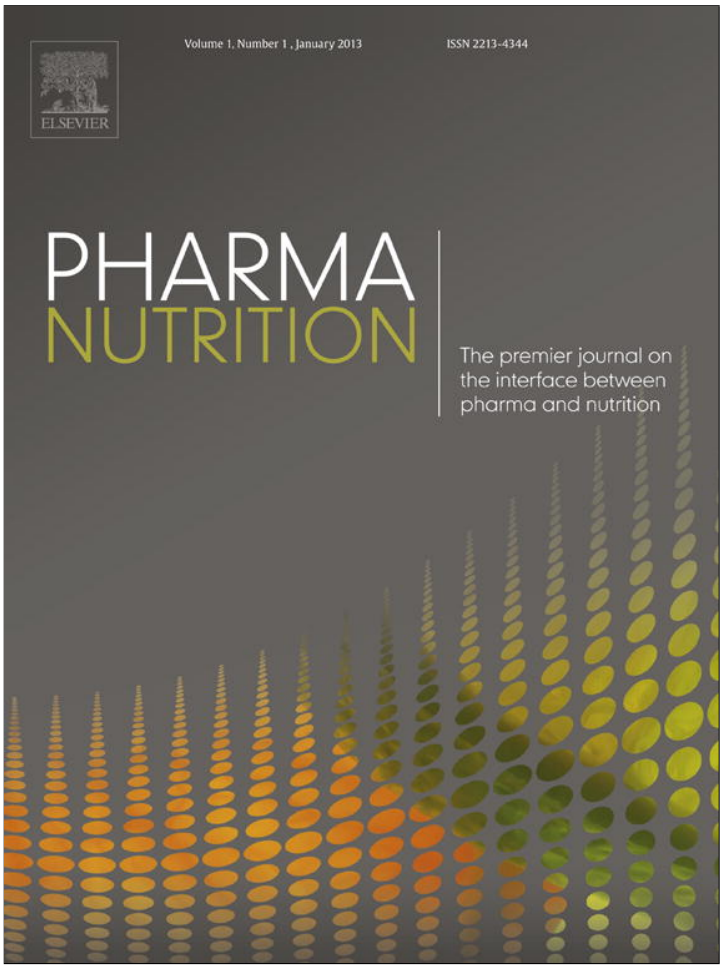

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Review

Microbial endocrinology and nutrition: A perspective on new mechanisms by which diet can influence gut-to-brain communication

Mark Lyte *

Department of Immunotherapeutics and Biotechnology, Texas Tech University Health Sciences Center, Abilene, TX 79601, USA

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ABSTRACT

The increasing recognition of the role which microorganisms within the intestinal tract (microbiome) play in reciprocal communication between the gut and brain is now only beginning to be elucidated. Microbiome driven gut-to-brain communication, for example, has been shown to influence cognitive states such as anxiety in humans and anxiety-like behavior in animals. One of the mechanisms that has been proposed to account for the ability of the microbiome to influence gut-to-brain communication has been by the microbial recognition and production of neuroendocrine hormones that otherwise have been exclusively associated with a mammalian nervous system. The study of such neuroendocrine–bacterial interactions is the interdisciplinary field known as microbial endocrinology that operates at the intersection of microbiology and neurobiology. The purpose of this mini-review is to expand the field of microbial endocrinology to nutrition and specifically examine the theoretical basis and evidence for a role of the microbiome in nutrition due to bacterial–neuroendocrine interactions contained within the interdisciplinary field of microbial endocrinology.

Contents

1. Proposal: nutrition influencing behavior through the microbiome – role of microbial endocrinology

The ability of diet to alter the composition of the microbiome has been recognized for decades (for review see [1]). What is not known, however, is if diet-induced changes in the microbiome can *directly* and in a *causal* manner lead to changes in behavior via microbial endocrinology-based mechanisms which involve the ability of bacteria to both recognize and synthesize neuroendocrine hormones that are *exactly* the same as their eukaryotic counterparts. Such a proposal, that diet can influence bacteria to produce neuroendocrine hormones that interact with the enteric nervous system (ENS), or directly are absorbed into the portal circulation, would represent a new mechanism by which nutrition could impact the host and ultimately influence various aspects of behavior as well as food preferences and appetite. It should be

* Correspondence address: Department of Immunotherapeutics and Biotechnology, Texas Tech University Health Sciences Center, 1718 Pine Street, Abilene, TX 79601, USA. Tel.: +1 325 696 0417.
E-mail address: mark.lyte@ttuhsc.edu.

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noted that a very recent paper by Norris et al. [2] has proposed that a positive feedback loop exists between the host's dietary preferences and the microbiome. The Norris et al. [2] paper therefore represents one of the first proposals that the nutritive state of the host and the microbiome influence one another through bi-directional microbial-based mechanisms that had not been previously envisioned as part of nutrition.

Caveat: As this paper is intended to introduce a new perspective concerning the microbial-based mechanisms by which nutrition may impact behaviors such as appetite, it should not be regarded as a comprehensive review of any of the specific fields. As such the author acknowledges the use of selective references to discuss the hypothesis and that other references which may represent important contributions to their respective fields have not been included due to space limitations.

2. Background

Within the fields of microbiology and neurobiology there has been growing recognition that bacteria have the ability to both produce and recognize neuroendocrine hormones that otherwise have only been associated with a vertebrate nervous system [3–6]. The first study that proposed and demonstrated that bacteria could directly respond in growth to neurochemicals was shown in the early 1990s when the co-culture of Gram-negative bacteria with the stress-related neurochemical norepinephrine resulted in a logs-fold increase in growth [7]. Subsequent studies by numerous laboratories have amply demonstrated that a wide-range of bacteria can respond to and recognize neuroendocrine hormones with changes not only in the rate of growth, but also production of virulence-related factors and other aspects of cell physiology *in vitro* [8–13] and *in vivo* [14,15]. This ability of microorganisms to both recognize through specific receptors and produce neuroendocrine hormones lies at the intersection of microbiology and neurobiology and has been termed microbial endocrinology (for review see [3,4]). Other terminology to describe such interactions between biological kingdoms has also been termed in a less microbial-specific manner as interkingdom crosstalk [16].

From a nutritional standpoint, the presence of neurochemicals, such as the biogenic amines dopamine and tyramine, in plants and processed foods has long been recognized [17–19]. Additionally, microorganisms used in food manufacture can contribute large amounts of biogenic amines to the final finished product [20]. From a nutritional standpoint, food-borne neurochemicals have not been viewed as a significant dietary energy source. The impact of biogenic amine consumption on health has been largely restricted to direct physiological effects in the host such as anaphylactic episodes that can occur following the ingestion of histamine-rich foods [21] or hypertensive crises following ingestion of tyramine [22]. Nutritive components, such as dietary catechols, have been demonstrated *in vitro* to increase the growth of Gram-negative bacteria commonly found in the gut [23]. That the microbiome is exquisitely sensitive to its neurohormonal environment can be seen following the *in vivo* release of endogenous stores of catecholamines which has been shown to result in a rapid change in the species composition of the gut bacteria [24]. As such, there seems to be a reasonable basis with which to propose that the composition of the microbiome can be influenced by both exogenous neurochemicals and their precursors as well as endogenous neurochemical stores.

It could be reasonably argued that many of the studies that have shown the ability of neuroendocrine hormones to influence microbial growth could have been predicted, in part, from observations from the early part of the last century. These early studies showed that administration of neuroendocrine hormones, such as epinephrine, to treat various physiological conditions as diverse as urticaria (itching) resulted in the rapid development of fulminating sepsis and death of the individual [25]. However, although subsequent studies of this phenomenon pinpointed the blame on contaminated needles and syringes, any ability of contaminating bacteria to increase growth in a neuroendocrine environment was attributed to the suppressive effects of the hormone on the surrounding immune cells, which permitted the growth of the bacteria. Direct interaction of bacteria with neuroendocrine hormones, otherwise viewed as solely belonging to vertebrates, was not even contemplated [26].

In putting forward this microbial endocrinology-based perspective on the interrelationship of nutrition and behavior, it is readily acknowledged that an extensive literature exits that has both proposed [27,28] and examined a large and varied number of dietary factors that could influence many aspects of behavior such as learning and appetite [29,30]. In these studies, the mechanisms(s) by which various nutritive compounds could influence behavioral processes have been largely been examined for their respective capacity to directly affect central nervous system (CNS) neuronal activity including the provision of neurochemical precursor substrates. Diets high in saturated fatty acids [31] and tryptophan [32] are but a few of the nutritive factors that have been shown to influence behavioral processes.

3. Intestinal environment – ENS and hormone production

Any attempt to understand the role that the microbiome may play in influencing behavior, and the subsequent proposal for the role of microbial endocrinology in nutrition, is dependent on an examination of the ENS and the elaboration of neuroendocrine hormones within the intestinal tract. Historically, the ENS has been the least understood component of the nervous system although it was first described in the late 1800s [33]. The ENS is comprised of over 500 million neurons which represents a number as great as that in the spinal cord (for review see [34]). What is most crucial in understanding the role of the ENS, at least in regard to the gut microbiome, is that the ENS innervation of the gut extends all the way to the intestinal villi. Our understanding of the sensing elements that comprise the ENS and where that communication goes (both within the ENS and communicated to the brain by the vagus nerve) is still very much in its infancy. However, experiments that have interrupted vagal (vagus nerve) communication from the gut to the brain have been able to show that microbial-driven changes in behavior can be abrogated by transection of the vagus nerve in a surgical procedure known as a vagotomy [35,36].

While direct physical interaction of bacteria or bacterial components such as toxins with components of the ENS has been shown to play a role in activation of neuronal afferents within the ENS [37], there is also another mechanism that is the topic of the present paper. This mechanism, which is only now becoming more apparent, is the direct production of neuroendocrine hormones within the intestinal tract by the microbiome. Although the number of different neuroendocrine hormones that are secreted into the gut lumen by elements of the ENS numbers at least 30, less is known about the ability of the microbiome itself to produce many of these very same chemicals. In fact, the spectrum of neuroendocrine hormones that may be produced by bacteria is extensive (for review see [38]). For example, production of corticotropin [39] and somatostatin [40] have been demonstrated in bacteria. Indeed, the presence of the complete biosynthetic pathway for catecholamines in bacteria has led to the theory that cell-to-cell signaling in vertebrates may be due to late horizontal gene transfer from bacteria [41].

Until recently, however, the examination of production by bacteria has mainly been confined to *in vitro* studies. The recent

publication by Asano et al. [42] has for the first time demonstrated that bacteria which constitute the normal microbiome in mice are capable of the *in vivo* production of large quantities of a neuroendocrine hormone, specifically the catecholamine norepinephrine. Further, adoptive transfer of the microbiome of mice that could produce norepinephrine *in vivo* to germ-free mice also resulted in the *in vivo* elaboration of norepinephrine within the intestinal tract [42]. Prior studies, such as those by Wikoff et al. [43], which utilized a metabolomics-based approach to study the metabolic products of the microbiome in mice which may impact health, had unexpectedly found that the majority of serotonin in the plasma was unexpectedly derived from the intestinal tract due to as yet unknown host–microbe interactions. Taken as whole, these studies, suggest that the microbiome has a hitherto unknown capacity to produce a spectrum of neuroendocrine hormones that may act both locally on components of the ENS as well as enter the systemic circulation via direct absorption through the gut into the portal circulation. As such, mechanistic routes exist whereby the microbiome can influence behavior, and possibly have an impact on nutrition as for example through food preferences.

4. Ability of the microbiome to influence behavior

While the ability of host physiological responses, for example the elaboration of stress-related neurochemicals such as the catecholamines, have been shown to affect microbial process such as growth [7–15], more recent has been the demonstration that bacteria within the intestinal tract may drive certain behavioral states both in humans and animals. It has been well recognized that intestinal bacterial infections that result in a robust immune response involving the production of inflammatory cytokines can alter behavior [44]. Recently, Gareau et al. [45] demonstrated that infection of mice with the non-invasive murine gut pathogen *Citrobacter rodentium* resulted in memory dysfunction. However, the ability of bacteria that do not cause active infection, and hence generate an immune response, to affect behavior is less well recognized.

The demonstration that a host's behavior could be influenced by a bacterium within the intestinal tract which did not infect the host nor generate an immune response (which in itself could influence behavioral responses) was achieved by the introduction into a mouse of a live, novel (not part of the mouse's normal gut microflora), replicating bacterium that resulted in the development of anxiety-like behavior [46]. This intestinal bacterial-driven induction of anxiety-like behavior was shown to be due to the activation of specific neuronal regions in the brain via vagally mediated communication from the gut to the brain [47]. More recently, studies by Bravo et al. [35] have been instrumental in demonstrating that the purported abilities of certain probiotics such as *Lactobacillus rhamnosus* are due to the ability of the specific probiotic to mediate gut-to-brain communication.

Gut-to-brain communication may proceed along multiple direct and indirect pathways encompassing both cellular and biochemical factors belonging to neural (vagus and ENS), endocrine (hypothalamic–pituitary–adrenal axis) and immune (innate and adaptive arms including cytokine production) pathways (for a review see [48]). While the complexity and multiplicity of interactions between all three pathways is extensive and beyond the scope of this perspective, a number of potential mechanisms other than that proposed in this perspective have been the subjects of continued concerted investigations. For example, activation of elements that comprise both the innate and adaptive arms of the immune system can result in the elaboration of pro-inflammatory and anti-inflammatory cytokines in the intestine that can then affect CNS function [44].

5. Nutrition influencing behavior through the microbiome – role of microbial endocrinology

The validity of the proposal that neuroendocrine–bacterial interactions which comprise microbial endocrinology may serve as a common mechanism through which nutrition influences host behavior as well as host preferences for food can be tested in a number of model systems. As such, a number of testable hypotheses can be proposed.

5.1. First, do diet-induced changes in the microbiome lead to changes in behavior?

Preliminary evidence to support the proposal that the diet can induce changes in the microbiome that then lead to changes in behavior has already been obtained using a meat-based diet. Feeding of a meat-based diet to mice had previously been shown in culture-based studies to result in reproducible changes in distribution of certain colonic bacterial genus such as *Bacteroides* [49]. Li et al. [50] utilized such a meat-based diet to examine whether feeding of a meat-supplemented diet could induce more global changes in the microbiome as a whole and if so, was there an impact on a measurable behavioral attribute. In this study the nutritive components were also examined in order to determine whether changes irrespective of those in the microbiome might have played a role in any observable differences in cognitive function. As reported by Li et al. [50] feeding of a meat-based diet resulted in a substantial shift in the microbiome to a more diverse population as compared to normal control chow fed animals. Biochemical analysis of the differences between the diets did not identify any one component that could account for the observed differences in performance in the behavioral tests that were used to measure memory. Most importantly, concomitant with the change in the microbiome, animals exhibited a significant increase in both working and reference memory [50]. It is important to note that while this study did not prove mechanistically that nutrition-induced changes in the microbiome accounted for an increase in cognitive function, it provided the first evidence that such a link is possible.

If the microbiome can influence cognitive function, what evidence exists that it is due to microbial-endocrinology-based mechanisms? Foods that contain high levels of neuroactive compounds themselves, such as biogenic amines [21] have amply been demonstrated. However, it is not presently understood how such food-borne neurochemicals may influence the composition and activity of the microbiome. Nevertheless, it has been shown that such neurochemical composition in foods *can* influence the growth of microorganisms. For example, an early report in which the ability of banana extracts to increase the growth of Gram-negative bacteria was demonstrated to be due to the level of catecholamines present in the banana preparation [51].

5.2. Can adoptive transfer of the microbiome result in transfer of food preferences?

If the proposal that production of microbial-based neuroendocrine hormones represents a mechanism by which behavior can be influenced, then adoptive transfer of the microbial flora from one strain of mouse with high anxiety-like responsiveness to one with low levels [52] should result in the transfer of the applicable behavior.

5.3. Does the composition of the microbiome drive food preferences?

The composition of the gut microbiome has recently been shown to be dependent on the diet [53]. If the prevalence of any

one bacterial species is dependent on the consumption of one particular nutritional based factor, whether a particular food or component therein, then from an evolutionary standpoint could it be possible that the bacterial species, in order to insure its own continued survival in the host, communicate that specific need for that food to the host? Such food preference-directed communication could be the production of a neuroendocrine-based factor that is elaborated at times of low bacterial population density that then signals to the brain via the ENS the need for that food that is required for its continued survival and growth. The design of experiments to test such a hypothesis would involve the continued feeding of a specific food or nutrient that results in the predominance of one species within the microbiome. A food preference taste test along the same line involved in standard saccharin testing to identify low and high preference for saccharin in rats [54] could then be used to determine whether the specific microbiome determines food preference.

5.4. Can probiotic bacteria be viewed as neurochemical-based drug delivery vehicles?

Probiotics such as those belonging to the genus *Lactobacillus* are potent producers of neurochemicals such as GABA [55]. Recently the microbial endocrinology-based theory has been introduced that probiotics function as pharmacological agents and hence function as drug delivery vehicles due to their ability to synthesize hormones, such as GABA (which can directly influence receptors both immune and neural within the ENS and CNS) [56]. Evidence to support this microbial endocrinology-based understanding of the mechanisms by which probiotics may influence host behavior and inflammation can be seen in the recent studies of Bravo et al. [35] and Thomas et al. [57]. Bravo et al. reported that the ability of the probiotic *L. rhamnosus* to influence emotional behavior in mice was due to alterations in GABA receptor expression that were dependent on communication from the gut to brain via the vagus nerve since vagotomy negated the effect of the probiotic. Experiments, which sought to examine the mechanisms by which the probiotic *L. reuteri* influenced inflammation in an *in vitro* model system, reported that the suppressive action of the probiotic was due to the production of a neuroendocrine hormone, specifically histamine, that inhibited the production of inflammatory cytokines such as TNF [57]. The microbial endocrinology-based hypothesis that probiotic organisms may function as drug-delivery vehicles equally applies to the large endogenous (non-probiotic) population of Gram-positive bacteria residing in the gut. Since many of these bacterial species possess the biochemical machinery to synthesize a neuroendocrine hormone such as GABA [58], it is reasonable to suggest that the examination of diets rich in the precursors of these neurochemicals may increase the production of the hormone within the gut which in turn may affect both host physiology (i.e. inflammation within the gut) and behavior.

5.5. Can the brain influence the composition of the microbiome as to affect aspects of nutrition such as appetite?

The proposal that gut-to-brain communication as mediated by microbial endocrinology-based mechanisms may be an important driver of appetite engenders the consideration of the reverse: does brain-to-gut communication influence appetite through the same neuroendocrine-bacterial mechanisms? Given that the composition of the gut microbiome can be driven by the intake of exogenous neurochemicals and their precursors, can the elaboration of neuroendocrine hormones by the ENS, independently or under the direction of the CNS, *into* the gut lumen have a role in nutrition. To date, it is still not understood why serotonin is secreted in large quantities into the gut lumen on a daily basis

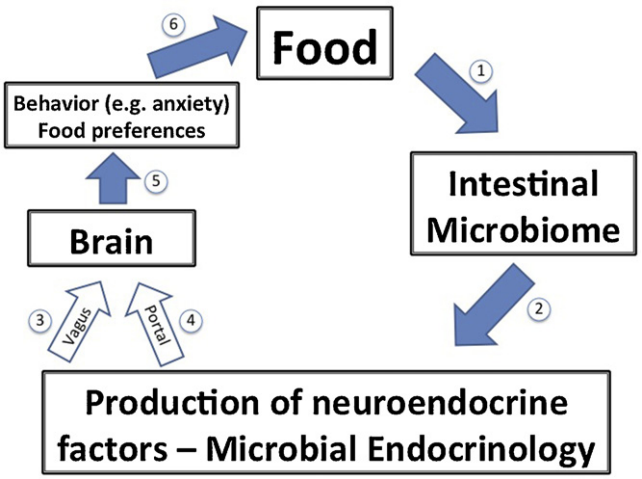

Fig. 1. Feedback loop illustrating the ability of nutrition to influence behavior through microbial endocrinology-based mechanisms. The ingestion of food (1) results in alterations of the intestinal microbiome (2) depending on the composition of the food, which may contain neuroactive components (e.g. biogenic amines), or neurochemical precursors. Microbial production and recognition of neuroendocrine factors (microbial endocrinology) within the microbiome in response to the diet can be communicated to the host via two pathways: via interaction with the enteric nervous system and communication to the brain via the vagus nerve (3) and via direct absorption into the portal circulation (4). The result of this microbial endocrinology-directed communication to the brain (5) is alteration of behavior (e.g. cognition) and food preferences (e.g. appetite) that then influences the choice of nutrition by the host (6) as determined by the needs of the microbiome.

where it comes into immediate contact with the gut microbiome. Elucidation of the underlying reasons why such secretion occurs for serotonin, as well as for other hormones contained within the ENS, will help test the feasibility of this bi-directional proposal on how microbial endocrinology may influence nutrition.

6. Conclusion

At this point it is critical to note that we do not fully understand the mechanisms by which intestinal bacteria may impact the ENS and hence communication to the brain, and in turn, possibly influence nutrition-related behavior such as appetite. The testable hypotheses that are proposed in this perspective article are intended to encourage new microbial endocrinology-based approaches in understanding the ability of nutrition to influence gut-to-brain communication. Already other investigators, notably Norris et al. [2], have also introduced the hypothesis of a feedback loop between the microbiome and the brain in determining food preferences and appetite (see Fig. 1).

It is well beyond the scope of this perspective to also discuss the intestinal sensing of food elements such as glucose within the gut for which many excellent reviews have been published. Instead, it is the intent of this paper to introduce the topic of microbial endocrinology that may not be familiar to many readers and at the same time propose how the intersection of microbiology and neurobiology, microbial endocrinology, may identify new mechanisms by which nutrition can influence the host.

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