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Microbial Endocrinology in the Pathogenesis of Infectious Disease

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ABSTRACT Microbial endocrinology represents the intersection of two seemingly disparate fields, microbiology and neurobiology, and is based on the shared presence of neurochemicals that are exactly the same in host as well as in the microorganism. The ability of microorganisms to not only respond to, but also produce, many of the same neurochemicals that are produced by the host, such as during periods of stress, has led to the introduction of this evolutionary-based mechanism which has a role in the pathogenesis of infectious disease. The consideration of microbial endocrinology–based mechanisms has demonstrated, for example, that the prevalent use of catecholamine-based synthetic drugs in the clinical setting contributes to the formation of biofilms in indwelling medical devices. Production of neurochemicals by microorganisms most often employs the same biosynthetic pathways as those utilized by the host, indicating that acquisition of host neurochemical-based signaling system in the host may have been acquired due to lateral gene transfer from microorganisms. That both host and microorganism produce and respond to the very same neurochemicals means that there is bidirectionality contained with the theoretical underpinnings of microbial endocrinology. This can be seen in the role of microbial endocrinology in the microbiota-gut-brain axis and its relevance to infectious disease. Such shared pathways argue for a role of microorganism-neurochemical interactions in infectious disease.

MICROBIAL ENDOCRINOLOGY: CONCEPTUAL FRAMEWORK

Microbial endocrinology represents the intersection of two seemingly disparate fields: microbiology and neurobiology (Fig 1). 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). Although the concept of microbial endocrinology was founded just over 2 decades ago (1, 3–5), there has been published evidence by numerous investigators over the preceding 6 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 the pathogenesis of infectious disease. It should be appreciated, however, that approaching microbiology through an interdisciplinary "lens" such as microbial endocrinology has relevance outside of the field of infectious disease. As will be discussed in this article, the ability of microorganisms to not only respond to, but also produce the very same neurochemicals that are more typically thought in the context of mammalian systems, means that host interactions with microorganisms are much more interactive than previously envisioned. This is the basis of microbial endocrinology (1, 2, 7–9). As such, microbial endocrinology has found applications outside of infectious disease (where it has its developmental roots) including

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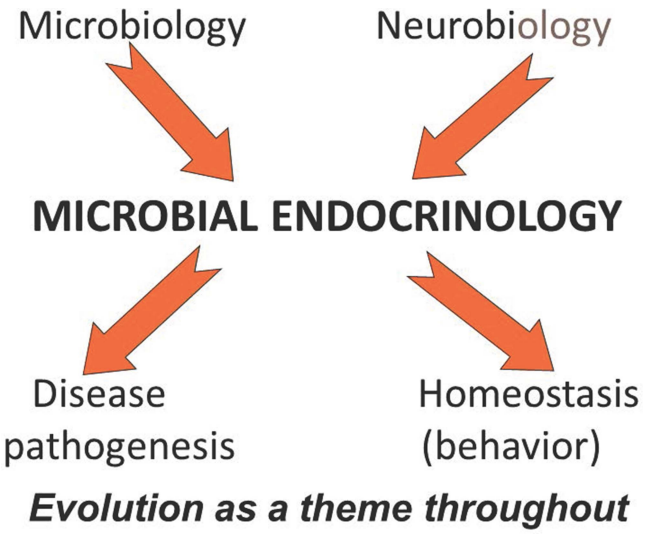

FIGURE 1 The conceptual basis of microbial endocrinology represents the intersection of microbiology and neurobiology and is based on the commonly shared neurochemicals that form the evolutionary basis of cell-to-cell communication in vertebrates (see text for in-depth discussion).

other aspects of host health such as the ability of the gut microbiota to influence the brain and behavior through the microbiota-gut-brain axis (10–12). This review will address how and why the fields of microbiology and neurobiology should intersect and what the relevance of this interaction is for infectious disease.

Note Regarding Definitions

When attempting to unite certain aspects of two seemingly disparate fields, the use of terms which originated in one field need to be addressed if they carry the same meaning in the other. The use of the terms "neurotransmitter," "neuromodulator," and "neurohormone" are designations that are associated with neurobiology and not microbiology. In neurobiology, a neurotransmitter is any chemical messenger that can act locally between two different neurons. In doing so, it is released from one neuron and diffuses across a small gap separating the two neurons, referred to as a synaptic cleft, where it binds to a receptor on the second neuron, thus communicating and possibly propagating a signal. A neuromodulator is similar to a neurotransmitter but does not need to be released at a synaptic site and can act across longer distances and possibly act through a second messenger. The term neurohormone is used to identify those substances secreted by neuroendocrine cells into the systemic circulation that can exert effects on distant sites. To further complicate matters, any one chemical can have multiple roles; a neurochemical such as norepinephrine can be both a neurotransmitter and a neurohormone.

Given that microorganisms can form communities, a case can be made that the local release by cells within one community adjacent to another in a section of the gut fulfills the requirement of a neurotransmitter. Or release by one community in the cecum can have downstream effects on another microbial community in the colon, thus fulfilling a neurohormone-type definition. How one should apply these neurobiological terms to microbiology has yet to reach any consensus within the scientific community. Thus, for the purposes of consistency and ease of presentation, any chemical produced by a microorganism that is also recognized within neurobiology as either a neurotransmitter, neuromodulator, or neurohormone in a mammalian system will be referred to in this article as simply a "neurochemical." For the neurochemicals discussed in this article, the reader is referred to any standard neuroendocrinology reference book such as reference 13 for the current definitions and spectrum of biological activities in animals, encompassing their role in homeostasis and various disease pathologies.

HISTORICAL EVIDENCE FOR MICROBIAL ENDOCRINOLOGY IN INFECTIOUS DISEASE

In 1983 a clinical report appeared which described the development of gas gangrene in a 13-year-old girl following the intramuscular injection of epinephrine (14). That the administration of a neurochemical more commonly associated with a stress response should result in the appearance of a life-threatening infection should not have come as a surprise to the authors. Even as late as 1968, Harvey and Purnell, commenting on a fatal case of gas gangrene in a 22-year-old man who had received an intramuscular injection of epinephrine, wrote that the practice of epinephrine administration in the buttocks must be discontinued due to the probability of the injection site harboring clostridial spores (15). However, knowledge of such associations between an injectable neurochemical that has varied uses from treatment of urticaria to suppression of local inflammatory reactions and the development of a life-threatening infectious disease had been known since the 1930s (6).

The curious history of a dreaded infectious disease, gas gangrene, and an injectable catecholamine (epinephrine is a member of the catecholamine family; Fig. 2) that is used to treat a wide spectrum of medical conditions ranging from anaphylaxis to urticaria is illustrative of the intersection of neurobiology and microbiology in the

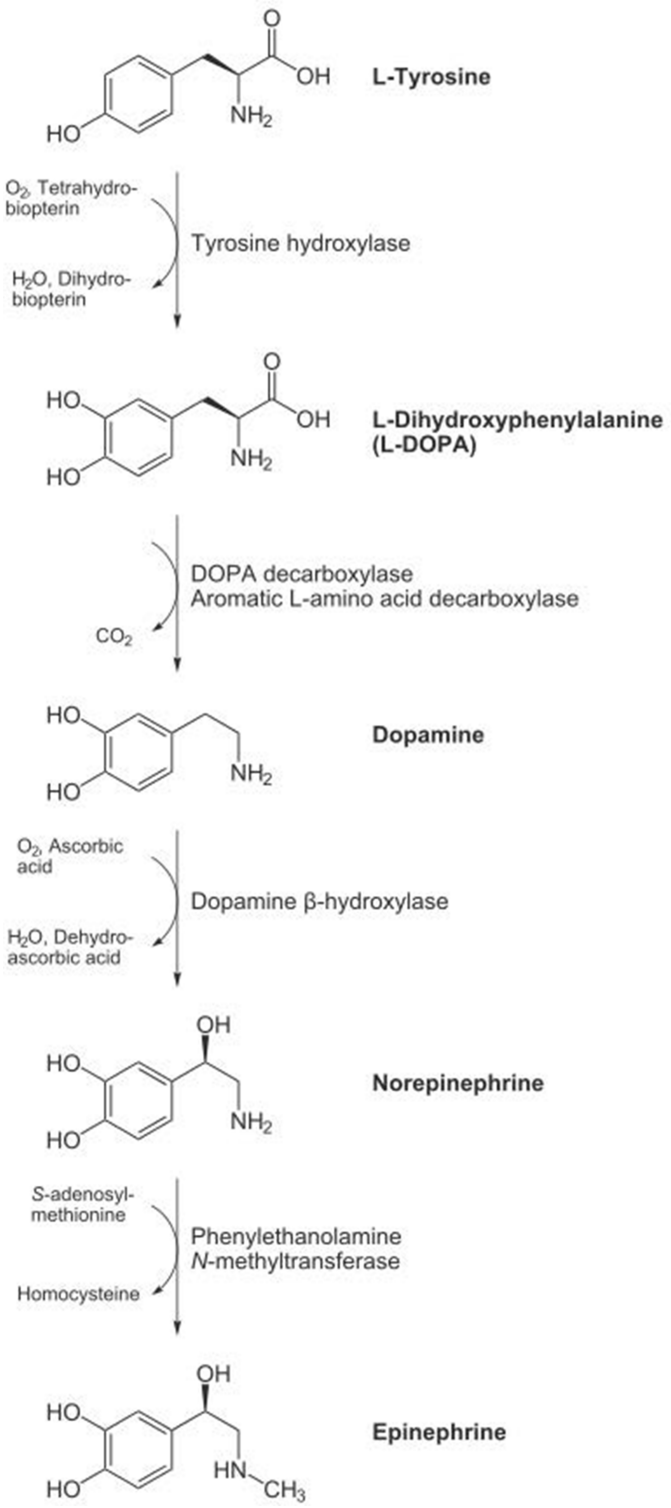

FIGURE 2 The chemical biosynthetic pathway for catecholamines utilizes the same pathway (substrates and cofactors) in microorganisms as it does in animals (47). Courtesy of NEUROtiker, licensed under CC-BY-SA 3.0 (https://creativecommons.org/licenses/by/3.0/us/).

pathogenesis of infectious disease. The latter part of the 19th century and early 20th century was a time that saw both the rise of modern endocrinology as personified by the first synthesis and application of a purified endocrine compound, epinephrine (16), and at the same time the continued development of modern bacteriology. Individually, each field continued its upward trajectory of increased understanding of the mechanisms by which they had respective roles to play in disease and homeostasis. Little research was done into how the fields might interact with one another. Undoubtedly, much of this was due to the prevailing view that the microbe could not be equated on the same level as multicellular organisms. However, a more interactive role of the microbiota with the host beyond the more fundamental aspects of pathogenesis was envisioned by some at the time. Concepts that were in many ways the forerunner of modern thinking in the ability of the microbiota-gut-brain axis to influence behavior (discussed later in this article) were advanced by a number of individuals at the time (17).

From the early to mid-20th century, both clinicians and microbiologists were aware of the association of endocrinology and microbiology thanks in large measure to the cases of epinephrine and gas gangrene reported in the literature. In fact, these researchers early on identified the mechanism by which the association of epinephrine with *Clostridium perfringens*, the causative agent of gas gangrene, often proved to be a fatal one for the patient. Prior to the advent of disposable syringes, metal needles and glass syringes were reused constantly between patients, with only a cursory cleaning in alcohol. Patient to patient transmission of infectious disease was frequently encountered due to the inadequate alcohol treatment of syringe needles, which could only marginally kill actively growing (vegetative) bacterial cells, but not bacterial spores. As is well understood today, certain vegetative bacteria such as *C. perfringens*, can undergo sporulation. Such spores, which are formed from the vegetative cells under conditions of nutritional deprivation, are totally resistant to alcohol treatment and can only be killed by autoclaving. From those early reports (6) it was determined that a previously used syringe needle that had been employed to treat a gas gangrene patient was then used to administer epinephrine to a patient for urticaria. Within 6 hours a fatal fulminating gas gangrene infection developed. These reports noting the rapidity of infectious spread in patients receiving epinephrine injections with contaminated needles led A. A. Miles and colleagues in 1948 to begin a series of experiments examining the role of

catecholamines in bacterial pathogenesis (18). In these experiments, the ability of epinephrine to modulate the *in vivo* growth of both Gram-positive and Gram-negative bacteria in a guinea pig model was conclusively demonstrated in tissue slices with enhancement of growth of bacteria coinjected with epinephrine that was log orders greater than that for control slices coinjected with saline (18). It should be noted that norepinephrine was not investigated. The authors concluded that the ability of epinephrine to dramatically enhance bacterial growth was due to some protective coating of the bacteria by epinephrine or an epinephrine-induced inhibition of immune cell function. The testing of each of these possible mechanisms, however, met with failure (18).

Significantly, at no time did these authors or others suggest that the action of epinephrine on bacterial growth was due to a direct, nonimmune effect as is discussed in this article. Interestingly, one technique that has been used by microbiologists to enable gas gangrene infections to "take" in mice has been the coinjection of epinephrine along with *C. perfringens* (19). As *C. perfringens* infections are difficult to establish in a mouse model, the finding that coinjection with epinephrine could enhance infectivity proved to be a valuable tool for medicinal chemists to use in the design of new chemotherapeutic drugs against infection. Interestingly, Traub (19) described that only fresh, and not oxidized, epinephrine solutions were successful in enhancing *C. perfringens* infectivity in mice. With a new generation of microbiologists and the advent of molecular techniques to evaluate potential antimicrobials *in vitro*, the use of animal models decreased, and this technique was no longer utilized. In a larger scope, this and the history that preceded it did not make its presence felt in mainstream microbiological thought. However, as detailed in the following section, a flurry of activity by a number of investigators highlighted the evolutionary relationship of host neurochemicals in microorganisms and what this meant for health and the pathogenesis of infectious disease.

WIDESPREAD PRESENCE OF NEUROCHEMICALS IN MICROORGANISMS

It is perhaps somewhat surprising to learn that neurochemicals which are more commonly associated with mammalian nervous systems are in fact widely dispersed throughout nature. For example, the biogenic amines, particularly the catecholamine family, have been identified in plants (20) as well as insects (21) and fish (22), in addition to most vertebrates. Although textbooks which deal with neurobiology, endocrinology, and neurophysiology certainly do not mention the presence of the very same neurochemicals in microorganisms, it should be recognized that their presence in microorganisms (both prokaryotic and eukaryotic) had been the subject of intensive research and debate in the 1970s and 1980s. But more importantly, these groups of investigators were among the first to ascribe an evolutionary basis to the shared presence of hormonal peptides in vertebrates and unicellular microorganisms (23, 24). Others, such as Mayer and Baldi (25), were among the first to propose that the evolutionary basis for these shared regulatory peptides represented a "universal structured code for biological communication" between individual systems. In discussing these earlier studies, the terms "hormonal peptide" and "regulatory peptide" are used as in the original text instead of "neurochemicals," as discussed in the note at the beginning of this article. The reason is that these early papers were chiefly concerned with shared peptides and not neurochemicals such as the catecholamines (23, 24).

What is perhaps most surprising to microbiologists and neurobiologists is that microorganisms themselves possess the very same neurochemicals that are found in vertebrates. The range of neurochemicals and the variety of microorganisms in which they have been identified is very large (26). These include, but are not limited to, acetylcholine (27, 28), histamine (29–31), serotonin (32–34), catecholamines (33–36), and agmatine (37, 38). All of the preceding neurochemicals are important components of an animal's nervous system. The presence of insulin-like material in microorganisms has also been extensively documented, with its biological activity demonstrated in every microorganism examined to date (26, 39). Other neurochemicals isolated from microorganisms which have been shown to have biological activity in mammalian cells include corticotropin from *Tetrahymena pyriformis* (40), somatostatin from *Bacillus subtilis* (41), and progesterone from *Trichophyton mentagrophytes* (42). Numerous other neurochemicals identified by radioimmunoassay and chromatographic behavior, as well as the presence of the corresponding putative receptor, have also been demonstrated in various microorganisms (for reviews see references 23, 26, 43).

Investigators have debated the significance of such neurochemicals in microorganisms for decades. The most widely accepted theory concerns the use of such neurochemicals as a form of intercellular communication (24, 44). Indeed, studies have shown that the growth of colonies of *Escherichia coli* involves a high

degree of specialization of function by individual bacteria (45, 46) and, presumably, the need for some form of intercellular communication to accomplish this goal. It should not, therefore, be surprising that the development of intercellular signaling systems in animals has been proposed to be due to horizontal gene transfer from bacteria (47). For example, the complete biosynthetic pathway for the catecholamines is found in bacteria. This includes all the same substrates and cofactors that are used in animals (47).

While the ubiquitous distribution of neurochemicals and receptors throughout nature is not fully appreciated in the fields of microbiology and neurobiology, it should be borne in mind that this widespread distribution implies that microorganisms have had ample opportunity to interact with multicellular systems along a very long evolutionary time frame. For example, there is an extensive literature documenting the presence of neurochemicals in normal plant physiology extending from pollen germination to stimulation of flowering and catecholamines in particular (48). From an evolutionary viewpoint, since the upregulation of neurochemicals in nonvertebrates is also temporally associated with times of increased rate of infection susceptibility, bacteria have probably evolved to exploit neurochemicals as biomarkers of stress and thus host weakness. It then follows during this evolutionary process that organisms, such as plants that have to combat bacterial challenges during periods of stress, have developed means based on interruption of the microorganisms-neurochemical interface to combat stress-induced infection.

Critically, evidence has been published that supports this line of reasoning. In response to the challenge with the plant pathogen *Pseudomonas syringae*, which causes bacterial speck on the leaves of tomato plants, especially during cold periods, tomato plants produce the metabolite *p*-coumaroylnorepinephrine (Fig. 3). As can be seen in Fig. 3, *p*-coumaroylnorepinephrine is a conjugate of hydroxycinnamic acid with norepinephrine. Although the purported mechanism of action of *p*-coumaroylnorepinephrine is in maintaining plant cell wall integrity (49), no data was actually presented to demonstrate this facet of activity. Instead a role for antimicrobial activity role was demonstrated by Zacares et al. (50), who reported not only direct antimicrobial activity of *p*-coumaroyldopamine against *P. syringae*, but also that tomato plants can also synthesize the hydroxycinnamic acid amides of dopamine to yield *p*-coumaroyldopamine (50). Interestingly, the production of these hydroxycinnamic acid amides of biogenic amines has also been reported in as diverse plant species

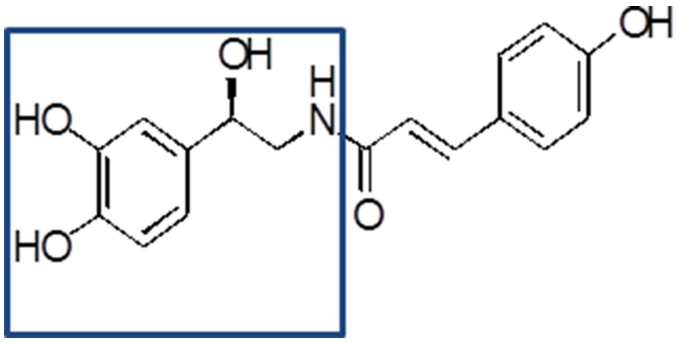

FIGURE 3 The plant metabolite *p*-coumaroylnorepinephrine is synthesized in response to stress and infection. This compound as well as *p*-coumaroyldopamine are hydroxycinnamic acid amides of norepinephrine (box designates norepinephrine part of the structure) and dopamine, respectively, and have been shown to have direct antimicrobial activity against the plant pathogen *Pseudomonas syringae* (50).

as pepper (51–53), potato (54, 55), and wheat (56), thereby indicating evolutionary conservation of an important metabolite that is only produced in times of plant stress to protect against bacterial pathogens. This phenomenon highlights that microorganisms can interact with potential hosts, be they other bacteria, plants, insects, fish, or vertebrates, through the microbial endocrinology-based mechanism of shared neurochemicals. The most thoroughly researched interactions between host (regardless whether the host is plant, fish, or animal) and infectious microorganism have been concerned in some fashion with stress, as will be discussed in the following sections.

Note Regarding Bidirectionality of Microbial Endocrinology

As discussed previously, there is a common evolutionary pathway in which stress-related neurochemicals first evolved in bacteria and, through lateral gene transfer, were acquired by mammals (47). This means that a "mechanistic bidirectional" signaling pathway for these neurochemicals exists between microbiota and the host in which neurochemicals produced by the host can influence the microorganism (Fig. 4A), and neurochemicals produced by the microorganism, in turn, can affect the host (Fig. 4B) (5, 57, 58). Although the direction shown in Fig. 4A is more thoroughly addressed in this article than the one shown in Fig. 4B, the latter is of no less significance in the ability of microorganisms to influence host health. For example, the ability of probiotics to produce neurochemicals has been known for decades (28). Recently, this ability has been proposed as a means to influence the microbiota-gut-brain axis

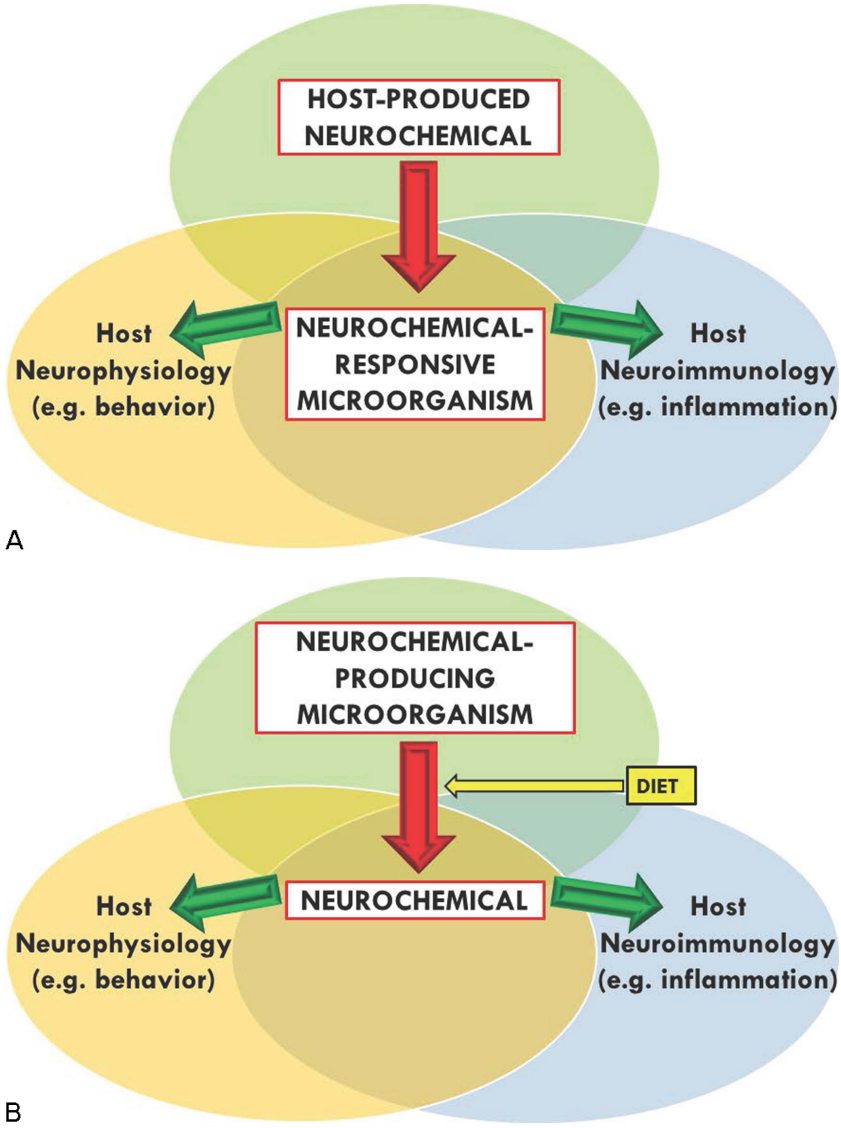

FIGURE 4 The evolution-based neurochemical signaling pathway between microorganism and host means that a neurochemical(s) produced by the host can influence the microorganism **(A)**, and at the same time a neurochemical(s) produced by the microorganism can, in turn, influence the host **(B)**. As shown in part B, diet plays a crucial part in the latter because it provides the substrates and cofactors necessary for the microorganism to produce a specific neurochemical according to a biosynthetic pathway that is the same as that found in the host.

and thereby influence host brain and behavior as well as potentially influence disease processes that have a neuroimmune component and can thus be regulated by compounds that interact with neurochemical receptors on immune cells (59, 60). It should be noted that in Fig. 4B, diet is included as it can provide the substrates and cofactors needed by the microorganisms to produce the neurochemical as part of the biosynthetic pathway (61–63).

NEUROPHYSIOLOGICAL CONSIDERATIONS AND THEIR RELEVANCE TO MICROBIAL ENDOCRINOLOGY

In considering the microorganism-host interface as regards infectious disease, the neurophysiological environment that is present becomes a pivotal factor influencing whether a productive infection may develop. It must be stated at the outset of this section that the dynamic and multifactorial nature of both host and

microbial factors underlying any infectious disease episode are highly complex. As such, it should be recognized that a microbial endocrinology-based mechanism represents only that which may be present at a specific time point during the infective process. Thus, it is expressly not the objective of this chapter to obviate or diminish in any way the multitude of other factors, whether host or microbial, that are involved in the pathogenesis of infectious disease.

At the same time, from a conceptual point of view, any consideration of the neurophysiological environment must take into account both the host and the microbe itself. This is because both are equally capable of producing and responding to neurochemical signals produced by one another. Further contributing complexity into this already complex equation is the recent demonstration that neurochemicals produced by one bacterial genera in the gut can affect another. A recent example of this can be found in the work by Strandwitz et al. (64), who showed that production of gamma-amino butyric acid (GABA) by one gut bacterial species is required for the growth of another. In this preliminary work, growth and subsequent isolation of the gut microbe *Flavonifractor* spp. from fecal matter was dependent upon a neighboring GABA-producing bacterium, such as *Bacteroides fragilis*. This preliminary report suggests that production of any neurochemical by a microbe may also affect neighboring microbial communities. Whether the consequences are beneficial or harmful in creating an environment which may favor or hinder any potential pathogen has yet to be investigated. Much will depend on a number of factors such as where in the gut the neurochemical-producing and neurochemical-responsive microbial communities are regionally located as well as whether the communities are luminal or mucosal associated. While an in-depth discussion of neurophysiology and the production of neurochemicals is beyond the scope of this article (the reader is directed to standard neuroendocrinological texts such as reference 13), a discussion of the neurochemical environment of the two main avenues in which pathogenic microorganisms can enter a host is warranted.

Lung Environment

The lungs are extensively innervated by nerves belonging to the autonomic nervous system. For example, adrenergic and cholinergic components of the autonomic nervous system have been demonstrated to extensively innervate pulmonary tissue in the pig (65). Such extensive innervation serves a number of functions in the regulation of normal pulmonary homeostasis such as control of smooth muscle tone, secretion of mucus from submucosal glands, and blood flow within the lungs themselves (66). While there is understandably a large body of literature on autonomic nervous system–related receptors in the human regarding treatment option for a number of pulmonary–related disease states, there is little knowledge of the neural innervation of the bovine lung and correspondingly little, if in fact any, reports of the neuroendocrine environment within the nonhuman lung following a stress-related event. It can reasonably be assumed that given the extensive blood flow in the lung, as well as the abundant noradrenergic nerve innervation which is also present throughout the organ, that a stress-related event would result in substantial amounts of catecholamines being present within the lung space. These stress-released catecholamines would be then available to interact with any bacterial pathogens that might also be present in the lung. One study which indicated that this would indeed be the case was performed in sheep where endotoxin-mediated injury to the lung resulted in elevated plasma levels of both norepinephrine and epinephrine within the lung space (67).

If concentrations of catecholamines such as norepinephrine are indeed elevated within the stressed lung, it is likely that it would contribute to the infective process by directly interacting with bacterial pathogens. Anderson and Armstrong (68) have shown that the *in vitro* growth of the respiratory pathogen *Bordetella bronchiseptica* is greatly increased in the presence of norepinephrine and that this ability is, in part, mediated by the ability of norepinephrine to increase acquisition of transferrin-bound iron by *B. bronchiseptica*. That the interaction of stress-related neurochemicals with the lung may be an area worth investigating can also be seen in a study which examined the interaction of the *Mycoplasma hyopneumoniae* with norepinephrine. Global transcriptional analysis of *M. hyopneumoniae* following exposure to norepinephrine revealed numerous changes within the overall pattern of upregulation of protein expression and downregulation of general metabolism (69).

Gastrointestinal Environment

A cursory examination of the papers dealing with gastrointestinal infections and the host environment will find a predominance of investigations dealing with immune responses. Fewer numbers of reports have dealt with the host nervous system that innervates the gut, specifically the division of the nervous system known as the enteric nervous system (ENS) (70, 71). The ENS is composed of over 500 million neurons and is in constant communication with the central nervous system

through nerves such as the vagus nerve, which directly connects portions of the gut to the brain. It is through this ENS-vagus connection that information derived from elements of the ENS that innervate the gut is transmitted to the brain (70). Further contributing to the amount of information obtained in the gut are the luminal epithelial chemosensors, which can respond to and transmit information regarding bacterial metabolites such as neuroactive compounds that are contained within the luminal space (72). This gut-to-brain communication has been the subject of intensive study for many years and is now recognized to play an important role in the ability of gut-related pathologies to also result in mental health–related issues such as depression (73). The inclusion and recognition that microorganisms interact with elements of the ENS and thereby contribute to the information that is received by the brain concerning the physiological state of the gut has led to the relatively new field of study known as the microbiota-gut-brain axis (11).

To give an idea how extensive is the neuronal innervation of the gut and that such innervation can contribute to neurochemicals being present at the mucosal interface as well as in the mesenteric organs that are available to interact with microorganisms, the stomach provides an instructive example since it is essentially a dopaminergic organ producing the highest amount of dopamine in the body (74, 75). In fact, the entire length of the gut contains extensive arrays of neuronal innervation extending to the tips of the gut villi that produce biogenic amines which can be detected in the luminal space and are accessible to the microbiota (76, 77). Recent data has also shown that even epithelial cells are capable of producing neurochemicals such as the catecholamines dopamine and norepinephrine, albeit in the vaginal tract (78). Brosnahan et al. (78) reported that in response to infection with *Staphylococcus aureus*, the production of norepinephrine and dopamine by vaginal epithelial cells contributed to an enhanced state of inflammation as reflected by increased levels of the cytokines IL-6 and IL-8 and the chemokine MIP-3α. This recently reported ability of a vaginal epithelial cell to produce neurochemicals further highlights that bacterial-neurochemical interactions can occur at a number of host-bacterial interfaces and that the possible anatomical sites that can serve as an infectious entry point where microbial endocrinology can play a part in the infective process should not be thought to be restricted only to the gastrointestinal tract (79). Indeed, corneal epithelial cells have been reported to contain detectable intracellular concentrations of epinephrine that would be available to an infectious agent to utilize as it seeks to establish a productive infection (80). Thus, the examination of gut epithelial cells for the production of neurochemicals would seem warranted.

While host contributions of neurochemicals into the lumen of the gut, as well as presumably interstitial spaces in the lung, are easily understood due to extensive neuronal innervation in surrounding tissue, contributions by the microbiota itself have recently been recognized. Asano et al. (35) reported that while the catecholamines norepinephrine and dopamine were produced in appreciable physiological amounts in the luminal contents of specific pathogen-free mice, in germ-free animals substantially lower amounts were detected. Critically, whereas the majority of catecholamines in pathogen-free animals were structurally determined to be free and biologically active, those found in germ-free animals were present in a biologically inactive, conjugated form. Inoculation of germ-free animals with the flora from specific pathogen-free mice resulted in the production of free, biologically active catecholamines within the gut lumen. As such, this report clearly established that *in vivo* the microbiota is capable of producing neurochemicals that are commonly only associated with host production (35).

Other neurochemicals for which host levels were solely thought to be only due to host-derived production have also been found to have a portion contributed by the microbiota. Production of serotonin had been noted in the intestinal tract of the parasitic nematode *Ascaris suum* nearly three decades ago (81, 82). Comparison of the plasma level of serotonin in conventionally colonized mice with that in germ-free animals revealed that plasma serotonin levels were nearly 3-fold higher in the conventionally colonized mice as compared to the germ-free animals due to the presence of the microbiota in the conventionally colonized animals (83). More recently, Sridharan and colleagues demonstrated that gut microbiota in specific pathogen-free mice are able to produce serotonin (84).

STRESS AND INFECTIOUS DISEASE AS A MODEL OF THE RELEVANCE OF MICROBIAL ENDOCRINOLOGY FOR UNDERSTANDING MECHANISMS GOVERNING THE PATHOGENESIS OF INFECTIOUS DISEASE

The study of stress and how it relates to infectious disease has been the most intensely studied facet of microbial endocrinology to date. It provides the best example of how the study of the intersection of microbiology and

neurobiology, otherwise referred to as microbial endocrinology, can lead to new insights regarding the ability of microorganisms to cause disease. The majority of our understanding of the neurochemical outflow from stress has been through the examination of blood-borne catecholamine levels (85), reflective of an extensive catecholaminergic system in the gut (86). A handful of studies have found high concentrations of neurochemicals being produced within the gut for which little explanation exists (75, 87). As already mentioned, the stomach is a dopaminergic organ producing the highest amount of dopamine in the body (74). The entire length of the gut contains extensive arrays of neuronal innervation extending to the tips of the gut villi that produce biogenic amines which can be detected in the luminal space and are accessible to the microbiota (76, 77, 79). Throughout the body, most of the neurochemical degradation that is associated with stress is due to enzymes contained within the gut, not by extragastrointestinal systems as was once commonly believed (85). The gut is, therefore, the site where stress and microbiota can interact with consequences for the pathogenesis of infectious disease.

Both physical and psychosocial stress, as well as alteration of circadian rhythm, have been shown to alter microbiota community structure within the gut (88–92). These studies have relied on the analysis of *ex vivo* biological samples, primarily fecal matter. Given that the gut is not homogenously innervated by the ENS, it is likely that the elaboration of stress-related neurochemicals is primarily located in areas of high innervation. Recent work performed in murine (89, 93) and porcine (94) models has shown that the ability of stress to alter community structure within the gut strongly depends on the anatomical region of the gut in which the community is located (presumably correlated with high enteric innervation as these studies did not also examine neuroanatomical innervation in the microbiota sample regions). This highlights the inability of simple examination of fecal material to gain an understanding of the degree to which stress can influence host microbiota. Because of these limitations in methods, regional differences in microbiota community structure throughout the different gut regions are only now beginning to be elucidated (89, 93, 94).

A pivotal study which demonstrated the rapidity with which the microbiota community structure within the gut can rapidly change due to the influx of host stress-related neurochemicals into the lumen was shown in a neurotoxin-induced model of trauma (95). One of the consequences of severe trauma is the massive release of stress-related neurochemicals, primarily the catecholamines (96, 97). At the same time, gut-related infections primarily due to the emergence of commensal microorganisms, such as *E. coli*, are a well-recognized surgical issue (98–100). The use of a neurotoxin-induced model of injury was able to demonstrate that these two events were not just correlated, but the sudden and massive release of stress-related neurochemicals was actually the cause of the altered microbial community structure in the gut and the emergence of potential Gram-negative pathogens (95). Within 24 hours following the administration of the neurotoxin 6-hydroxydopamine, the release of catecholamines from neurotoxin-injured enteric neurons into the lumen resulted in the rapid alteration of microbiota community from one that was dominated by Gram-positive taxa to one dominated by a single Gram-negative bacterial species, namely *E. coli* (95). Further evidence of the association of neuronal activity to microbiota composition was observed as injured nerves rehealed over a 2-week period; the microbiota community structure returned to normal (95). Examination of a number of commensal *E. coli* strains obtained from the feces of healthy donors demonstrated their ability to rapidly increase their rate of growth in response to physiological levels of norepinephrine, thereby suggesting that the release of catecholamines within the gut may be a contributory factor in trauma-related sepsis (101).

Note Regarding Experimental Design Used in the Examination of Microbial Endocrinology–Based Mechanisms in Infectious Disease

As the spectrum of neurochemicals that have been identified in microorganisms is quite extensive, there is not one mechanism that can be identified that applies to all. Although it could quite correctly be proposed that another reason for the lack of common mechanisms being identified to date is the sheer number and diversity of microorganisms, the principal reason can, in part, be found in the art of microbial culture itself. The use of the word "art" is not taken lightly since many of the media which are used today, especially the rich media, had their origins in clinical diagnosis and surgical treatment where the rapid growth and quantitation of bacterial numbers determined when to amputate an infected limb or to simply debride (102). These media were, and still remain, largely of animal origin and contain highly undefined source materials such as brains and hearts as can be found in a prototypical example of

brain-heart infusion broth. The end result is that each microbiological medium will contain variable amounts of substrates and cofactors that can be used by the microorganism in the production of any one specific neurochemical. Further, the origin of the source material can change, especially if it is of animal origin. For example, media producers will obtain meat from the lowest-cost providers, leading to use of cattle from different regions and countries. In this common case, cattle will be of different genetic origins and undoubtedly will have been raised on different feed sources. The end result is that the concentration of neurochemical precursors and cofactors that are needed as part of the biochemical synthesis pathway for a particular neurochemical will vary greatly, leading to incorrect conclusions concerning the ability of a microorganism to produce or respond to a specific neurochemical.

An example of this can be seen in a report which concluded that the addition of epinephrine to trypticase soy broth did not result in any change in growth (103). The authors did not even consider that the medium employed already allowed optimal growth of their test bacterial species, which in this case was *S. aureus*. Further increases in growth were therefore highly unlikely. The principal difference between this report from Magee et al. (103) and the large numbers of other reports discussed in this article which have demonstrated the ability of a wide range of microbial species to respond to catecholamines is that the former used a rich microbiological medium while the latter studies used more *in vivo*–relevant media. That an incorrect interpretation of *in vivo* results can arise from results based on a less than ideal *in vitro* experimental design can be seen in a report which demonstrated the ability of epinephrine at a wound site to increase the rate of *S. aureus* growth by log orders over the nonepinephrine control (104). In explaining this *in vivo* result, Tran et al. (104) dismissed any consideration of a direct effect of the epinephrine on the microorganism itself based on the *in vitro* results obtained by Magee et al. (103) and instead ascribed the result due to inhibition of immune responses, although prior reports, such as those by Miles and colleagues (18, 105), found no evidence of immune suppression as a mechanism by which epinephrine potentiated intradermal infections. It should be noted that subsequent studies have shown that epinephrine actually potentiates the ability of neutrophils to accumulate at the site of infection (106), which would lead to less bacterial growth, not more.

Other considerations in experimental design have been covered in detail elsewhere (for review see reference 107). Among the specific points that need to be emphasized in addition to those already discussed regarding medium selection is that of inoculum density. O'Donnell et al. (108) reported that the lower the inoculum density in *in vitro* culture, the greater the response to exogenously added catecholamines. This is not an unexpected result if considered from an infectious disease standpoint where the host most often encounters not high infectious loads, but instead, low doses that then result in disease. Inoculum densities in the millions or even hundreds of thousands of colony forming units in tissue culture are not reflective of the *in vivo* situation, where as little as 10 colony forming units of an infectious bacterium such as *E. coli* O157:H7 can result in infection (109). Utilization of doses of microorganisms that reflect the amount that actually results in the development of a productive infection in the host is critical to elucidating the mechanism(s) by which host and microbial factors interact in the pathogenesis of infection. As such, the overall consideration that must govern any examination of the microbial endocrinology–based mechanisms underlying the pathogenesis of infectious disease is the design of an experimental system which more closely mimics the *in vivo* milieu that the microorganism finds itself in at the time of initiation of the pathogenic process.

Stress-Related Neurochemicals as Prototypical Neurochemicals Used in the Examination of the Role of Microbial Endocrinology in Infectious Disease

Throughout this article, stress has served as a unifying theme to illustrate the extent to which microbial endocrinology plays a role in infectious disease. This is not as much owing to any specific editorial design but instead due to the majority of publications which have utilized stress-related neurochemicals in experimental design. As such, the mechanisms underlying the ability of the main family of stress-related neurochemicals, the catecholamines (Fig. 2), to influence the pathogenesis of infectious disease will be the primary focus of this section. Other neurochemicals not related to the stress response will also be discussed following the catecholamines.

Catecholamine biochemistry

Principal among the catecholamines that are released during stress events are epinephrine from the adrenal medulla and norepinephrine from sympathetic nerve terminals. Interest in the role that catecholamines may play in bacterial pathogenesis has been heightened by the demonstration that catecholamines can directly

stimulate bacterial growth and elaboration of virulence-associated properties as well as production of autoinducer-like substances (4, 9, 77, 108, 110–117). The biochemical pathway for the synthesis of catecholamines is L-dopa (most commonly derived from food sources) → dopamine → norepinephrine → epinephrine (Fig. 2). Given the close structural similarity between the 2,3-dihydroxybenzoylserine ring of catecholamines to the catecholate siderophores, it is not surprising to find the involvement of iron as a mechanism (113).

The question may be asked whether most of the results seen are simply due to the catecholamine-facilitated provision of iron. Results from a number of studies in which iron was *not* a limiting factor demonstrate that this is not the case. These include, but are not limited to, studies such as that of Peterson et al. (118), who showed that exposure to norepinephrine increased the ratio of horizontal gene transfer of antibiotic-resistant genes between enteric pathogens. They further demonstrated that the ability of norepinephrine to increase horizontal gene transfer between bacteria was blocked by α but not β-adrenergic receptor antagonists and that, critically, these results were observed in iron-replete medium.

Other studies have also demonstrated that the effects of stress-related neurochemicals are not simply due to the facilitated provision of iron; some of these include studies in which exclusively enteric pathogens such as *Yersinia enterocolitica* increase growth in the presence of norepinephrine and dopamine, but not when exposed to epinephrine (4), despite having been shown in other studies to increase provision of iron (113). This specificity in the utilization of specific catecholamines may have an evolutionary explanation in that bacteria may have developed the ability to recognize host neurochemicals based on the evolutionary association with specific anatomical regions of the host. In the case of epinephrine in the gut, enteric microorganisms would not encounter this neurochemical since the neurons contained within the ENS that innervates the entire length of the gut do not possess the enzyme phenylethanolamine-*N*-methyltransferase, which is needed for conversion of norepinephrine to epinephrine in the catecholamine biosynthetic pathway (Fig. 2) (119). As such, intestinal pathogens which are not commonly associated with extraintestinal infection, such as *Y. enterocolitica*, have not developed the ability to respond to the stress neurochemical epinephrine despite its ability to facilitate the provision of iron.

Work performed in the 1970s further points out that iron is simply not the only mechanism. Okamura et al. (120) demonstrated that while dopamine and norepinephrine can be oxidized by membrane-bound tyramine oxidase at relative rates of 99% and 77%, respectively, epinephrine cannot be utilized at all. Again, specificity in the utilization of individual members of the catecholamine family of stress-related neurochemicals by unique microorganisms provides key insights into mechanisms and demonstrates that we need to look beyond simple, albeit critical, mechanisms such as the provision of iron. That iron provision may be happening at the same time as part of an infectious microorganism's response to any neurochemical should not obscure the search for other mechanisms. More recently, Xu et al. in 2015 (121) demonstrated that analysis of the transcriptomic profiles of the food-borne pathogen *Campylobacter jejuni* NCTC 11168 grown in iron-restricted medium in the presence or absence of norepinephrine or epinephrine revealed that each catecholamine elicited the expression of unique numbers of genes. For example, of the 183 and 156 genes that were differentially expressed by *C. jejuni* as a result of growth in epinephrine- or norepinephrine-containing medium, respectively, only 102 genes were common to both catecholamine conditions. Those genes that were differentially expressed encompassed a wide variety of cellular functions beyond simply iron uptake extending from DNA repair and metabolism to oxidative stress response and ribosomal protein biosynthesis as well as virulence and motility (121). In a similar fashion, earlier work by Li et al. (122) demonstrated that culture of the respiratory pathogen *Actinobacillus pleuropneumoniae* with epinephrine or norepinephrine resulted in the differential expression of 158 and 105 genes, respectively, as compared to controls. Critically, among the catecholamine-induced differentially regulated genes, only 18 genes were common to both epinephrine and norepinephrine, which suggested that bacterial pathogens such as *A. pleuropneumoniae* may possess multiple responsive systems for individual members of the catecholamine family that impact bacterial physiology.

One of these possible neurochemical-related mechanisms may be the induction of growth factors produced by microorganisms as part of their response to neurochemicals. The first description of a neurochemical-induced growth factor produced by a bacterium was reported in 1996 when *E. coli* O157:H7 cocultured with norepinephrine resulted in a supernatant that contained a growth factor that when applied to naïve *E. coli* O157:H7 increased the growth rate over 5 logs as compared to controls (110). Remarkably, only amounts as low as 0.391% of conditioned supernatant from norepinephrine-stimulated bacteria were needed to induce

rapid growth in naïve cells. Subsequent work demonstrated that a number of bacterial strains were capable of production of neurochemical conditioned medium that could stimulate the growth of naïve cells (123). Use of this neurochemical-produced conditioned media has been successfully employed in the resuscitation of *Salmonella enterica* serovar Typhimurium and enterohemorrhagic *E. coli* from the viable but nonculturable state (124) as well as used in the design of a new selective chromogenic plating medium for the identification of *Bacillus cereus* (125). To date, concerted attempts at elucidating the chemical structure of this neurochemical-induced growth factor have been unsuccessful (M. Lyte, unpublished work), although prior work has shown it not to be a siderophore (110). However, a report by Burton et al. (126) disputed the nonsiderophore nature of the norepinephrine-conditioned medium and argued that it was in fact enterobactin and its breakdown product 2,3-dihydroxybenzoylserine.

Catecholamine receptor pharmacology

Catecholamines bind to specific receptors: norepinephrine to adrenergic receptors (divided into α and β types) and dopamine and related synthetic compounds based on catecholamine structure such as dobutamine to dopaminergic receptors (divided into D1 to D5 subtypes). Dobutamine is a synthetic derivative of dopamine and is widely used in the treatment of congestive heart failure. Although the vast majority of catecholamine receptor pharmacology has been done in mammalian systems, the characterization of adrenergic receptors in nonmammalian systems utilizing pharmacological reagents developed for mammalian systems has enabled the identification of adrenergic receptors in *T. pyriformis* (127) and *Trypanosoma cruzi* (128). The small numbers of studies that have attempted to examine adrenergic receptor pharmacology in bacteria have produced conflicting results. The first reported study which examined the ability of adrenergic receptor antagonists to block the ability of norepinephrine to induce growth of *E. coli* suggested the presence of a novel non-α, non-β adrenergic receptor in a variety of Gram-negative bacteria (129). Work by Sperandio and colleagues (130, 131) has shown that α-adrenergic antagonists could block the ability of catecholamines to induce the production of autoinducer-3 in *E. coli* 0157:H7, suggesting cross-communication between host endocrine signals and bacterial quorum sensing system(s). Additionally, Freestone et al. (132) demonstrated the ability of involvement of dopaminergic antagonists to block catecholamine-induced growth in *E. coli* O157:H7, *S. enterica*, and *Y. enterocolitica*.

Catecholamines in the hospital setting and relevance to infectious disease susceptibility

A majority of infections that are life-threatening occur in the hospital setting (133). Among these nosocomial pathogens, two specific genera stand out: *Staphylococcus* spp. (134) and *Clostridium* spp. (135). In the case of the former, coagulase-negative staphylococci, specifically *Staphylococcus epidermidis*, and for the latter *Clostridium difficile*, are the primary species contributing to high rates of infection (135–137).

In the hospital setting patients are exposed to high levels of stress either through clinical protocols involved in treatment or through the administration of drugs that dramatically elevate the level of systemic catecholamines. Treatments that contribute to high levels of circulating stress-related neurochemicals include mechanical ventilation and parenteral feeding. Mechanical ventilation is a method of assisted breathing in which positive pressure is applied via an endotracheal or tracheostomy tube to force air into the patient's lungs. Parenteral nutrition refers to feeding nutritional formula to a patient via an intravenous tube thereby bypassing the normal oral route of digestion. Human studies have shown that both mechanical ventilation and parenteral nutrition result in a sustained elevation of circulating levels of catecholamines (138, 139). As will be described in the following sections, these procedures ultimately play an iatrogenic role in the development of nosocomial infections.

Coagulase-negative staphylococci as nosocomial pathogens

Of the 5 million intravascular catheters employed each year, approximately 250,000 catheter-related bloodstream infections are reported, with an attributable mortality of 12 to 25% (140, 141). The organisms most commonly isolated from indwelling medical devices belong to the coagulase-negative staphylococci (C-NS). The C-NS constitute a major component of the skin microflora and were for many years regarded as saprophytes, or at least as organisms with no or low virulence. However, the C-NS, in particular *S. epidermidis*, have become recognized as serious nosocomial pathogens associated with indwelling medical devices such as catheters (142–145) and prosthetic joints (146). The increasing incidence of infections caused by these bacteria can be attributed to their particular affinity for the biomaterials of the invasive technologies integral to much of modern medicine. In association with appropriate biomaterial surfaces, such as those ranging from polysilicone in catheters to steel in hip replacements,

S. epidermidis adheres and proliferates to form biofilms, highly complex structures that represent functional communities of microbes (147, 148). Understanding the environmental factors that can contribute to the ability of C-NS to act as nosocomial pathogens would be of obvious benefit to high-risk patients.

Evidence to support a role for catecholamines in the formation of *S. epidermidis* biofilms

S. epidermidis biofilms are multilayered microbial cell clusters embedded within a diffuse extracellular polysaccharide (EPS) matrix often referred to as slime (149). Although the mechanics of biofilm formation are not yet fully understood (150), it is generally agreed that the process takes place in two stages: rapid attachment to the surface followed by a prolonged phase that involves cellular proliferation and intercellular adhesion (151). Adherence depends on cell-surface characteristics of the bacteria, in particular, hydrophobicity (152, 153), the presence of adhesive surface-associated proteins (154, 155), EPS production (156), the nature of the biomaterial (157, 158), and the presence on the indwelling device of deposited host proteins, such as fibrinogen, fibronectin, and vitronectin (151). Characterization of transposon mutants of *S. epidermidis* deficient in biofilm formation (159, 160) has shown that initial attachment is mediated in part by the *atlE* gene product, a surface-associated autolysin which also possesses vitronectin-binding activity (161). Intercellular adhesion and the formation of multicellular layers requires EPS synthesis, which is composed of the polysaccharide intercellular adhesin (PIA), a linear 1,6-linked glucosaminoglycan (149). Production of PIA is dependent on the *icaABC* operon (162). While relatively little is known about control of *atlE* expression in *S. epidermidis*, synthesis of PIA has recently been shown to be phase-variable (163).

Initial studies had shown that among the Gram-positive bacteria that could respond to micromolar concentrations of neurochemicals were members belonging to *Staphylococcus* genera (164). In particular, norepinephrine increased the planktonic growth of *S. epidermidis* by log orders (164). As the vast majority of infections occur not as planktonic growth, but instead as biofilms, Lyte et al. (114) examined the ability of the catecholamines, and synthetic drugs based on catecholamines such as dobutamine that are most often employed in the clinical setting, to influence the formation of *S. epidermidis* biofilms. The exposure of *S. epidermidis* to pharmacologically relevant concentrations of the widely used inotropic drugs, dobutamine and norepinephrine, resulted in increased biofilm growth and production of EPS as shown by both scanning electron microscopy and immunofluorescence, respectively (114). In demonstrating catecholamine and catecholamine-based synthetic drug-induced induction of *S. epidermidis* biofilm, two methodological aspects were employed that differed from previous studies of biofilm formation and emphasize the importance of experimental design in the examination of possible microbial endocrinology–based mechanisms in an infective process as already discussed.

First, only 10 to 100 colony forming units of *S. epidermidis* were used to seed the biomaterials (114). This small amount of bacteria was chosen to reflect physiologically relevant infecting doses that were likely to be encountered in the clinical setting. This is in contrast to the majority of prior biofilm studies which have used log-orders higher amounts of bacteria to establish biofilms (165–167). Second was the use of the culture conditions which employed a plasma-supplemented minimal media. This also differs from other studies which have used rich microbiological media to study biofilm formation, but which may be argued do not reflect *in vivo* conditions in which host factors present in plasma which are recognized to play a role in initial bacterial adhesion are not present. This observation is of particular consequence since a number of previous publications had noted that plasma actually prevented *S. epidermidis* biofilm formation (167–169). Thus, this work was the first demonstration that catecholamines and synthetic drugs based on the catecholamine structure may serve as an etiological factor in the bacterial colonization of indwelling medical devices due to their ability to stimulate *S. epidermidis* growth and biofilm formation (114, 164).

Possible mechanisms by which stress-related neurochemicals and catecholamine-based synthetic drugs influence infection in the clinical setting

Due to their catechol moieties (as previously discussed), catecholamines have been shown to facilitate the provision of iron from host iron-sequestering transferrin enabling *S. epidermidis* biofilm formation (114, 164). The recognized inability of *S. epidermidis* to grow in normal human plasma without extra iron supplementation has been ascribed to the presence of transferrin (170, 171). The ability of transferrin to sequester iron, coupled with the lack of a demonstrable mechanism by which *S. epidermidis* could acquire such bound iron except in the presence of therapeutic administration of catecholamines and synthetic catecholamine-based drugs, suggests that the use of catecholamine antagonists may provide a means by which to prevent biofilm formation (172).

Another report which has expanded the relevance of understanding microbial endocrinology–based mechanisms in the clinical setting concerns the ability of catecholamines to facilitate physiological recovery of antimicrobial-damaged bacteria (173). In an effort to decrease the incidence of catheter-related bloodstream infections, the use of antimicrobial-impregnated catheters has taken on increasing usage (174, 175). However, the utilization of these catheters, which are usually impregnated on their surface with the antimicrobials rifampin and minocycline, has not decreased the incidence of catheter-related bloodstream infections. Freestone et al. (173) demonstrated that while exposure of C-NS to concentrations of rifampin and minocycline that exceeded the minimum inhibitory concentration resulted in nonviable bacteria as confirmed by failure to grow in culture, the addition of norepinephrine and dopamine at clinically relevant concentrations resulted in the physiological and growth recovery of antimicrobial-damaged C-NS.

More recent examinations of the role of catecholamines in the formation of biofilms and their relevance to the clinical setting have been published. Lanter et al. (176) have reported that addition of physiologically relevant amounts of norepinephrine induced the ability of individual clusters of bacteria under conditions of low iron availability to break off from established *Pseudomonas aeruginosa* biofilms. The authors proposed that this may be a mechanism by which bacteria such as *P. aeruginosa* that can colonize atherosclerotic plaques can break off due to the hormonal state of the patient, thereby causing disruption of the plaque integrity ultimately increasing the chance of heart attack and stroke (176). An earlier report by Freestone et al. (177) had demonstrated that catecholamines and catecholamine-based synthetic drugs may also be a causative factor contributing to the ability of *P. aeruginosa* to colonize the airways of critically ill patients, leading to ventilator-associated pneumonia. Another clinically important bacterium that forms biofilms as part of its infectious etiology, *Streptococcus pneumoniae*, has also been shown to be responsive to neurochemicals. Sandrini et al. (178) demonstrated that *S. pneumoniae*, which is responsible for community-acquired and nosocomial pneumonia, is responsive to clinically relevant concentrations of norepinephrine such that exposure not only increased the expression of genes that are functionally relevant in metabolism and subsequent host colonization, but also resulted in increased growth and biofilm formation.

It must be emphasized, however, that (as already discussed previously) the ability to provide iron may not be the sole mechanism by which catecholamines and catecholamine-based synthetic drugs may interact with microorganisms in the clinical setting to promote growth and alter virulence-related properties. Data from other laboratories have shown that catecholamines may modulate bacterial physiology and virulence in nongrowth-, noniron-related contexts. Vlisidou et al. (179) used a ligated ileal loop model of virulence to show that norepinephrine significantly enhanced attachment of *E. coli* 0157:H7 to calf intestinal tissue, while it has been reported that epinephrine stimulates expression of a type III protein secretion apparatus and motility in *E. coli* 0157 in a *LuxS* mutant as well as production of an autoinducer-3 molecule (180). Interestingly, both the autoinducer-3 and epinephrine-dependent motility responses could be blocked by the adrenergic receptor blockers propranolol and phentolamine, suggesting the presence of a receptor-mediated, non-iron-related, process.

More recently, Pasupuleti et al. (181) has shown that the ability of norepinephrine to function as a chemoattractant for enterohemorrhagic *E. coli* is dependent on the conversion of norepinephrine to 3,4-dihydroxymandelic acid following the norepinephrine-dependent induction of genes encoding tyramine oxidase. The continued production of a chemoattractant by enterohemorrhagic *E. coli* already colonizing the intestinal mucosa due to exposure to host norepinephrine has been proposed by the authors to serve as a recruitment vehicle by which additional *E. coli*, and potentially other bacteria, may be attracted to the infection site, thereby contributing to the pathogenic process (181). And as regards the role of catecholamines in the ability of bacteria to attach onto surfaces as a first step in biofilm formation, recent data has further shown the involvement of non-iron-dependent mechanisms. For example, Park et al. (182) has demonstrated that exposure of engineered *E. coli* which displays a catecholamine-based surface moiety results in increased adhesion onto a variety of surface materials.

SPECTRUM OF INFECTIOUS DISEASE–ASSOCIATED MICROORGANISMS IS EXTENSIVE AND GROWING

As can be expected, the more one digs into the literature to find instances of where neurochemicals and bacteria have been examined, the more one finds papers which provide tantalizing clues that these two systems, one the neurophysiological and the other microbial, could interact in totally unexpected ways. For example, *C. jejuni* is a highly prevalent food-borne pathogen that requires a microaerophilic environment in the laboratory

for its propagation. However, the addition of norepinephrine to the microbiological growth medium was shown by Bowdre et al. to result in tolerance to and growth of *C. jejuni* in an aerobic environment (183). At the time, the wider implications of this important finding as to the role of neurochemicals in general in the pathogenesis of infectious disease had not yet been fully envisioned.

Examination of the literature often reveals interesting reports of the association of neurochemicals and infectious disease in the same manner as in the case of the early reports on the role of catecholamines in the development of gas gangrene. These reports can stimulate insightful ideas that inform the design of microbial endocrinology–based experimental design. For example, it has been well recognized that certain strains of bacteria that are associated with food spoilage can produce histamine (184–186). Based on these reports, an examination of microorganisms that can colonize the respiratory tract revealed that infectious bacteria can produce histamine by decarboxylation of histidine (29). The possible role of bacteria-produced histamine as an inflammatory mediator contributing to respiratory illness was subsequently proposed (187). Subsequent to these studies, Voropaeva (188) examined a large cohort of microbial strains isolated from children with bronchial asthma for antimicrobial resistance and the ability to produce histamine (188). It was demonstrated that a positive correlation existed between the ability of a particular infectious strain to produce histamine and antimicrobial resistance. Whether this could causally account for the ability of the infectious microorganisms to colonize the airways of children with bronchial asthma has yet to be shown.

As already noted, a number of groups have shown the ability of neurochemicals to influence virulence-related properties of infectious microorganisms in an increasing number of studies (4, 9, 77, 108, 110–117). In terms of known virulence factors that contribute to invasion of host cells, exposure of enterotoxigenic *E. coli* to norepinephrine was shown to increase the expression of the K99 pilus adhesion that facilitates attachment to the gastrointestinal mucosa by over 235-fold (111). Stress-related neurochemicals have been shown to increase conjugative transfer of antibiotic-resistant genes between enteric bacteria, thereby contributing to the increased prevalence of antibiotic-resistant food-borne bacterial pathogens in the food supply (118). Additionally, the ability of monoamines such as norepinephrine and dopamine to alter gene expression has now been shown for a number of pathogenic microorganisms including *M. hyopneumoniae* (69), *S. enterica* serovar Typhimurium (189), and *Vibrio parahaemolyticus* (190).

More recently, the motility and biofilm formation of the aquatic Gram-negative bacterium *Vibrio harveyi* has been shown to be responsive to norepinephrine and dopamine (191). Since *V. harveyi* is an opportunistic pathogen for a wide variety of marine animals including shrimp and oysters, it has been suggested that stress in these marine animals (such as cold stress) and the subsequent elaboration of stress-related neurochemicals represent a microbial endocrinology–based mechanism facilitating infection (192). Similar results have also now been reported by others for other pathogenic *Vibrio* spp. such as *Vibrio anguillarum* and *Vibrio campbellii* (193).

It should be noted that although this article has dealt mainly with prokaryotic microorganisms, the role of neurochemicals in infectious disease involving eukaryotic microorganisms such as yeasts and parasites has also been well documented. In the case of yeasts, the production and response of yeasts to neurochemicals such as the stress-related biogenic amines has been demonstrated (194). An excellent review of the role of endocrinology in the pathogenesis of fungal infections has been published (195). Interestingly, reports dealing with the interaction of parasites with neurochemicals have also consistently appeared in the literature. For example, *Plasmodium falciparum* was shown to produce a somatostatin-like peptide similar in structure to that of mammalian somatostatin (196). The ability of intracellular forms of the parasite *T. cruzi* to differentiate from the amastigote for the trypomastigote form was shown to be able to be triggered when exposed to adrenergic ligands present in host cells (197). Coppi et al. (198) have reported that catecholamines could induce the ability of the enteric parasites *Entamoeba invadens* and *Entamoeba histolytica* to differentiate into the infectious cyst stage. Remarkably, only mucin had previously been shown to be able to induce cyst stage formation (199). As such, the authors have proposed that *Entamoeba* spp. possess an autocrine catecholamine system to stimulate encystation and thereby increase subsequent infectivity for other animals (198).

Another protozoal parasite, *Cryptosporidium parvum*, has also been shown to be responsive to a neurochemical. Pretreatment of infant mice with agmatine inhibited infection with *C. parvum* by altering the cellular metabolism to such a degree that colonization of the intestine was reduced (200). Agmatine, which is a polyamine synthesized within the gastrointestinal tract, has a number of functions including that as a novel neurotransmitter whose spectrum of host targets within the nervous system

is still poorly understood (201, 202). This incomplete understanding of the cellular targets for agmatine only further highlights the relevance of the intersection of microbiology and neurobiology that forms the theoretical basis of microbial endocrinology. Since agmatine is also synthesized by bacteria (37), the possibility that a bacteria-produced neurochemical affecting host neurophysiology must be considered. Such bacteria-host interactions which are governed by a neurochemical produced by both points out the bidirectionality of microbe-host interactions inherent in a microbial endocrinology–based approach.

MICROBIAL ENDOCRINOLOGY AND THE MICROBIOTA-GUT-BRAIN AXIS: WHY IT MATTERS IN INFECTIOUS DISEASE

The concept that bacteria in the gut can communicate with the brain, thereby influencing behavior, and that the host nervous system can, in turn, influence the composition of the gut microbiota, has given rise to the concept of a microbiota-gut-brain axis (11). An ever-growing number of studies have demonstrated the ability of bacteria to influence brain function, for which a number of possible mechanistic routes have been proposed (10, 12, 59, 60, 203–207). Due to shared neurochemicals between host and microbe, microbial endocrinology has been proposed as one of the mechanisms by which such reciprocal communication between brain (nervous system) and microorganisms in the gut can occur (208, 209).

A number of anatomical similarities can be found between the ENS and the central nervous system (210). Multiple pathways underlie communication from the gastrointestinal tract to the brain, with sensory neurons in the gastrointestinal tract providing a route, via the vagus nerve, to provide early signaling to the brain regarding the presence of potential pathogens within the gut (211, 212). These studies clearly demonstrate that host-derived central nervous system–based mechanisms are capable of detecting changes in the microbial flora contained within the gastrointestinal system. From an evolutionary viewpoint, this should make elegant sense that over the long evolutionary period in which host and microorganisms have coexisted, that this evolutionary symbiosis should, in addition to the well-recognized functions of nutrition etc., also contain an element in which monitoring of the microbiota is in the best interests of the host. The bidirectional nature of microbial endocrinology implies that the microbiota also responds to the host with the microbiota-gut-brain axis (7, 208, 209).

While the role of microbial endocrinology in the microbiota-gut-brain axis as regards behavior is straightforward and immediately apparent, its role in infectious disease may be less so but of no less consequence. Microbial endocrinology, as previously discussed, is an evolutionary-based concept (2, 5). And as highlighted already, a number of past investigators have also utilized evolution as a theoretical basis for examining the possible health implications of shared messenger molecules between host and microbe, albeit not in the context of infectious disease (23–25, 213). Such consideration of clinical-related disease which has an infectious disease etiology, as will be discussed in the following section, holds the potential for the development of new clinical-based therapies in which the consideration of the recognition of the infectious agent as a neurochemical-responsive organism plays a central role.

SIRS: A Possible Model for the Use of Microbial Endocrinology in Treatment of Disease with Infectious Etiology

As the prototypical example of how microbial endocrinology can lead to potential new therapies in which the microbiota-gut-brain is involved, the clinical condition of systemic inflammatory response syndrome (SIRS) will be employed. SIRS is one of the leading causes of mortality and morbidity in the surgical intensive care unit (214). The development of SIRS is characterized by the production of multiple cytokines as part of an inflammatory cascade due to an insult that may be of infectious origin (215). The incidence of mortality and morbidity increases dramatically if SIRS progress on to multiple organ dysfunction syndrome or multiple organ failure (216). While a number of theories, most prominently the gut as a motor organ of failure (217–219), have offered some insight into the pathophysiology, treatment still remains problematic (220). Ongoing research into the microbial-based mechanisms responsible for injury-induced alterations in gut bacterial diversity has continued in an effort to identify mechanisms that can lead to effective therapies (221–223). For example, enteral nutrition contributes favorably to changes in bacterial populations, but also to maintenance of mucosal integrity including the nerves within the villi that serve as sensory reporters of gut status, and its use has contributed to a reduction in mortality (224). Intestinal villi are innervated by catecholaminergic nerves within the ENS. Although these adrenergic nerves terminate near the basolateral membranes of the mucosal epithelial cells within the gut, they are nonetheless responsive to general sympathetic activity since enteric adrenergic neurons are

located in the prevertebral ganglia outside the gut wall (extrinsic to the gut) and hence are susceptible to modulation by central nervous system activity.

The continued development of new theories emphasizing the interplay of the intestinal mucosa with the altered gut microbiota emphasizes the critical role of the gut microbiota in the development of inflammation. Indeed, use of a probiotic/synbiotic combinatory therapy has resulted in improvement in mortality and morbidity in critically ill patients to reduce complications such as the development of SIRS and multiple organ failure following trauma (225). However, none of the current treatments specifically address the contributory role of altered bidirectional gut-brain neural communication resulting from damaged intestinal mucosal integrity to the development of inflammation.

Acknowledging that infectious agents are only infrequently isolated from patients who have already undergone multiple rounds of antibiotics during hospitalization, the proposed microbial endocrinology–based hypothesis proposes that the central nervous system promotes an inflammatory response directed against an iatrogenically transformed enteric microbiota. During hospitalization, the immediate and sustained induced changes in microbial ecology coupled with the widespread damage to intestinal villi, and the enteric nerves which innervate them, along with the overall high levels of circulating catecholamines, all synergistically exacerbate the altered neurophysiology of the individual. Critically, these profound gut-related changes cannot go unnoticed by the brain in the overall regulation of homeostasis and may, therefore, represent the perceived threat that is responsible for the ever-escalating inflammatory response.

Why Current Treatment Regimens Promote Microbial Endocrinology–Based Interactions

As viewed from an evolutionary perspective, two distinct, but interrelated, phases evolve in the development of SIRS. In the immediate phase following the initial inciting traumatic event, the pronounced release of large amounts of stress-related catecholamines coupled with the loss of enteral nutrition leads to alteration of the gut microbiome, the so-called undrained abscess of multiple organ failure (226). Following trauma, altered bacterial diversity within the gut is well recognized to occur in the intensive care setting to the extent that the gut has long been viewed as a reservoir of occult infection (227). Animal models have revealed an association between the release of catecholamines and a dramatic shift from largely Gram-positive anaerobic bacteria to Gram-negative bacteria, with *E. coli* as the overwhelmingly predominant Gram-negative species increasing by log orders in absolute numbers (95, 228). Further, Alverdy et al. (229) demonstrated that increases in luminal levels of norepinephrine following surgical stress resulted in increased expression of the PA-I lectin/adhesin of *P. aeruginosa*, leading to greater attachment and colonization of the gut and increasing the eventual likelihood of lethal gut-derived sepsis. The gut has therefore long served as a focal point of inquiry (230).

Within the intensive care unit, interventional strategies may enhance the unwanted consequence of ramping up the inflammatory cycle. Interventional support, notably the use of total parenteral nutrition, exacerbated by the administration of synthetic catecholamine-based drugs, and mechanical ventilation, all contribute to increased sympathetic activation (138, 139). The resultant highly increased systemic level of catecholamines contributes to the maintenance of a Gram-negative bacterial population in the gut through direct neuroendocrine-bacterial interactions as defined by microbial endocrinology (231). The overall effect of current interventional care thus perpetuates the altered gut environment and most importantly provides continuous signaling to the central nervous system that the initial inflammatory response has been inadequate to deal with the altered gut microbiota. Indeed, as the patient progresses along a path leading to SIRS, heroic interventional support measures further increase the components of the "fight or flight response," thereby ensuring a continuing high level of circulating stress-related neurochemicals derived from both endogenous and exogenous sources. Thus, from an evolutionary perspective, the response of an organism to a threat (altered Gram-negative predominant gut microbiota perceived as an infectious threat) which has not been contained by an initial response (inflammatory response) is to continually increase that response until it proves effective. The end result of this interventional-driven evolutionary response is the continual ramping up of the inflammatory response and the eventual development of SIRS (231).

How a Microbial Endocrinology–Based Understanding Can Lead to New Treatment Modalities

Since one of the principal drivers of an altered, largely Gram-negative, microbiota in the gut is the continual provision of high levels of catecholamine-based synthetic drugs as previously discussed (as well, of course, as the patient's own trauma-induced host production), more judicious administration of such drugs, the currently

accepted conversion from total parenteral nutrition to enteral nutrition, and the use of selective beta blockers should each diminish the overall stress response and allow the microbiota to return to a more normal composition. Beta blockers have already been used successfully in the management of severe pediatric burns to reverse burn injury–induced muscle-protein catabolism (232). Other points of entry exist that may serve as potential targets for therapeutic intervention. A dual motor system based on the microbial endocrinology and the evolutionary symbiosis between the gut and the brain has been proposed as the basis for the design of new treatment modalities for SIRS (231).

CONCLUDING THOUGHTS

In the nearly quarter of a century since the introduction of the proposal that microbial endocrinology has a role to play in the pathogenesis of infectious disease, increasing numbers of reports (as discussed in this article) have begun to examine the ability of a wide panoply of neurochemicals to influence the infectivity of microorganisms. There is a rich historical context dating back to the early 1930s which has shown that neurochemicals have a decisive role to play in infection. As already discussed, the use of an experimental design that seeks to more closely mimic the *in vivo* milieu will continue to play a critical role in furthering continued examination of the mechanisms by which microbial endocrinology can influence the pathogenesis of infectious disease. This is not an easy undertaking, as experiments cannot be conducted in the same manner that is widespread in current microbiological research, namely the use of rich medium that does not reflect the host environment that the microorganism must deal with during the infective process. And the continued development of the microbiota-gut-brain axis and its relevance regarding infection will continue to be an area of high interest. The intersection of microbiology and neurobiology as embodied in microbial endocrinology represents a translational-oriented research direction that may yield new insights into the mechanisms responsible for the development of infectious disease but also point the way to interrupt such interactions and in this aspect provide a new generation of anti-infective strategies.

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