THE INFLUENCE OF MICROBIOTA ON MENTAL HEALTH

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ABSTRACT

Recent scientific advances have begun to clarify the role of the microbiota and its interaction with the human body on health and general wellbeing. The fact that the brain affects the gastro-intestinal system is proven by the natural evolution of functional digestive disorders such as irritable bowel syndrome and chronic intestinal diseases together with psychiatric symptoms. This axis of communication turns out to be bidirectional with centripetal messages being delivered through the vagus nerve, through alterations of neurotransmitter concentrations and through humor al messengers. By altering neurotransmitter metabolism, by producing inflammatory states and by dysregulating the hypothalamic–pituitary–adrenal axis, elements that often run in parallel with mood disorders, dysbiosis can manifest itself as an affective disturbance. In depth research has shown how these processes can alter gene expression of receptors and neuromodulators in cerebral regions tied to mood disorders, findings that have been confirmed by behavioral studies.

Keywords: microbiota, mood disorders, inflammation, vagus nerve

The beginning of this decade has sparked new interest in the microflora hypothesis and its implication in the fields of neuroscience and clinical psychiatry. Hypotheses and speculations regarding the influence of microorganisms on the human body and psyche date back to more than a century ago as first proposed by the Russian Nobel laureate Élie Metchnikoff. Studies aimed at investigating the pathogenesis of mood disorders have begun to unravel how seemingly insignificant changes in the diversity of the intestinal microbiota can have real, quantifiable effects on neuronal functioning and behavior.

The human body and its microbial communities are in a delicate state of symbiosis. Dysbiosis can have negative effects on general wellbeing often translated into inflammatory states [1] and their eventual consequences.

This paper aims to review the possible routes of communication between gut and brain, the impact of inflammation and hypothalamic–pituitary–adrenal (HPA) dysregulation on mood, the effects of the gut flora on these processes and the ultimate effects of these interactions on behavior and affect.

THE HUMAN MICROBIOTA AND THE GUT-BRAIN AXIS

The main organisms that constitute the microbiota are bacteria, predominantly strictly anaerobic, archaea, viruses, fungi and protozoa with a diverse and almost unique distribution per individual, forming what is known as enterotypes [2].

Each person carries some $10^{13}$-$10^{14}$ microorganisms in their gut, ten times the body’s cell count, comprising some 150-160 species per individual out of the 1000 possible species and 7000 possible strains that can inhabit the gastrointestinal (GI) tract [3].

This makes the microbiome 150 times richer from a genetic and metabolic perspective [4] than the human body.
The colonization of the GI tract begins at birth [5]. The microbiota to first inhabit the gut are a faithful copy of the mother’s own flora. Depending on delivery method [6], this initial colonization has proven to be effective against inflammatory disease at later stages in life. Alterations to this diversity have been pined as causative for a number of prevalent pathologies linked to obesity, hyperalgesia, inflammation, GI disorders, allergic and metabolic diseases [7] and recently, to cognitive, affective and behavioral disturbances.

The nervous system influences the functioning of the GI tract through the enteric nervous system [8], which represents a pillar in hypotheses explaining digestive symptoms correlated with psychological stress [9], as is the case especially with irritable bowel syndrome (IBS). More than 50% of persons suffering from IBS present psychiatric comorbidities with the prevailing consensus being that the latter is responsible for exacerbation of digestive symptoms [10].

Only in recent studies has this model been turned upside down, suggesting that the gut may play an important role in emotional and behavioral regulation [11], an interaction nicknamed the gut-brain axis.

THE PATHWAYS OF COMMUNICATION

The metabolic pathways the microbiota use to signal the brain of homeostatic variations appear to be as diverse as its microbial diversity. However, some key routes have already been identified. Surprisingly, these pathways of communication already represent points of intervention for certain psychiatric therapies or are investigated for their possibility in this respect.

Inflammation and humoral signaling

The immune system is disproportionately distributed throughout the body, with more than 70% of immune cells gathered in the gut-associated lymphoid tissue. The gut flora is in constant interaction with the immune system, maintaining a balance with a delicate tipping point.

GI infections can lead to increased gut permeability, termed “leaky gut syndrome”, determined by reduced transcription of zona occludens-2 and occludin mRNA. A similar response can be recognized at the blood-brain barrier. “Leaky gut syndrome” determines an increase in interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) which alter the indoleamine 2-3 dioxygenase (IDO) activity [12]. IDO degrades tryptophan to kynurenin, a competing metabolic pathway to serotonin synthesis. Inflammation activated microglia convert kynurenine further into quinolinic acid [13], an N-methyl-D-aspartate (NMDA) agonist involved in various neuropsychiatric illnesses including mood disorders.

Proinflammatory states are correlated with mood disorders [14, 15]. Numerous studies confirm a link between IL-6, interleukin-1β (IL-1β), TNFα, C-reactive protein (CRP) and depression [16]. Otherwise healthy individuals with depressive symptoms have a plasmatic increase in these markers. Also, this inflammatory panel fails to change in patients with treatment resistant depression [17], while those who recover under antidepressive therapy show a return to normal values. Elevation of proinflammatory cytokine levels as well as TNFα treatment [18] is enough to cause depression-like symptoms while immunomodulatory agents, such as infliximab, revert the symptoms. Low levels of IL-6 and CRP [19, 20] are stated as being predictive of low likelihood to develop depression over several years.

While studies have highlighted this link between mood disorders and inflammation [21], no prevailing mechanism has been put forward, although hypotheses on the subject have emerged. Antidepressive treatment [22], as well as some strains of Lactobacillus increase anti-inflammatory and antinociceptive cytokines, particularly interleukin-10.

Effects on neurotransmitters

The gastroenteric system is capable of storing neurotransmitters, with 90% of the body’s serotonin residing within the GI tract. Several gut-based microorganisms impact concentration or availability of clinically relevant neurotransmitters [23]. Lactobacillus and Bifidus, two commensal strains, are capable of secreting γ-aminobutyric acid (GABA) as well as nitric oxide, a neuronal and immunological regulator. Escherichia coli and Saccharomyces produce epinephrine as a metabolic byproduct. Commensal strains of Candida, Streptococcus and Enterococcus represent important sources of enteric serotonin. A particular case is Bacillus Romanian Journal of Child and Adolescent Psychiatry
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enseratia, which is able to synthesize and secrete dopamine.

Studies conducted on germ-free (GF) mice have hinted at the importance of these enteric neurotransmitter reserves. Lack of these microorganisms can reduce plasma neurotransmitter levels by as much as three times [24], especially in the case of serotonin.

Effects on the HPA axis

HPA axis dysregulation, present as increased plasmatic levels of corticosterone and a faulty feed-back mechanism, has become a mainstay of mood disorders [25]. Elevated levels of corticoids and failure to suppress further secretion generally lead to an inflammatory status [26] by increasing gene transcription for proinflammatory cytokines. This cascade has been observed in studies of GF mice with normalization of HPA activity [11] obtained after fecal transplant or administration of Bifidus infantis.

Infections, particularly of the GI tract, are notorious in hijacking the HPA axis and disrupting its physiological feed-back mechanism [27]. During such an infection with E. coli, IL-1 levels surge and activate cerebral perivascular macrophages that induce cyclooxygenase cascades. The resulting products, notably prostaglandin E2, are capable of promoting further corticosterone release independent of adrenocorticotropic hormone (ACTH) values [28].

Vagal signaling

The vagus nerve has been a central point of interest for numerous psychiatric investigations, with vagal stimulation emerging as a potent treatment option for refractory depression [29]. Vagal stimulation decreases corticotropin-releasing factor mRNA, yet increase plasmatic ACTH with a net effect of HPA inhibition.

The vagus nerve is an important pathway of communication between the central and enteric nervous system [29]. Vagal efferent fibers are primary messengers of the cortico-limbic-pontine network - colloquially called the emotional motor system, a network responsible for GI function and pain perception via descending serotonergic, noradrenergic and opiodergic nerves [30].

Central effect of dysbiosis are also vagally mediated, with signals from the vagus nerve reaching the para-ventricular hypothalamus and the amygdala [31] and altering norepinephrine and serotonin concentration at a cortical-wide level.

In light of these observations several studies have conducted experiments comparing effects of GI dysfunctions on healthy mice compared to subdiaphragmatically vagotomized mice. Anxiogenic effects of chronic colitis as well as anxiolytic effects of the commensal strain Bifidobacter longum are annulled by disruption of the vagus nerve [32], thus confirming its importance in digestive homeostatic signaling as well as its effect as a mood regulator.

CENTRAL EFFECTS

Most studies evaluating the effect of intestinal flora on behavioral and neurochemical processes utilize GF mice. A large body of literature confirms that GF mice have altered plasmatic serotonin levels, elevated ACTH and corticosterone [33]. Decrease in the expression of NR2B mRNA, a subunit of the NMDA receptor, at the level of the central amygdala has also been noted. GF mice may also present decreased levels of hippocampal and cortical brain-derived neurotrophic factor (BDNF) [34], although this finding is inconclusive and may be dependent on mouse strain and sex [35, 36]. Elevated levels of 5-hydroxyindoleacetic acid and 5HT1A mRNA in the hippocampus have been observed only in male rodents. Behaviorally, the majority of studies report heightened anxiety-like behavior in GF mice [37] by using various fear tests. Only few studies highlight increased motor activity. Examined outcomes produced by lack of gut microbiota can be reverted only if colonization takes place in early childhood [35, 37], although some experiments conclude that neurochemical effects, but not behavioral ones, cannot be reverted [38].

Other papers involve the comparison between gnotobiotic mice and mice infected with various pathogenic strains [39]. Most notable are Campylobacter jejuni, Citrobacter rodentium, Clostridia and Bacteroides. C. jejuni activates the nucleus of the solitary tract and
the lateral parabrachial nucleus and induces anxiety-like behavior [40]. Strains of Clostridia and Bacteroides are known to increase anxious and aggressive behavior in rodents. Infections with Citrobacter rodentium increase anxiety-like behavior [41] 8 hours after administration and maintain stress induced memory dysfunction 10-30 days after infection.

One study [38] has shown that intestinal repopulation can modify postsynaptic density protein-95 (PSD-95) and synaptophysin transcription in the striate during development and correlates these findings to reduced anxiety and motor hyperactivity in adulthood.

A probiotic formulation comprised of Lactobacillus helveticus and Bifidus longum decreases symptoms of depression and anxiety, somatization, anger and hostility in human subjects and normalizes hippocampal BDNF values after an induced infectious colitis [42].

A series of experiments [43] have documented the effects of Lactobacillus rhamnosus on GABA receptor expression. GABA_B receptor subunit transcription is increased in the prefrontal cortex and decreased in the hippocampus while GABA_A mRNA is decreased in the central amygdala. Enhanced fear extinction and spatial working memory and diminished anxiety-like behavior are noted consequences of these neurochemical changes. All effects, molecular and behavioral, could not be reproduced in vagotomized mice.

With mood disorders slowly edging their way towards the top of chronic illnesses of the 21st century [44], novel and more potent treatment options are called for. This necessity has forced new insights regarding affective symptoms and their underlying pathogenesis. Corollary findings from other fields, neuroscience and genetics in particular, have presented modern approaches to these problems.

The human gut flora appears to play an important role in this respect [31], although questions regarding its possible future utility as a robust treatment option for depression or anxiety have yet to be answered. Spanning several orders of magnitude in diversity compared to the human body, the microbiota is a heterogeneous assortment of living organisms in constant chatter with the body and brain. To determine whether these lines of communication can be pharmacologically or otherwise manipulated in order to heal or prevent mental illness remains a task for upcoming studies. What is clear however, is that quantifiable, salient influence is exerted by the intestinal flora on nervous functioning, affecting metabolic and signaling processes already established as paramount for mood disorders.

REFERENCES

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