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Microbial Endocrinology

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Microbial Endocrinology: The Microbiota-Gut-Brain Axis in Health and Disease

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Prof. Mark Lyte: "To my loving wife and my two remarkable sons who are my pillars of strength"
Prof. John F. Cryan: "To Colleen, Oisín & Alannah: For constant support and patience"

Foreword

This book is the second volume of a continuing series. The first volume published by Springer in 2010, "Microbial Endocrinology: Interkingdom Signaling in Infectious Disease and Health", contained little in regard to brain and behavior, but instead focused almost exclusively on aspects of infectious disease. Health consequences as such were mainly concerned with the role that stress could play in altering the interface between host and microbiota. The present volume is therefore a testament to the great strides during the intervening years which have illuminated the myriad ways in which microbiota interfaces with the host. It is anticipated that future volumes in this series will reflect the ever increasing acceleration of research into the microbiota–gut–brain axis.

Abilene, TX, USA
January 2014

Mark Lyte
Series Editor

Preface

If one was to ask whether a book dealing with the ability of the microbiota to influence the brain, and ultimately cognition and behavior, would have been possible just a few short years ago, the answer would most likely be no. A simple search of PubMed using the index words "microbiota AND gut AND brain" reveals only 134 publications as of 16th January 2014. However, this would not be an accurate reflection of the work that has been ongoing for many decades, but yet remained on the outer fringes of the disciplines that constitute the study of the mechanisms by which the microbiota and the brain communicate with each other. A comprehensive series of articles by Bested and colleagues [1] catalog the numerous studies going back over a century which amply demonstrate that the investigation of the role of the microbiota in brain function, and by extension mental health, has a long and varied (some may say checkered) scientific history. During this time it remained, for large measure, outside mainstream scientific inquiry following an initial burst of enthusiasm both in the scientific and public arenas at the turn of the twentieth century. That such scientific skepticism remained, and in many cases became entrenched, in the very scientific disciplines that form the basis of the microbiota–gut–brain axis is owed to a number of factors. One of these is surely the increasing specialization that occurred within each discipline over the years and the inherent lack of interdisciplinary thought that accompanied such specialization. With the advent of the concerted research into the microbiota and the microbiome, as best evidenced by the tremendous strides that the Human Microbiome Project has made over the last decade in cataloging the incredible diversity in the microbiota in health and disease, the realization that the microbiota has a role to play in the development and function of the nervous system and hence behavior and cognition, has once again entered into mainstream scientific and medical thought. However, old beliefs die hard. The recent experience of one of us (ML) as described in the prologue to Chap. 1 is but one example of the resistance that is still being encountered today for a role of the microbiota in the functioning of the brain. In many conservative Learned Societies the concept that the gut and indeed the gut microbiota can have such an influence on brain & behavior is still looked upon with incredulity. However, this is changing.

This book represents the realization that any attempt to understand the ability of the microbiota to interface with the brain (and by association any part of the host's neurophysiology) must attempt to address multiple disciplines, such as microbiology, anatomic neuropathology, and endocrinology to name but a few, that while on the first examination appear to be rather disparate from each other but on further examination are in fact highly interconnected as evidenced, for example, by the development of the field of microbial endocrinology itself. As described in Chap. 1, as well as detailed in a chapter in the first book of this series [2], the field of microbial endocrinology developed out of need to understand the paradox in which stress resulted in increased death from a bacterial challenge at the same time greatly increasing the phagocytic activity of the immune system. In considering the microbiota as an interactive player in the host that can both respond to signals from the host and influence the host through the provision of the very same host signaling molecules (i.e., neurochemicals) that are more commonly associated only with vertebrates, but in fact have a long evolutionary history involving the prokaryotes, the potential role of the microbiota in brain functioning and its potential for treatment of mental disorders becomes apparent.

As such, the book is organized along three thematic lines which will provide the reader not only a fuller understanding of the capabilities of the microbiota to interface with the brain and form the microbiota–gut–brain axis, but will also provide detailed examination of the consequences of the microbiota-driven gut-to-brain communication for both health and disease. The first four chapters cover the "Basic Concepts Underlying the Microbiota–Gut–Brain Axis"; the next eight chapters examine the "Mechanistic Factors Influencing the Microbiota–Gut–Brain Axis" and the concluding seven chapters address the "Microbiota–Gut–Brain Axis in Health and Disease".

We have assembled a group of contributors who are recognized to be at the front of their respective fields to review the state of the art of this growing field. As the chapters in this book amply demonstrate, the field of microbiota–gut–brain axis is still in its infancy although its origins are now over a century old. With the advent of modern techniques ranging from deep pyrosequencing of the microbiota to brain imaging, the tools are in place to address those questions which were raised many decades ago. Given our evolving understanding of the complexity of the microbiota which when one couples that to the complexity of the brain and nervous system, this book represents only one more chapter in what promises to be a long and challenging story.

Abilene, TX, USA — Mark Lyte
Cork, Ireland — John F. Cryan
January 2014

References

1. Bested AC, Logan AC, Selhub EM (2013) Intestinal microbiota, probiotics and mental health: from Metchnikoff to modern advances: Part I – autointoxication revisited. Gut Pathog 5(1):5
2. Lyte M (2010) Microbial endocrinology: a personal journey. In: Lyte M, Freestone PPE (eds) Microbial endocrinology: interkingdom signaling in infectious disease and health. Springer, New York, pp 1–16

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Part I
Basic Concepts Underlying the Microbiota-Gut-Brain Axis

Chapter 1
Microbial Endocrinology and the Microbiota-Gut-Brain Axis

Mark Lyte

Abstract Microbial endocrinology is defined as the study of the ability of microorganisms to both produce and recognize neurochemicals that originate either within the microorganisms themselves or within the host they inhabit. As such, microbial endocrinology represents the intersection of the fields of microbiology and neurobiology. The acquisition of neurochemical-based cell-to-cell signaling mechanisms in eukaryotic organisms is believed to have been acquired due to late horizontal gene transfer from prokaryotic microorganisms. When considered in the context of the microbiota's ability to influence host behavior, microbial endocrinology with its theoretical basis rooted in shared neuroendocrine signaling mechanisms provides for testable experiments with which to understand the role of the microbiota in host behavior and as importantly the ability of the host to influence the microbiota through neuroendocrine-based mechanisms.

Abbreviations

CNS	Central nervous system
ENS	Enteric nervous system
GABA	Gamma aminobutyric acid

Prologue

"*If you are right that the bacteria in the gut can communicate with the brain and induce cognitive behavioral changes such as anxiety, then why aren't all the patients we give*

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antibiotics to in the hospital running around the floors crazy?" NIH Director's Pioneer Award Study Section Member—July, 2008

In July 2008 I found myself as a finalist for the coveted NIH Director's Pioneer Award being asked that very question following my PowerPoint presentation by a study section member in front of not only the other assembled study section members but also the representatives of all the NIH Institutes and the Director's office. Earlier that year I had submitted an application for the Pioneer Award entitled "The Microbial Organ in the Gut" where I proposed that bacteria in the gut were not only able to communicate with the brain and influence behavior, but also that the brain could likewise communicate with the gut bacteria to achieve regulation of microbial populations that would benefit the host. The mechanism by which this bi-directional communication was governed was proposed to be that of microbial endocrinology—the ability of bacteria to respond to as well as produce the same neurohormones found in the host. The study section member's question of why people weren't "running around crazy" was the first one asked following a short presentation to all present. I had anticipated that questions during the 15 min following my presentation would be probing given that from hundreds of applicants for the first round, only 25, including myself, had been selected for a live presentation to a completely new panel of experts at the Lawton Chiles International House on the NIH campus. I also knew that the presentation would meet with some skepticism but hadn't been prepared for the very same study section member spitting water in a veritable geyser after taking a drink and hearing me say, not 2 min into my talk, that bacteria can communicate with the brain and change behavior (the incident was witnessed by all in the room for which I did receive a telephone apology for the member's behavior weeks later from the Director's office). So, the sarcastic, condescending nature of the question came as no surprise. And it was no surprise that my answer (which in many ways forms the basis of this chapter) satisfied neither the member nor the rest of the panel and I did not receive one of the Pioneer Awards that year. But, as they say, times change and science marches on.

Microbial Endocrinology: Conceptual Framework

Microbial endocrinology represents the intersection of two seemingly disparate fields, microbiology and neurobiology. The field of microbial endocrinology was founded in 1993 when the term was first coined by Lyte [1, 2] based on experimental data obtained the prior year [3, 4]. As will be seen in this chapter, although the concept of microbial endocrinology was founded just two decades ago [1, 3–5], there has been published evidence by numerous investigators over the preceding six decades going back to 1930 [6] that demonstrate the validity of uniting the fields of microbiology and neurobiology as a conceptual framework with which to understand interactions between the microbiota and the host in homeostasis and disease.

That these two fields should intersect and play a role in not only infectious disease, but also microbiota-gut-brain communication can be best understood when one considers how the two fields are similar to one another. The presence of neuroendocrine hormones that are exactly the same in structure, as well as share the same biosynthetic pathways, to that found in mammalian systems has been recognized for decades (for review see [7]). Prominent examples include members of the catecholamine family that have been found not only in bacteria [8], but in fish [9], plants [10] and insects [11]. The complete biosynthetic pathway including co-factors for catecholamines, from tyrosine through epinephrine, is found in *Escherichia coli* as well as other bacterial species [12]. Acetylcholine [13], histamine [14], serotonin [15, 16], and even more newly described neurotransmitters such as agmatine [17–19] have all been shown to be produced by microorganisms. The spectrum of neuroactive compounds produced by bacteria that can potentially interact with the host also includes a number of neuropeptides [20]. *That many of the described neurohormones produced by bacteria also function in mammals as part of the neurophysiological system suggests, as will be discussed in the succeeding sections, that their production within the mammalian host can impact the neurophysiological aspects of the host including cognition.*

The ubiquitous presence of neuroendocrine hormones in non-mammalian systems means that the presence of the very same neuroendocrine hormones in mammalian systems has a long evolutionary shared history. Iyer et al. [12] proposed that acquisition of cell-to-cell signaling systems, such as those that characterize neuroendocrine pathways in mammalian systems, are due to late horizontal gene transfer from bacteria. The theory that neurochemical signaling in mammalian cell systems is due to bacterial gene transfer has been bolstered by recent results from the human microbiome project. Riley et al. [21] have shown that such bacterial-mammalian cell lateral gene transfer of bacterial DNA into the human somatic genome occurs via integration of a RNA intermediate and is more common than previously recognized.

In non-mammalian systems the presence of neuroendocrine hormones often serves in a similar capacity to that seen in mammals. For example, tomato plants exposed to various stressors such as cold temperatures can produce large amounts of stress-related catecholamines. As in mammals [22], stress and the production of stress-related hormones such as norepinephrine and epinephrine in tomato plants are also associated with increased susceptibility to infectious agents such as the plant fungal and bacterial pathogens [23, 24]. Interestingly, in response to an infectious insult during periods of stress and increased production of catecholamines tomato plants produce antimicrobial compounds that use as their backbone the complete structure of catecholamines such as norepinephrine and dopamine [23, 24]. Whether evolution has afforded other non-plant-based systems a similar way to deal with stress-induced susceptibility to infectious challenge by constructing antimicrobial compounds based on neurochemical structures has not yet been fully examined.

What is still incompletely understood for the majority of bacteria from which neuroendocrine hormones have been isolated is the simple question of "why". Why

do bacteria produce neuroendocrine hormones? In large part, most reports of neurochemical production by bacteria are mainly descriptive and the "why" aspect is too often left unanswered. However, for some bacterial species which are known to produce certain neurochemicals via the same mechanism found in animals, such as gamma aminobutyric acid (GABA) which utilizes α-decarboxylation of L-glutamic acid catalyzed by glutamate decarboxylase, a reason for its production has been reported. For example, production of GABA can confer resistance to acidic pH for a number of *Lactobacilli* species such as *Lactobacillus reuteri* [25] as well as have a role in the germination of bacterial spores [26]. As an acid-protective mechanism, the GAD system employed by *Lactobacilli* may offer a sound explanation concerning survival of the bacterium following ingestion and subsequent transfer through the acidic conditions within the stomach and into the intestine, but falls short to explain from an evolutionary perspective why *Lactobacilli* that normally reside in the gut should possess the biosynthetic pathway to produce GABA. Nor for the reports that other commensal microbiota such as those belonging to the *Clostridia* also possess the ability to decarboxylate glutamic acid and produce GABA [27]. Can it instead be proposed that the production of GABA by bacteria can also serve as a mechanism by which such bacteria can not only influence the host through interaction with host cell receptors for GABA that can be found in the intestinal tract both in neuronal cells that belong to the enteric nervous system (ENS) [28] as well as immune cells [29], but additionally as a way by which one bacterial species can communicate with another within the microbiota that also possesses receptors for GABA? In fact, the presence of a high affinity receptor for GABA in *Pseudomonas* spp. had formed the basis for the use of a bacterial-based system to quantify nanomolar concentrations of GABA in clinical fluids such as cerebrospinal fluid [30]. The isolation and characterization of the high affinity receptor for GABA in *Pseudomonas* was reported a few years later [31].

The concept that the production of neuroactive chemicals by members of the microbiota can not only serve in the capacity of interacting with the host, but also as a means of signaling among other members of the microbiota, has been proposed [32]. Such neurochemical-signaling mechanisms between members of the microbiota would constitute a type of primitive nervous system and satisfy the requirements contained with any definition of an organ—namely, that the cellular elements which comprise the organ can be influenced, and in turn influence, the host. From a microbial endocrinology-based standpoint the microbiota contained within the gut can therefore be termed as a microbial organ [32].

Origins of Microbial Endocrinology: Evidence from the 1930s to Present

Over the last decade the number of reports which have demonstrated the ability of bacteria to respond to neuroendocrine hormones produced by the host, especially

during times of stress, have steadily increased. The first report that a stress-related neurochemical could influence bacterial growth appeared in the early 1930s due to an unfortunate set of occurrences. Epinephrine (adrenaline) as the first hormone purified to homogeneity was beginning to find increasing use in the clinical arena. One of those uses was for the treatment of urticaria. Reports began to appear almost immediately following its use in the clinic of patients dying from fulminating sepsis within hours after administration of epinephrine [6]. The cause was traced to the glass syringes and metal needles that pre-dated the modern use of disposable syringes and needles [33]. Although glass syringes and needles were cleaned with various agents between patients, it was quickly discovered that such cleaning of a needle and syringe set used to drain infected abscesses of patients with infections such as the spore-forming *Clostridium perfringens* was inadequate. The combination of epinephrine and the very small number of spores or injured bacteria left in the syringe and needle proved to be a dangerous combination. Since all patients who died from epinephrine injections were traced back to syringes and needles that had been used to drain bacterial abscesses it became standard medical practice for decades that a syringe and needle set could not be used for epinephrine injections if it had been recently used to drain a bacterial abscess. Although this association has been largely lost to history, it should be noted that on occasion such associations have proved beneficial for the evaluation of drugs to treat infectious bacteria such as *C. perfringens*. Traub et al. [34] demonstrated that in order to get *C. perfringens* to infect a mouse it was necessary to co-inject fresh, non-oxidized, adrenaline and that by utilizing such a neuroendocrine hormone-based model system one could evaluate the efficacy of antimicrobial candidate drugs to treat gas gangrene infections.

The majority of reports that have dealt with various aspects of neuroendocrine hormone production by bacteria or their recognition of host-produced hormones have done so in the context of infectious disease. This is not surprising given the fact that the first reports of hormones having a role in host health started in the 1930s with the reports of gas gangrene following injection of epinephrine. The first report that described a *direct* interaction of bacteria and neuroendocrine hormones and ascribed a role in infectious disease was the demonstration 60 years later in 1992 that the stress-related neurohormones norepinephrine and dopamine could increase the growth of human intestinal bacterial pathogens by over six orders of magnitude within hours [3, 4]. Importantly, intestinal pathogens which are not commonly associated with extra-intestinal infection, such as *Yersinia enterocolitica*, do not respond to the stress hormone epinephrine. This is a critical observation as it indicates that bacteria may have developed the ability to recognize host hormones based on evolutionary association with specific anatomical regions of the host. Reports, such as Sperandio et al. [35], which have subsequently appeared and suggest that epinephrine plays a key role in the pathogenesis of bacteria within the gut critically have not recognized (or even ignored) the fact that epinephrine does not exist in appreciable amounts within the gastrointestinal tract. This is due to the fact that neurons contained with the enteric nervous system (ENS) that innervates the entire length of the gut do not possess the enzyme