: An uncharted frontier

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Funding information
National Science Foundation International Research Experience for Students, Grant/Award Number: 1559223; Indiana University Bloomington, Department of Anthropology, Grant/Award Number: Skomp Research Grant

Abstract

Gut microbial communities communicate bidirectionally with the brain through endocrine, immune, and neural signaling, influencing the physiology and behavior of hosts. The emerging field of microbial endocrinology offers innovative perspectives and methods to analyze host-microbe relationships with relevance to primate ecology, evolution, and conservation. Herein we briefly summarize key findings from microbial endocrinology and explore how applications of a similar framework could inform our understanding of primate stress and reproductive physiology and behavior. We conclude with three guiding hypotheses to further investigate endocrine signaling between gut microbes and the host: (a) host-microbe communication systems promote microbe-mediated stability, in which the microbes are using endocrine signaling from the host to maintain a functioning habitat for their own fitness, (b) host-microbe communication systems promote host-mediated stability, in which the host uses the endocrine system to monitor microbial communities and alter these communities to maintain stability, or (c) host-microbe systems are simply the product of coincidental cross-talk between the host and microbes due to similar molecules from shared ancestry. Utilizing theory and methodology for studying relationships between the microbiome, hormones, and behavior of wild primates is an uncharted frontier with many promising insights when applied to primatology.

KEYWORDS
microbe–hormone interactions, neuroendocrine system, reproduction, stress physiology

1 | INTRODUCTION

Often referred to as a second brain, the enteric nervous system of the gut is in constant communication with the brain. This complex bidirectional communication system, referred to as the gut–brain axis, operates through multiple pathways, including the endocrine system via microbial metabolites and gut hormones, the immune system via proinflammatory cytokines, and the neural system via the enteric nervous system, vagus nerve, and the spinal cord (Farzi, Fröhlich, & Holzer, 2018). As such, gut microbes that modulate hormones and neurotransmitters can use this communication pathway to elicit physiological and behavioral outcomes in the host (Bonaz, Bazin, & Pellissier, 2018; Clarke et al., 2014). For example, neurotransmitters such as dopamine, serotonin, and norepinephrine are directly produced by microbes (Clarke et al., 2014; O'Mahony et al., 2009; Sarkar et al., 2016), with more than 90% of host serotonin synthesized in the digestive tract (Gershon & Tack, 2007). Thus, the gut microbiota has been described as an additional endocrine organ (Clarke et al., 2014; Lyte, 2010).

Microbial endocrinology is an emerging area of interdisciplinary research that combines approaches from microbiology, neuroscience, and endocrinology to elucidate relationships between microbes and their host as mediated by hormones and other components of the host endocrine system. One guiding hypothesis in this field is that microbes have evolved mechanisms to recognize vertebrate host hormones to utilize them as environmental cues (Freestone, Sandrini,

Haigh, & Lyte, 2008; Lyte, 1993). Results thus far mainly stem from research on serum-based culture medias, laboratory rodents, and domesticated animals, with a focus on how microbes interact with hormones and endocrine functioning of the stress response and reproduction. Herein we briefly summarize these key findings from other systems and outline how applying a similar framework to primates will benefit our understanding of primate ecology, evolution, and conservation.

2 | MICROBIAL ENDOCRINOLOGY OF THE STRESS RESPONSE

Hormones involved in the stress response, such as catecholamines (e.g., epinephrine, norepinephrine, dopamine) and glucocorticoids, have long been known to interact with mammalian gut microbes (Eriksson, 1970; Liu, 2017). Using Gram negative bacteria cultures, Lyte and Ernst (1992) observed a significantly increased growth rate of *Yersinia enterocolitica*, in response to norepinephrine. They later hypothesized that this growth was due to pathogenic microbes evolving mechanisms to identify stress-related hormones (Freestone & Lyte, 2010), which could be an indicator of a suppressed host immune system. One mechanism allowing pathogenic bacteria to increase growth is extraction of otherwise inaccessible iron from the host after brief exposure to catecholamines (Freestone et al., 2000).

For glucocorticoids, which are the most commonly measured biomarker to quantify the stress response noninvasively in primates, microbes are known to metabolize host steroid hormones (Groh, Schade, & Hörhold-Schubert, 1993). For example, *Eggerthella lenta*, *Escherichia coli*, *Klebsiella* sp., and *Proteus mirabilis* correlate with an increase in 21-dehydroxylase activity, an enzyme that removes the 21-OH group from certain corticosteroids before they are excreted (Bokkenheuser, Suzuki, Polovsky, Winter, & Kelly, 1975). A variety of additional bacterial glucocorticoid-metabolizing enzymes have also been discovered (Devlin & Fischbach, 2015; Morris & Ridlon, 2017). Amato and Righini (2015) suggest that it is possible for increased glucocorticoid levels to coincide with decreased microbial diversity, since primates in degraded habitats have reduced microbial diversity and presumably experience higher allostatic load. Although no primate study has yet tested this hypothesis, in wild red squirrels (*Tamiasciurus hudsonicus*) it was found that fecal glucocorticoid metabolites were negatively correlated with bacterial diversity and that there was a positive relationship over time between fecal glucocorticoid metabolite concentrations and bacterial abundance of Pasteurellaceae, a family with known epizootic pathogens (Stothart et al., 2016). On the contrary, experimentally elevated basal glucocorticoid levels reduced pathogenic bacteria, including *Mycoplasma* and *Microvirga*, in the intestines of yellow-legged gulls (*Larus michahellis*; Noguera, Aira, Pérez-Losada, Domínguez, & Velando, 2018).

The processes by which changes in hormones of the stress response relate to host behavior is less clear. As described in the examples above, endocrine active chemicals are produced and/or regulated by microbes in the gut, which can then pass the intestinal epithelium to enter the bloodstream (Clarke et al., 2014). Host behavior could be affected if those altered levels of endocrine active chemicals enter the brain and bind to receptors that influence fear, aggressive, social, and reproductive behaviors. Thus far, the most reliable method used to test the effect of gut microbes on behavior compares germ free mice (GF) to specific pathogen free (SPF) mice. For example, Neufeld et al. (2011) found that the absence of intestinal bacteria in GF mice decreased anxiety-like behaviors when compared to SPF mice, and that this was accompanied by a baseline increase of plasma corticosterone. They determined that anxiety was affected by the upregulation of brain-derived neurotrophic factor messenger RNA expression in the dentate gyrus of the hippocampus.

Conducting primate field studies that simultaneously collect data on behavior, glucocorticoid levels, and gut microbial diversity will allow for novel examinations of the role of microbes in the primate stress response and how variation in allostatic load corresponds with microbial communities across individuals, groups, or populations of the same primate species. Furthermore, analyzing how gut microbial community dysbiosis (i.e., a state of microbial imbalance that typically leads to negative physiological outcomes) contributes to the observed outcomes of high allostatic load (e.g., cardiovascular, metabolic, reproductive, and immunological diseases) will be beneficial for both the conservation of endangered species and our general understanding of primate health, including humans. Given the unique ability to follow primates for long periods of time and collect detailed datasets in wild settings, such research will not only inform primatology, but will provide a new avenue for testing hypotheses postulated in microbial endocrinology.

3 | MICROBIAL ENDOCRINOLOGY OF REPRODUCTION

Gut microbes can influence the production of sex steroid hormones, such as androgens, estrogens, and progestins, having implications for primate reproductive physiology and behavior. Antibiotic treatments have been shown to cause declines in estrogen levels (Adlercreutz, Pulkkinen, Hämäläinen, & Korpela, 1984), and increased prevalence of *Clostridia* sp. and three genera of Ruminococcaceae bacteria have been correlated with higher urinary estrogen levels (Mittelstrass et al., 2011). Additionally, Ridlon et al. (2013) demonstrated that the commensal gut bacterium *Clostridium scindens* produces enzymes that allow for glucocorticoid conversion to androgens. Similarly, *Toxoplasma gondii*, an apicomplexan protozoan parasite processed in the gut of mammals, alters testosterone and progesterone levels in males and females, respectively, which has been suggested to explain increased risk-taking behavior in rodents with toxoplasmosis (Golcu, Gebre, & Sapolsky, 2014; Lim et al., 2013). Rodent studies have also demonstrated that sex differences are exhibited in the gut microbiota-sex hormone interplay (Jašarević, Morrison, & Bale, 2016; Tetel, De Vries, Melcangi, Panzica, & O'Mahony, 2018). For example, castrated male mice were more likely to have a similar microbe

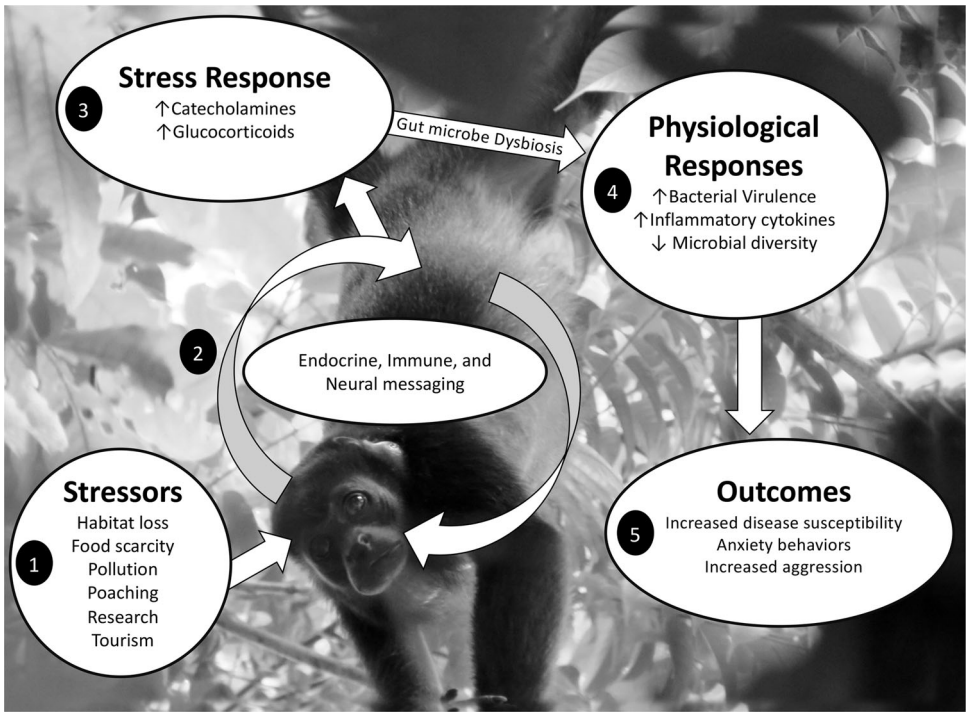

FIGURE 1 Gut–brain axis of wild primates. Stressors can impact the bidirectional communication systems between the gut and the brain. (1) Primates experience a number of stressors, including many from human activities, resulting in physiological and behavioral outcomes via the gut–brain axis. (2) Microbiota of the gut communicate with the brain via a variety of messaging pathways including direct interactions with the endocrine system, immune cells, and neural endings. (3) When primates experience a stress response, microbes are exposed to stress-related hormones. (4) This can introduce dysbiosis in the gut creating perturbations in signaling pathways and having potentially negative downstream physiological impacts. (5) Outcomes of these perturbations can include a variety of responses, many of which hold negative implications for primate fitness

composition to females, implicating gonadal sex hormones as a critical influence on gut microbiome (Yurkovetskiy et al., 2013). Likewise, androgenization and ovariectomy in rodents changed the abundances of Firmicutes and Bacteroidetes in the gut (Moreno-Indias et al., 2016).

During mammalian pregnancy, the body undergoes radical and specific changes in hormone levels and microbial composition (Newbern & Freemark, 2011). For example, both Proteobacteria and Actinobacteria increase as pregnancy progresses (Neuman, Debelius, Knight, & Koren, 2015). In an experiment that introduced third trimester gut microbes to a group of GF mice and first trimester gut microbes to a second group of GF mice, it was found that the treatment with third trimester microbiomes had a heightened inflammatory response and insulin-desensitization compared to the first trimester treatment (Koren et al., 2012). In endangered wild black rhinos, rare microbes (Aerococcaceae, *Atopostipes*, Carnobacteriaceae, and *Solobacterium*) were related to increased fecal progesterone metabolite levels, as well as the likelihood of pregnancy success (Antwis, Edwards, Unwin, Walker, & Shultz, 2019).

Conducting primate field studies that simultaneously collect data on sex steroid hormone levels, gut microbial diversity, and reproductive success will allow for novel examinations of the role of microbes in primate reproduction and how variation in sex and reproductive state interacts with microbial communities across individuals, groups, or populations of the same primate species. Moreover, since gut microbial communities undergo a dramatic shift when primates are kept in captivity (Amato et al., 2016; McKenzie et al., 2017), understanding the causes and mechanisms behind these shifts could have important implications for breeding success.

4 | CONCLUDING STATEMENT

Based on mounting evidence, it is clear that microbial community dysbiosis plays an important role in host endocrine function and subsequent physiological and behavioral outcomes (Figure 1). However, it is equally important to determine how gut microbial community stability is maintained in the absence of disease, thereby potentially offering the host benefits such as increased reproductive success and the ability to handle changing environments. Utilizing a community ecology framework that analyzes the costs and benefits of microbe–hormone communication systems will shed light on microbial functionality within the host, as is currently discussed for human health (Gilbert & Lynch, 2019). Therefore, we propose three guiding hypotheses for future studies regarding microbe–endocrine interactions in primates: (a) host-microbe communication systems promote *microbe-mediated stability*, in which the microbes are using endocrine signaling from the host to maintain a functioning habitat

for their own fitness, (b) host-microbe communication systems promote *host-mediated stability*, in which the host uses the endocrine system to monitor microbial communities and alter these communities to maintain stability, or (c) host-microbe systems are simply the product of *coincidental cross-talk* between the host and microbes due to similar molecules from shared ancestry.

Herein we have briefly discussed the rich opportunities of incorporating microbial endocrinology into primate field studies, with a focus on stress physiology and reproduction. Primatologists should use these methods not only to improve our general understanding of primate ecology and evolution in more pristine settings, but also to analyze the effects of anthropogenic threats on primate physiology and behavior to improve conservation initiatives and captive breeding programs given that up to 60% of primate species are threatened with extinction largely as a result of human actions (Estrada et al., 2017). Although we have focused on hormones of the stress response and reproduction, this study avenue is a versatile field which can greatly contribute to understanding the role of microbes in various components of the endocrine system with relevance to primate fitness, including nutritional ecology and social interactions, especially in the face of a rapidly changing global ecosystem.

ACKNOWLEDGEMENTS

We would like to thank Katharine Amato for the invitation to write this review, Jan Gorgarten and Bradford James Westrich for their extensive reviews of this manuscript, and two anonymous reviewers and editor Karen Bales for their constructive feedback through the publication process. K. M. B. thanks the Department of Anthropology Skomp Fellowship and A. I. T. thanks the National Science Foundation International Research Experience for Students (#1559223) for financial support that funded preliminary research leading to the ideas presented here.

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How to cite this article: Benavidez KM, Iruri-Tucker A, Steiniche T, Wasserman MD. Primate microbial endocrinology: An uncharted frontier. *Am J Primatol*. 2019;e23053. https://doi.org/10.1002/ajp.23053