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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1661827> since 2018-11-06T15:55:52Z

Published version:

DOI:10.1111/jne.12548

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Article type : Review Article

Steroids, Stress, and the Gut Microbiome-Brain Axis

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Short Title: Steroids and Gut-Brain Axis

Key words: microbiota, steroid hormones, estrogen, androgen, stress

Acknowledgements: We thank Kiran Sandhu for her expertise in making Figure 1 and the Fondazione Cavalieri-Ottolenghi (Torino), Department of Neuroscience (Torino), and University of Torino for their support for the organization of the International Meeting on Steroids and Nervous System, which hosted the roundtable that was the impetus for this review.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jne.12548

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Abstract

It is becoming well established that the gut microbiome has a profound impact on human health and disease. In this review, we explore how steroids can influence the gut microbiota, and in turn how the gut microbiota can influence hormone levels. Within the context of the gut microbiome-brain axis, we discuss how perturbations in the gut microbiota can alter the stress axis and behavior. In addition, human studies on the possible role of gut microbiota in depression and anxiety are examined. Finally, we present some of the challenges and important questions that need to be addressed by future research in this exciting new area at the intersection of steroids, stress, gut-brain axis and human health.

Introduction

Within each human gastrointestinal tract there is an exclusive combination of different communities of organisms, including bacteria, viruses, archaea, protozoa and fungi, which are collectively referred to as the gut microbiota and outnumber the total amount of human cells in the human body (1). The collection of these microorganisms, their genomes and the factors they produce are all part of the gut microbiome (2).

Increasing evidence suggests that these microorganisms actively participate in shaping and maintaining our physiology almost as an extra organ (3).

Gut microbiota composition is associated with many health benefits, including maintenance of intestinal homoeostasis, protection against pathogens, and appropriate immune responses (4, 5). Conversely, many gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease (6) are associated with an imbalance

in this microbial population. Furthermore, differences in diversity and composition of the microbiota have been linked to extra-intestinal diseases ranging from obesity (7) and asthma (8) to a variety of brain disorders (3, 9-14). The gut microbiota helps break down food, and in doing so produces metabolites that can directly influence the physiology of host cells, including brain cells. Moreover, immune responses to pathogenic bacteria produce cytokines and lymphokines that can affect brain physiology (15). As the nervous system is a master regulator of host function, this allows microbes to influence a broad range of complex physiological processes. An improved mechanistic understanding of how bacterial molecules act on the nervous system could yield improved therapeutics for treating behavioral and neurological disorders (16).

The human gut microbiota is usually stable and resilient to transient perturbations (17). However, microbial composition or activity of the gut can be modified by variety of factors, including internal factors such as hormonal changes, or external factors such as diet, antibiotics, and stress (3, 18). In this review, the influence of steroids and stress on the gut microbiome-brain axis will be discussed, as well as the challenges that face future research in this area.

Steroid hormones influence the gut microbiota

There is mounting evidence that steroid hormones can affect the gut microbiota. In support of steroids influencing the gut bacterial communities, sex differences have been noted in the composition of the gut microbiota with specific phyla, family and genera variances occurring with clear effects of gonadectomy and hormone replacement on gut bacteria in rodents (19-21). In mice, sex differences in the gut

microbiota observed between males and females are decreased after castration, indicating a role for gonadal steroids in modulating the gut microbiota (22).

Administering testosterone propionate (1250 µg) to female rats on the day of birth decreased the diversity of the gut microbiota in adulthood by increasing the *Firmicutes*-to-*Bacteroidetes* ratio (23). In adult rats, ovariectomy caused shifts in the relative abundances of two major phyla, *Bacteroidetes* and *Firmicutes* (23). In this study (23), the authors found that hormonal changes (either early androgenization or ovariectomy) were more impactful on the gut microbiota than the nutritional changes of switching to a high fat diet. Another study using female ERβ knock out mice found that ERβ influences the gut microbiota in a diet-specific manner (24). When mice were switched from a diet containing estrogenic isoflavones to one lacking isoflavones, the major phyla including *Proteobacteria*, *Bacteroidetes* and *Firmicutes* differed dependent on ERβ status (24). However, it is important to note that ERβ knock-out mice have reduced ovarian function (25, 26), which could have contributed to some of the alterations in the gut microbiota that were detected. Finally, in rats bred based on their running capacity, ovariectomy alters gut microbes compared to sham controls more in rats with low running capacity than in those with high running capacity, which the authors link to a potential role for gut microbiota in protecting individuals with increased aerobic capacity to the cardiometabolic risks associated with menopause (27).

Sex differences in the gut microbiota have been reported in humans as well. For example, men have higher levels of *Bacteroidetes* and *Prevotella* than women (28, 29), suggesting a role for sex factors such as differential sex chromosomal gene expression or differences in gonadal hormone levels in the modulation of the gut microbiota.

However, it should be noted that more recent metagenomic studies have found mixed results with respect to sex differences in microbiota in humans. Some studies report modest to no effects of sex on the human gut microbiota (30, 31), while other findings reveal substantial sex differences (32). Other studies suggest that steroids influence the gut microbial communities. For example, the gut microbiota undergoes profound changes during pregnancy in women (33). The authors found a large shift in the gut microbiota from the first to third trimester, with an increase in overall diversity and a proliferation of *Proteobacteria* and *Actinobacteria*, resulting in changes in metabolism (33). While the dramatic shift in steroid hormones (*e.g.* estrogens and progestins) could very well contribute directly to these changes in the gut microbiota, the authors also suggest that changes in the immune system at the mucosal surfaces could alter the microbiota (33).

While gonadal steroids can alter the gut microbiota, it appears that, in turn, the gut microbiome can influence hormone levels (34). In postmenopausal women, gut microbiota diversity was positively associated with the ratio of estrogen metabolites in urine (35, 36). In mice, transferring the gut microbiota of adult males to immature females caused an elevation in testosterone levels and metabolomic changes in recipient females (37). In addition, transfer of gut microbiota from male non-obese diabetic (NOD) mouse model of type 1 diabetes (T1D) to the female NOD T1D mice led to increased testosterone, metabolic changes, and protection against type 1 diabetes, which usually shows a strong female-to-male sex bias (37). These studies highlight the reciprocal connections between sex hormones and gut microbiota. Taken together,

these studies provide strong evidence that the gut microbiota is influenced by gonadal steroid hormones and steroid levels can be altered by the gut microbiome.

In addition to gonadal steroid hormones influencing the gut microbiota, there is evidence that some endocrine disrupting chemicals (EDCs), such as bisphenol A (BPA) or ethinyl-estradiol (EE), may alter the gut bacterial composition. BPA, which binds to estrogen receptors, is classified both as an EDC and as a metabolism-disrupting compound (MDC) that can cause obesity (38). EE, which is present in birth control pills, is secreted in urine and can accumulate in regenerated drinkable water. EDCs and MDCs exert their effects on peripheral organs and the central nervous system throughout life, but can be particularly dangerous during the critical period when they can have permanent deleterious effects that may drive a variety of diseases in adulthood (38). In a recent study (39), California mice, which are biparental, were fed diets containing BPA, EE, or a control diet around conception through weening to study their effects on the gut microbiota in parents and their offspring. The gut microbiota differed in both males and females of the parental generation exposed to BPA or EE compared to non-exposed controls. Similar effects were observed in the offspring that were exposed indirectly to EDCs through the placental exchanges and milk of their mothers (39). Presumably, EDCs may affect the gut microbiota partly by disrupting the endocrine equilibrium of animals and perhaps also by directly acting on the gut microbiota.

The Gut Microbiome-Brain Axis

The communication between the gut microbiome and the central nervous system (CNS) occurs in a bidirectional fashion and is referred to as the gut microbiome-brain axis (Figure 1) (9, 11, 40, 41). This axis includes immune, neural, endocrine and metabolic pathways (42-45), which work together to permit each end organ to communicate and influence the functioning of the other. The enteric nervous system (ENS), and the sympathetic and parasympathetic divisions of the autonomic nervous system, play major roles in the communication within this axis (44, 46, 47). Changes to the microbial environment, due to different stressors, are associated with changes to gut barrier, motility, and immune system activation. Conversely, perturbation of this axis results in alterations in the stress-response and behavior, which have been proposed to be involved in several CNS diseases such as anxiety (48, 49), depression (50, 51), autism (52, 53), Parkinson's disease (54, 55), Alzheimer's disease (56), and stroke/brain injury (57).

In the case of autism, there are several independent lines of evidence indicating that the gut microbiota is a factor. Compared with neurotypical controls, children with autism show an increase in *Clostridium*, *Bacteroidetes*, and *Lactobacillus* species, whereas *Firmicutes* species are higher in neurotypical controls (58-60). Moreover, treatment with the antibiotic vancomycin, which is poorly absorbed and therefore preferentially affects the gut microbiota, improves autism symptoms (61). Autism has been associated with reduced levels of short chain fatty acids, including acetate, propionate, and valerate, which indicates poorer fermentation of carbohydrates, presumably due to a relative absence of beneficial bacteria (60). In addition, there is a

correlation between the severity of autism and gastrointestinal symptoms (62). Studies using a variety of mouse models of autism support the concept that the gut microbiota is involved in autism (63, 64). However, in the clinical studies above, it should be noted that causality is difficult to prove given that children with autism often have different eating habits than neurotypical children.

As reported in clinical studies, Parkinson's Disease (PD) is accompanied by dysbiosis of the gut microbiome, resulting in altered levels of microbes (*e.g.* Bifidobacteriaceae, Christensenellaceae, Lachnospiraceae, Lactobacillaceae, Pasteurellaceae and Verrucomicrobiaceae families) (65) and concentrations of short chain fatty acids (66). Animal models of PD support these findings and have enabled functional manipulation of the gut microbiota. For example, mice that overexpress α -synuclein reveal that bacteria within the gut regulate motor deficits and neuroinflammation (67). Indeed, antibiotic treatment ameliorates, while microbial colonization with microbiota from PD patients promotes, the neurological phenotype in these mice (67). These clinical and basic studies suggest that the gut microbiota has an important role in the physical impairments associated with PD.

In regard to Alzheimer's Disease (AD), a clinical study investigating the role of gut microbiota in AD pathogenesis reveals that cognitively impaired patients with brain amyloidosis, compared to controls, have lower levels of the anti-inflammatory *Eubacterium rectale* and an increase in the pro-inflammatory *Escherichia/Shigella* (68). In support of these clinical findings, altered gut microbiota have been observed in a variety of mouse models of AD (69-71). Furthermore, in an APP_{SWE}/PS1 Δ E9 mouse model of AD, changes in the gut microbiota by long-term antibiotic treatment decreases

amyloid-beta plaque formation (69). Germ-free APP transgenic mice have decreased amyloid-beta pathology compared to control mice (70). Moreover, colonization of these germ-free APP mice with the microbiota of conventionally-raised APP mice increased amyloid-beta levels (70). These findings suggest that dysbiosis of the gut microbiota can contribute to AD pathology and manipulation of the gut microbial community may offer therapeutic opportunities for AD treatment.

There are several mechanisms by which the gut microbiome influences brain function and these work in concert with reciprocal signaling from the brain (72). For example, gut bacteria may influence central neurotransmitters by altering systemic levels of precursors of neurotransmitters (73). Moreover, neurotransmitters such as serotonin, which is involved in pain transmission and affect, can be produced by *Candida*, *Streptococcus* and *Enterococcus* spp. (74-77). *Lactobacillus* and *Bifidobacterium* species have been shown to synthesize and release gamma-aminobutyric acid (GABA) while *Bacillus* and *Saccharomyces* species can produce norepinephrine (54). These microbially synthesized neurotransmitters can act locally and also cross the mucosal layer of the gut to influence systems in the periphery and potentially the CNS. It has been proposed that serotonergic enterochromaffin cells in the gut epithelium act as chemosensors and transduce chemosensory information to the nervous system (78). In future studies, it will be important to determine if these serotonergic cells function in disorders, such as depression, within the gut microbiome-brain axis.

The gut microbiota also produce active mediators including short chain fatty acids (79, 80), which can inhibit histone deacetylases and lead to epigenetic changes

(81, 82). These substances also use the vagal nerve to signal the brain and influence behavior and other centrally mediated functions, such as the stress response (83). Indeed, studies show that modulation of the gut microbiome can impact on the development of the stress system (84) as well as reducing stress levels (85).

Similar conditions that alter the composition and diversity of the gut microbiota can result in changes in metabolites that influence signaling systems. The chemical signals generated by these bacteria, may also alter the accessibility of these signals to the periphery and the brain, *e.g.* by altering the lining of the gut. In close association with the gut microbiota is the intestinal epithelium, which acts as a physical barrier that protects against luminal contents as well as being involved with the development and maintenance of the mucosal immune system (86). Dysregulation within the epithelial layer can increase its permeability, thereby disrupting intestinal immune homeostasis (87). A disruption of the gut barrier, sometimes referred to as “leaky gut”, allows microbial products and viable bacteria to translocate from the intestinal lumen (88). A compromised gut barrier is associated with consequences beyond the gastrointestinal tract including an altered blood brain barrier (89) and alcohol dependence (90).

The Gut Microbiota and Depression & Anxiety

Disorders of the CNS, such as depression and anxiety, are highly debilitating and can profoundly impact quality of life (91). Over-activity of the main stress axis, the hypothalamic-pituitary-adrenal (HPA) axis, is characterized by elevated levels of cortisol and disruption of negative feedback and is commonly associated with depression (92). Interestingly, activity of the HPA axis can be impacted by the gut microbiota. Germ-free

raised BALB/c mice show an exaggerated HPA axis stress response compared to mice raised under specific pathogen-free (SPF) conditions, which have a microbiota that lacks specific pathogenic microbes. The HPA axis stress response can be normalized in adulthood by colonizing the gut with *Bifidobacterium infantis* (78), while reconstitution with the enteropathogenic *Escherichia coli* heightened the stress response even further (84).

In addition to these acute effects of the gut microbiota on brain function, microbiota also seem to have programming effects. If BALB/c mice are exposed to feces from SPF mice early in life (6 weeks of age), the previously germ-free mice show a normal stress response, whereas those reconstituted as adults (≥ 8 weeks) do not (84). Germ-free mice of the NMRI strain also show reduced anxiety-related behavior, and conventionalizing them (*i.e.*, exposing them to feces of conventionally colonized or SPF mice) at birth, but not in adulthood, normalizes this behavior (93). These findings suggest that microbiota influence brain development as well. Indeed, a recent study found that Germ-free Swiss Webster mice were less sociable and did not show the typical preference for investigating novel mice found in conventionally colonized mice (3). Conventionally colonizing these mice at day 21 only partially normalized their behavior (3), suggesting that gut microbiota must be present even earlier for normal social behavior.

Reduced anxiety and depressive-like behaviors, as well as changes in the GABAergic system, were seen following treatment of mice with *Lactobacillus rhamnosus* (JB-1) (83). Interestingly, these behavioral and neurochemical changes do not occur following vagotomy, indicating that the vagus nerve is a key route of

communication between probiotic bacteria and the brain (83). A recent study has shown that fecal microbiota transplantation from depressed patients (characterised by decreased microbial richness and diversity) to antibiotics-treated recipient animals induces a depressive-like phenotype in the recipient animals compared to the control recipient group (51).

The maternally separated rat model is a model of depression that has been used to demonstrate the role of the gut microbiota in stress-related disorders (94). Maternally separated rats present with behaviours indicative of depression and anxiety, had increased systemic immune response and dysbiosis of the fecal microbiota when compared with non-separated controls (94). Furthermore, maternal separation reduced swimming and increased time spent immobile in the forced swim test, induced changes in central neurotransmitters and enhanced peripheral IL-6 release (73). However, treatment with the probiotic *Bifidobacterium infantis* reverses these behavioral changes and restores the immune system response and the basal noradrenaline concentrations in the brainstem of rats undergoing maternal separation (73). *Lactobacillus plantarum* treatment of mice exposed to early life stress ameliorated anxiety- and depression-like behaviors, balanced the immune response, and modulated neurotransmitters related to affective disorders (95). Altered HPA axis activity and gut physiology are retained in germ-free mice that are subjected to maternal separation, while both anxiety- and depression-like behaviors are not (96). Interestingly, the behavioral phenotype is re-established when germ-free mice are colonised in adulthood with the gut microbiota from non-maternally separated control mice, but not the gut microbiota of maternally

separated animals. These findings suggest a convergence of microbial and host factors (96).

Bilateral olfactory bulbectomy in mice induces depression- and anxiety-like behaviors in mice, which are associated with increased immediate early gene expression, serotonin levels, gut motility and alterations in intestinal microbiota profiles (97). Given that similar changes in behaviors, motility and microbiota composition were also induced via central corticotropin-releasing hormone administration, the authors suggest that the altered HPA axis activity functions in this model (97). Both manipulations show the impact of the brain on microbiota composition and indicate that the gut microbiome-brain axis is a two-way street.

While much of the evidence on the role of gut microbiota in stress-related disorders is from animal models and other basic research studies, findings from recent human studies are coming to the forefront. The analysis of fecal samples from patients with depression reveals differences in alpha diversity and levels of specific gut bacterial taxa compared to controls (98). In particular, levels of *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* were increased, whereas *Firmicutes* were reduced, in samples from depressed patients compared to controls (98). Another study indicates that depression is associated with increased levels of *Enterobacteriaceae* and *Alistipes*, but a reduction of *Faecalibacterium*. In contrast, Naseribafrouei and colleagues (99) reported no differences in species richness or diversity between depressed patients and controls. However, this same study did find a general underrepresentation of *Bacteroidetes* in depressed patients and a significant interaction between the genus *Alistipes* and *Oscillibacter* with depression (99).

Steenbergen and colleagues (100) showed that a multispecies probiotic reduced negative thoughts associated with sad mood, which the authors suggest supports the concept of probiotics intervention as a preventive approach for depression (100). Patients affected by chronic fatigue syndrome often suffer from anxiety and depression (101). Rao and colleagues (102) found that treating these patients with *Lactobacillus casei strain Shirota* caused an increase in *Lactobacillus* and *Bifidobacteria spp.* and a decrease in anxiety symptoms. The authors suggest that the improvement seen in the stress-related symptoms is a result of improved gut physiology by the *Lactobacillus casei strain Shirota* (102).

Future Directions

Given the mounting evidence of the effects of the gut microbiome on brain function, future research may be targeted to finding efficient ways of promoting a healthy microbiota, *e.g.*, by identifying pre- and probiotics that produce relatively stable changes in the microbiota. Conversely, identifying dietary habits and food additives that negatively impact the brain will be just as important. Diet has profound effects on the structure and activity of gut microorganisms (103-107). For example, a diet rich in fats promotes the growth of the proinflammatory gram-negative microorganisms, which in turn can alter immune homeostasis (108, 109). In addition, the gut microbiota of obese individuals has higher percentages of energy-efficient bacteria than that of lean individuals (110-113). As changes in diet affect the gut microbiota, these changes may also influence brain and behavior. For example, a recent study focused on the negative effects of emulsifiers (common additives in foods such as peanut butter, mayonnaise, salad dressings, bread, ice cream, and many other processed foods) on gut microbiota.

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Addition of emulsifiers to the diet of mice induced systemic inflammation, metabolic syndrome, and obesity (114). These emulsifier-induced effects appear to occur by compromising the mucus lining of the gut, allowing gut microbiota to encroach on the epithelium, and altering the species composition of the gut microbiota, thereby increasing its pro-inflammatory potential. Physiological effects were absent in germ-free mice fed emulsifiers, suggesting that the microbiota probably mediates these effects (114). Preliminary results suggest that the same emulsifiers also increase anxiety-related behaviors and brain neuropeptide systems involved in these behaviors (*M.K. Holder, B. Chassaing, N.V. Peters, J. Whylings, A. Gewirtz, and G.J. deVries, preliminary observations.*).

Adding factors to the diet that promote a healthy microbiota, and avoiding factors that do the opposite, appear to be the most direct way to promote brain health. However, as indicated in this review, the gut microbiota is influenced by a variety of factors, including hormones and the activity of the gut microbiome-brain axis. Identifying the links between the gut microbiome and brain is clinically important and may provide insight into the etiology of behavioral disorders discussed above that have an important social component (62).

Understanding the role of the gut microbiome in human health presents a number of challenges. While germ-free mice have been very effective in studying the gut microbiome, they have their limitations and caveats as discussed above, including alterations in blood-brain barrier, neuroanatomy, stress response, and behavior (84, 93, 96). Good animal models are essential to study causal links and identify potential targets for therapeutic interventions. However, it is critical to move beyond strictly

correlational studies in animal studies that reveal changes in the gut microbiota under different conditions. In the future, more functional studies that manipulate the gut microbiota in specific and directed ways will serve to move the field forward. To achieve this more specific manipulation of the gut microbiota, the use of bacteriophage therapy has been proposed (115). Bioengineered phages may be able to provide targeted infection and lysis of bacteria in the gut, and thus offer therapeutic options and a much more complete understanding of the gut microbiome-brain axis. In addition, the isolation and growing in culture of specific anaerobic microbes will enable essential add-back experiments in animal models and provide important tools for treating human disease in the future. Given the profound effects of the endocrine system on human health, it will be critical to gain a better understanding of how hormones influence the gut microbiome-brain axis. For example, it will be essential to determine how age-related changes in estrogen and androgen levels affect the gut microbiota and the impact on vulnerability to disease. In addition, due to the interesting sexually dimorphic relationship between the gut microbiome and steroid hormones coming from peripheral glands (*e.g.*, testis, ovary and adrenal glands), it will be important in the future to study the role of neuroactive steroids (*i.e.* steroids directly synthesized and/or metabolized in the nervous system) in the gut-brain axis. Indeed, in this context it is important to highlight that neuroactive steroids represent important physiological regulators of the nervous system and that their levels are differentially affected in the two sexes by nervous pathologies, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, traumatic brain injury, spinal cord injury, stroke, diabetic encephalopathy, autism, anxiety and depression (116, 117). Moreover, neuroactive

steroids play an important role in neuroinflammatory processes in the brain, which in turn modulate behavioral states (118-120). As these neuroinflammatory processes are responsive to peripheral immune activation, *e.g.*, by gut dysbiosis, these molecules may play an important integrative role in the gut microbiome-brain axis.

Figure Legends

Figure 1. The gut microbiome-brain axis.

The gut microbiome (which consists of the microbiota, their genomes and their products) can influence brain function through a variety of mechanisms, including the production of neurotransmitters and short chain fatty acids (SCFAs), the modulation of the release of cytokines by immune cells and the vagus nerve. Conversely, the brain can influence the gut microbiota via regulation of endocrine systems (*e.g.* HPA and HPG axes).

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