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Mini-Review

Microbial Endocrinology in Microbiology: A Mini-Review -

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ABSTRACT

Microbial endocrinology represents the intersection of two seemingly desparate fields, microbiology and neurobiology. Current research developments in intestinal microbiota and microbial endocrinology are considered. Its relationship with behavior, metabolism and a variety of diseases are discussed. Pathogenesis, pathophysiology and possible therapeutic applications to the intestinal microbiome communities are reviewed.

INTRODUCTION

Microbial endocrinology represents the intersection of two seemingly desperate fields, microbiology and neurobiology. This is based on the shared presence of neurochemicals that are exactly the same in the host as well as in the microorganism. 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 signalling system in the host may have been acquired due to lateral gene transfer from microorganisms. Current perceptions of how stress influences the outcome of infections focus upon the immunology and leave the microbe largely as a bystander.

Stress by the central nervous system leads to release a variety of hormones, neurochemicals and neuropeptides, which can directly affect immune function, usually resulting in impairment [1]. Nearly all immune cell classes possess receptors for the stress-related neurohormones adrenaneline and noradrenaline [2]. The ability of bacterial pathogens to influence behavior has been recognized for decades, most notably bacteria that invade the nervous system. The term microbial endocrinolgy and the concept of the "gut microbiome-brain axis" developed in the early 1990's. Since their introduction both concepts have been the subject of growing investigations. In this mini-review pathogenesis, pathophysiology and the therapeutic applications of the microbial endocrinology in microbiology will be discussed.

PATHOGENESIS

Although most microbial endocrinology studies have focused on the interaction of gut bacteria with the fight and flight catecholamines adrenaline, noradrenaline and dopamine, it is important to realize that bacteria and fungi can recognize a surprising number of eukaryotic hormones and other signals [3]. Structurally, the catecholamine stress hormone family are a group of widely acting acting effector compounds derived from tyrosine and other dietary aminoacids. They chemically comprise a benzene ring with two adjacent hydroxyl groups and an opposing amino side chain which contributes to receptor specificity [4]. The catecholamines use the second messenger adenylate cyclase system to exert their downstream effects after receptor binding [5].

The synthesis pathway for catecholamines begins with dietary L-dopa, which is enzymatically converted into dopamine, norepinephrine and finally adrenaline. Noradrenergic and dopaminergic receptors containing nerve terminals are widely distributed within the mammalian body, including the GI tract where they are components of the enteric nervous system. Further research of microbial endocrinolgy discovered hormone receptors in microorganisms and it was hypothesized that they represent a form of intercellular communication [8]. Pathogenic neurotoxins such as neurotoxin 6-hydroxydopamine were shown to alter norepinephrine levels in mice presenting the bi-directional nature of the host-microbe interaction [9]. Iyer et al. [10] showed that many enzymes involved in host hormone metabolism (including epinephrine, norepinephrine, dopamine, serotonine, melatonin etc.) might have evolved horizontal gene transfer from bacteria.

More clues to the existence of crosstalk between bacteria and the endocrine system came from the discovery of inter-kingdom, including the hormonal communication between microorganisms and their hosts [11]. It appeared from the initial observation that bacteria perform Quorum Sensing (QS), communication based on producing and sensing Autoinducer (AI) molecules. These AI molecules are hormone-like elements that regulate functions, including bacterial growth, motility and virulence [12]. In addition, to affecting bacteria, these signals can modulate host cell signal transduction. Some AI molecules have crosstalks with host hormones for activating signalling pathways [13].

Host hormones also affect bacterial gene expression which in turn can have consequences on their hosts [14]. For example, catecholamines enhance bacterial attachment to host tissues [12]. Quorum sensing is enhanced by catecholamines, but inhibited by the human sex hormones estriol and estradiol [15].

PATHOPHYSIOLOGY

Endocrine effects of bacteria influence a variety of host responses including, behavior, metabolism and appetite and immune response. Much of the advances in this field in its infancy have been made through experiments, using germ-free animals, as well as experiments using probiotics (specific microbes thought to be beneficial to the host) and prebiotics (non-digestible carbohydrates that act as food for probiotics), together with advances in sequencing and bioinformatics platforms.

Behavior

The ability of pathogens to influence host behavior has been known for long times. An example is Toxoplasma gondii infections of rodents, that result in such a profound decrease in anxiety, that infected animals no longer showed fear of feline predators [15]. Humans suffering from inflammatory bowel diseases, which are characterized by disturbed enteric microbial diversity, demonstrated poorer emotional function such as anxiety and depression [16]. Release of host immune factors, such as cytokines and inflammatory mediators, that have neuronal targets, both within the CNS and the Enteric Nervous System (ENS) are believed to be involved [17].

The first study that demonstrated the ability of a bacterium within the gut to influence behavior was shown in a series of studies using *Campylobacter jejuni* in mice [18]. In this series of studies, a low per oral dose of *C. jejuni* was able to induce anxiety-like behavior in mice through a vagal-mediated pathway in the absence of immune activation [19]. Within the gut neuronal projections from the ENS can innervate the entire length of the microvilli [20,21]. Coupled with the presence of a myriad of cells within the gastrointestinal tract, such

as enterochromaffin cells and luminal epithelial chemosensors, there is a host of information, that can be shared with the CNS, such as he brain [22]. Neufeld et al. showed that excitability of gut sensory neurons located within the myenteric plexus of the ENS, isolated from jejunal segments of the intestine, relied on the presence of the normal commensal microbiota for proper functioning [23].

Synthesis of benzodiazepine receptor ligands by gut bacteria can contribute to the development of encephalopathy that can accompany fulminant hepatic failure by accumulating in the brain and enhancing GABA (gamma-aminobutyric acid) inhibitory neurotransmission system. Subsequent reports identified the neural substrates both within the brain and vagal-mediated gut-to-brain pathway [19]. For example, the ability of cetain probiotic bacteria such as *Lactobacillus rhamnosus* to infkuence emotion behavior in mice has been shown to be mediated via GABA receptors [25]. Changes in diet such as feeding of meat, which can dramatically alter the composition of the microbiome, have been shown to improve memory and learning in rodents [26]. It should not be surprising that the intestinal microbiome plays a critical role in the development of the brain itself from the time of birth [27].

Appetite and metabolism

A classic role of the gut microbiota is in digesting a variety of carbohydrates and fermenting them into short-chain fatty acides (SCFAs). Germ-free (GF) mice have different metabolic profiles than conventionally raised mice, including low concentrations of SCFAs, hepatic triacylglycerol and glucose. Subtherapeutic doses of antibiotics, which do not eliminate the gut microbial community, but rather cause significant changes in the composition, lead to increased levels of SCFAs and to weight gain in mice [28]. These metabolic effects of the microbiome may further affect hormone production. For instance SCFAs have been shown to stimulate release of 5-HT (5-hydroxytryptamine or serotonine) and the peptide YY, a hormone released after feeding involved in appetite reduction and slowing gut motility [29,30]. Although a lot of neuropeptides that have a role in controlling appetite and regulating metabolism could be affected by the gut microbiome, this is until now more speculative than evidence-based.

Potential candidates are; alpha-MSH (melanocyte-stimulating hormone, neuropeptide YY, agouti-related protein, ghrelin, leptin, insulin and others. Somatostatin, which suppresses the release of the GI and pancreatic hormones is of interest too [31]. Several pieces of evidence link the microbiota function to leptin levels. Use of antibiotica (vancomycin) in rats leads to a a dramatic decline (38%) in crculating leptin levels [32]. Several bacteria genera (e.g., *Allobaculum, Clostridium, Bacteroides and Prevotella*) correlate negatively with leptin levels, while others(e.g., *Mucispirillum, Lactococcus, Bifidobacterium*) correlate positively with circulating leptin concentrations in mice These correlations may stem from bacteria affecting hormone levels, or vice versa. One proposed mechanism is that diet composition may impact leptin concentrations which, in turn, may change the microbial community composition through inflammatory and or regulation of mucus production [33,34]. Rajala et al. [35] showed that leptin might also influence the gut microbiota independently of diet. Another model proposes that Lactobacillus plantarum specifically suppresses leptin by reducing adipocyte cell size in white tissue fat [32,36]. This fits the finding that the use of the probiotic *L. plantarum* in a group of human smokers reduced their serum leptin levels [37]. Leptin is involved in appetite inhibition, metabolism and behavior and therefore its possible interconnections with bacteria could be of great interest.

Grhelin, another appetite-regulating hormone is negatively correlated with the abundance of *Bifidbacterium*, *Lactobacillus* and B, coccoides-Eubacterium rectale group, and positively correlated with a number of *Bacteroides* and *Prevotella* species [34]. Intake of oligofructose (a prebiotic that promotes growth of *Bifidobacterium and Lactobacillus*) decreases secretion of grhelin in obese humans [38].

Insulin may provide another link between the microbiome and hormones. Significant variations in microbiome composition have been observed in diabetic patients compared to healthy controls. Certain bacterial species have been positively or negatively correlated with insulin levels [39,40]. Transfer of the intestinal microbiota (including butyrate producing microbiota) from lean donors to metabolic syndrome patients enhanced insulin sensitivity [41].

Glucagon-like peptide1 (GLP1) is associated with appetite and insulin secretion.Intestinal microbiota have been implicated in lowering levels of GLP1 and thereby slowing intestinal transit [42]. However, alterations of the microbiome [43] or bariatric surgry [44-46] decrease adiposity and increase GLP1 levels in mice.This is primarily attributed to butyrate production by commensal bacteria which can induce GLP1 production by intestinal luminal cells. [43].

Butyrate is propsed to increase the expression of the hormone angiopoietin-like protein4 (Angptk4), also known as fasting-induced adipose factor, a hormone implicated in the regulation of glucose and insulin sensitivity and lipid metabolism, inhibiting Lipoprotein Lipase (LPL) and thereby reducing fat storage. Despite the general trend toward repression of Angptl4 by the microbiota, specific bacteria can increase hormone expression. Mice treated with *L. paracasei* were leaner than controls, had lower ciculating lipids and elevated levels of Angptl4 [47]. This is probably mediated by butyrate. So, butyrate may play a role in the microbiota-induced weight maintenance changes that involve hormonal changes.

One interesting mechanism by which microbiota affect peptide hormones is through autoantibodies. Fetissov et al. [49] found that autoantibodies against peptide hormones involved in appetite control exists in healthy humans and rats, and affect feeding and anxiety. In GF rats, levels of these autoantibodies are altered, suggesting a novel mechanism by which the microbiome can affect appetite. These findings may have implications for the potential role of the microbiota in eating disorders such as anorexia nervosa and healthy controls.

New data among microbiota composition come from studies of gastric bypass surgery, in which the relative abundance of *Gammaproteobacteria* (Escherichia) and *Verrucomicrobia* (Akkermensia) is increased. While, microenvironment changes such as reduced food intake and reduction of bile acids, this is likely due to alterations in the levels of GIP (gastrointestinal inhibitory peptide), GLP1 and insulin following surgery [45,46,50-52].

Immune function

Gut microbiota play a role in modulating the immune response, both locally and systemically, beyond repressing pathogenic microbes [53]. In the absence of commensal bacteria, GF mice have impaired development of the innate and adaptive immune system [54-57]. reduced number of IgA producing plasma cells [58], and a decreased percentage of CD4+ T cells [59]. Additionally, T helper 17 Th 17

cells which produces proinflammatory cytokines are regulated by gut bacteria and are promoted specifically by segmented filamentous bacteria (SFB) [60]. Autoimmune Disease (AD) has been correlated with alterations of the microbiome (dysbiosis) The most extensively studied example is type 1 diabetes [61,62]. A different example linking the microbiota hormones and immunity comes from a study in mice, which showed that *L. reuteri* enhances wound -healing properties in the host through up-regulation of the neuropeptide hormone oxytocin, by a vagus nerve-mediated pathway [63].

Sepsis

Microbiome disruption may have a key role in sepsis and Acute Respiratory Distress Syndrome (ARDS). Dickson et al. have found culture-independent evidence that the lung microbiome is enriched with gut bacteria, both in a murine model of sepsis and in patients with ARDS (n=68). In more severely critically ill patients, lung bacteria were more outnumbered by the misplaced gut bacteria [64]. A large rural Indian trial (n=4556) showed the combination of the probiotic *Lactobacillus plantarum* plus the prebiotic fructooligosaccharide can help prevent sometimes deadly cases of sepsis and decrease lower respiratory tract infections in newborns. Panigrahi et al. [65] found that the synbiotic combination, which costst only one dollar per treatment, reduced neonatal sepsis and death by 40% from 9% in the placebo arm to 5, 4% among babies given the experimental treatment. This report underscores the importance of gut colonization on the maintenance of optimal immunological function.

It is believed intestinal microbiota not only act as a key defense system by locally supporting mucosal immunity, but also have proposed modulatory effects on systemic immunity. Schuyt et al. found that the gut microbiota play a protective role for the host during pneumococcal pneumonia, as reflected by increased bacterial dissimination, inflammation, organ damage and mortality in microbiota-depleted mice compared to controls. Fecal microbiota transplantation in gut microbiota-depleted mice restored local host defense. Whole genome mapping of alveolar macrophages showed up-regulation of metabolic pathways in the absence of a healthy gut microbiota. The up-regulation correlated with an altered cellular responsiveness, reflected by a reduced response to Lipopolysaccharide (LPS) and lipoteichoic acid. Compared to controls, alveolar macrophage derived from gut microbiota-depleted mice showed a diminished capacity to phagocytose *S. pneumoniae* [66].

The microbial ecosystems of the gut and the lungs change substantially in critically ill patients, resulting in dramatic changes to bacterial communities. In animal studies of shock the microbial contents of the gut determine the severity of multiorgan failure and the risk of death, an observation supported by trials of selective manupulations of the gut microbiome [67]. The mechanisms that drive gut-derived sepsis are incompletely understood and multifactorial, offering numerous unexplored therapeutic targets. During lung injury, the bacterial ecosystem of the alveolar shifts to a state of abundance in nutrients and growth-promoting host stress signals, leading to a positive feedback loop of inflammation and dysbiosis. The microbiome is a key therapeutic target for the prevention and treatment of critical illness [67]. However, large knowledge gaps remain [68].

Miscellaneous

Growth: No direct connection has been shown to date between the microbiota and growth hormones. The microbiome's effect on grhelin and sex hormones may indirectly promote release of growth hormones [69]. Additionally, SCFA's have been shown to inhibit growth hormones in cows, by affecting gene transcription in a cAMP/PKA /CREB- mediated signalling pathway [70]. Furthermore, bacteria produce somatostatin, which is a known growth inhibitor [71].

Sex hormones: Results regarding the relationship between sex hormones and the microbiota and vice versa are inconclusive. For example, *Prevotella intermedius* takes up estradiol and progesterone, which enhances its growth [72] Changes in expression of the estrogen receptor, ER-beta, also affect the intestinal microbiota composition [73]. This interaction goes both ways, as several types of bacteria have also been implicated in steroid secretion or modification [74]. For example *Clostridium scindens* converts glucocorticoids to androgens [74]. Intestinal bacteria also play a role in estrogen metabolism, because use of antibiotics leads to lower estrogen levels [75].

Pheromones: Pheromones are hormones that play important roles in sexual recognition, attraction and mating behavior as well as agression behavior and dominance. Pheromones are also termed ectohormones, chemicals secreted outside of the body of one individual and affecting the behaviors of others. In Drosophilia studies pheromones were affected by antibiotics and levels were related to a specific gut microbe [76]. These findings suggest a mechanism, whereby the microbiota affect host pheromone levels. Human date relating pheromones to the human microbiome are not available until now. Anyway, there are still considerable doubts about the existence of the human counterpart of putative pheromones. Actually, forty years of research of putative pheromones in humans is inconclusive and reserch in human pheromones should make a restart from scratch [77].

Treatment: Our perception of the microbiome has chamged rapidly the last decade, due to the metagenomic sequencing of the DNA and RNA repertoire present in the intestinal ecosystem and the re-emergence of gnotobiotic approaches enabling controlled microbial colonization of a mammalian intestine [78]. In contrast to the host's genome, the microbial metagenome is highly dynamic and amenable to change over an individual's lifetime [79]. Assuming a metagenomic contribution to disease susceptibility, this contribution is not stable, but rather undergoes fluctuations over time and depends on environmental inputs, that modulates its constitution [80]. Therefore, the therapeutic modulation of the microbiome might be harnassed to alter an individual's risk for the manifestation of a certain disease. To design dietary or biotic interventions microbiota composition should be better understood [67,68].

One prototype microbiome-based intervention has recently been introduced in clinical practice as Fecal Microbiota Transplantation (FMT). Fecal microbiote transplantation is used in case of recurrent intestinal infection with antibiotic-resistant *Clostridium difficile* [81]. In the last 5 years FMT has become a widespread and broadly recommended approach in the treatment of recurrent *C. difficile* infections. Although standardization efforts are still underway, the procedure typically involves a certain level of donor screening [82]., sample homogenization and filtration, followed by administration via retention enema, endoscopy, nasogastric, or nasojejunal tubing, or in recently developed capsule formula. Several hundred cases of successful FMT have been reported , with cure rates up to 90% [83]. Despite the success and clinical effectiveness, the procedure remains poorly controlled. FMT involves the transfer of a large number

of bacteria, viruses, and unicellular and multicellular eukaryotes, the individual function of which is largely unknown [84]. Such functions can manifest in phenotypic consequences, as seen in a case of unexpected weight gain, reported after familial FMT [84]. Also, in some cases, it might be the non-bacterial rather than the bacterial content, that mediates the efficacy of FMT. This has been exemplified by filtrated fecal transfer, in which only bacterial cell components, bacterial derived molecules, and viruses are retained [85]. Thus, more exact knowledge about interventions through specific microorganisms that mediate the benificial effects of FMT is crucial.

The success of FMT in treating recurrent pseudomembranous colitis has given rise to the hope that a similar procedure might prove effective against either intestinal or even extra-intestinal diseases. Indeed, cases of FMT trials have since been reported not only for gastrointestinal and infectious conditions, but also for metabolic, autoimmune, hematologic, and even neurologic conditions [86]. However, in contrast to recurrent *C. difficile* infections, the data from these trials are not sufficiently conclusive to recommend the immediate inclusion of FMT in standard clinical practice [87]. For instance, in the case of Inflammatory Bowel Disease (IBD), FMT has not yet proven to be the"magic bullet" in the form of a long awaited therapy across different manifestations of the disease, despite the fact that the microbiome is clearly involved in disease etiology. One reason could be that in IBD, the microbial community is not so disrupted as in recurrent pseudomembranous colitis after heavy prior antibiotic use. Another reason could be the microbiome in IBD is changing by environmental changes making it less amenable for FMT. Also, the microbiome in IBD might have enormous interindividual variations [88].

If FMT is not suitable for most microbiome-based therapeutic developments, what are the potential alternatives? One of the approaches could be the refinement of microbiotic engineering by more targeted approaches, selecting a single bacterium, that is as powerful as FMT-based community replacement, with respect to a clinically desired effect. Indeed in the case of C.difficile infection, this may be possible with only one strain, the already mentioned *Clostridium scindens*, which effectively inhibited C.difficile via the production of secondary bile acids in a rodent model [89].

Further developments of this strategy include the biological engineering of biotic interventions through system biology approaches in bacteria to enhance their functionallity [90]. Additonally, targeted interventions with the microbial ecosystem could be achieved through bacteriophages, a prominent component of the intestinal microbiome, with the capacity to re-gut the microbial gene pool [91]. Indeed, several clinical trials employing bacteriophage strategies are underway and have so far proven safe in the first phases [92].

However, the establishment of such viral therapies would necessitate an improved understanding of ecological interactions between the bacterial and bacteriophage communities in the intestine [93] and proof of efficacy [94].

As most modern drugs find their origin in endocrinology, a pharmacological approach could be based on future research in microbial endocrinology [95].

CONCLUSION

Microbial endocrinology shares the presence of neurochemicals that are exactly the same as in neurobiology of the host as well as in the microorganism. More clues to the existence of crosstalks between bacteria came from the discovery of the inter-kingdom, including the hormonal communication between microorganisms and their hosts. It appeared from this initial observation that bacteria perform quorum sensing. Endocrine effects of bacteria influence a variety of host responses, including behavior, metabolism and appetite and immune response. Butyrate may play a role in gastrointestinal hormone expression. Microbiota can also produce autoantibodies, increasing the expression of peptide hormones. New data on microbiota came from studies of gastric bypass surgery. Gut microbiota plays a role in modulating the immune response. Microbiome disruption may have a key role in sepsis and ARDS.

Our perception of the microbiome has changed rapidly the last decade, due to the metagenomic sequencing of the DNA and RNA repertoire present in the intestinal ecosystem and the re-emergence of gnotobiotic approaches. Fecal Microbiota Transplantations (FMTs) showed a cure rate up to 90% in recurrent antibiotic resistant *Clostridium difficile* infections. Results of FMTs for inflammatory bowel disease are less convincing. If FMT is not suitable for most microbiome-based therapeutic developments, refinement of microbiotic engineering by selecting a single bacterium could be a solution. Bacteriophage treatment is another possibility, but this needs an improved understanding of ecological interactions between bacterial and bacteriophage communities in the intestine. Also, bio-functionallity of bacteria can be enhanced.

As most modern drugs find their origin in endocrinology, a pharmacological approach could be based on future research in microbial endocrinology.

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