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GUT MICROBIOTA DISTURBANCES EFFECTS ON THE HYPOTHALAMUS-PITUITARY AXIS: A REVIEW OF LITERATURE

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Abstract:

Background: *Gut microbiotahas emerged as an environmental factor that modulate the host function and is linked to various psychiatric and organic diseases.*

Objectives: *The current study aimed to review the literature to answer the question: Is microbiota affecting the structure or function of the hypothalamus-pituitary axis [HPA]?*

Methods: *Eligibility criteria were experimental or human studies in English language assessing the effects of microbiota on hypothalamus-pituitary axis published during the period from 2008-2018. A manual search in PubMed and Google scholar was conducted using the terms microbiota, effects, modulation, hypothalamus-pituitary axis. Among the two hundred and forty articles identified, 33 were assessed and eighteen[15 experimental and three human studies] were included. The author name, year of publication, country, methods of the study and the conclusions were reported.*

Results: There were 240 articles, 33 were assessed for eligibility and 18 were included in the systematc review. The microbiota disruption altered neurotransmitters and vasopressin receptor 1a mRNA expression in the hypothalamus, ameliorated the HPA response to acute stress, reduced insulin and leptin resistance, increased IFNγ, IL2 and IL4 at the expense of TNFα and IL6, modified specific gene expression, and induced inflammation in the hypothalamus.

Conclusion: Gut microbiota disturbances induced structural and functional changes in the hypothalamus and can be targeted as a useful affordable intervention in various diseases including stress, anxiety, and depression.

Keyword: *Gut microbiota, Effects, Hypothalamus-Pituitary, Axis.*

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INTRODUCTION:

The human body contain as much microbiome as the total number of body cells [1-2 kg, 100 trillion and possess 100 times the number of genes in the human genome]. The hypothalamus-pituitary axis [HPA, a major physiological stress system that also control feeding behavior] may shape various aspects of brain development through cortisol release. The earlier years of life cansubstantially affect the development of both microbiota and HPA due to the rapid growth and the effects of environmental stressors. Early gut microbiota adversity, may lead to long term unbalances in both, as well as to psychopathological behavior and emotions [1-4]. It is interesting to note that, transplantation of vaginal microbiota from stressed dam to naïve pups delivered by caesarian section lead to stressed phenotype which were not seen in control group [5].

Gut microbiota is currently viewed as the chief modulator of the gut-brain talk [bidirectional dialogue]. It is suggested that, microbiota may play a key role in neurodevelopment, neurodegenerative, and neuropsychiatric disorders including Autism, parkinsonism, anxiety, and depression. Although a cause and effect cannot be insured and whether the microbiome effect are the cause or it is secondary to these disorders and if the findings of experimental studies can be generalized to humans [6], further studies are warranted, such search may give more insight regarding the mechanisms through which the gut microbiome communicate with the brain including the hypothalamus-pituitary axis to improve the management of neuropsychiatric disorders and obesity.

Alternating feeling of hunger and satiety dominate all animals life. Gut microboita depends entirely on the host for nutrients and has intrinsic ability to control and maintain their growth suggesting a role in controlling energy balance in the host through satiety pathways . The role of microbiome in controlling satiety may be short term and under the long term control of neuropeptidergic circuitry in the hypothalamus. Interestingly, several microbiota products are detected in the systemic circulation and may act directly on the hypothalamic neurons [7]. On the other hands, Gonadotrophin releasing hormones [GRH] receptors are found in the gut of humans and animals, furthermore, autoantibodies against GRHs are present in certain subgroups of patients with motility disorders including irritable bowel syndrome and motility disorders associated with diabetes [8].

Gut microbiota is emerging as an environmental factor that control energy balance, it produces metabolites and microbial products including secondary bile acids, short chain fatty acids, and lipopolysaccharides that modulate gut motility, appétit, energy storage, and expenditure. Germ free mice are leaner than conventionally raised counterparts, while obese people have altered microbiome with a lesser diversity compared to lean humans. Furthermore, transplantation of obese subjects microbiota to germ free mice can transfer obese phenotype indicating a role of gut bacteria in obesity [9]. Microbiota is a neglected endocrine organ, it produces short chain fatty acids from carbohydrates, and influence the production of various hormones including glucagon-like peptide-1, peptide YY, ghrelin, and leptin [10].

There is an emerging role of microbiota in modulating host communicative and social behavior, performance in learning and memory tasks, and stressor induced behavior [11].McGavigan et al. [12] used mice model of vertical sleeve gastrectomy and found that the blood pressure lowering effect of this form of metabolic surgery may be mediated through hypothalamus endoplasmic reticulum stress signaling, inflammation and the abundance of Gammaproteobacteria and *Enterococcus*, and decreases in *Adlercreutzia* microbiota in addition to weight reduction.The microbiome may be harmful or beneficial, in depression Bacteroidetes, Proteobacteria, and Actinobacteria strongly increased in level, whereas that of Firmicutes was significantly reduced [13] .The influence of gut microbiota may extend beyond one generation. Studies on microbiota and their cross-talk with hypothalamus-pituitary-adrenal axis and various aspects of inflammation give insight regarding the treatment of depressive and high body mass index disorders [14]. Thus we conducted this review to assess the interaction between the gut microbiota and the hypothalamus-pituitary-adrenal axis.

MATERIALS AND METHODS:

Eligibility criteria:

Animals and human studies in English language assessing the effect of micobiota disruption on hypothalamus-pituitary axis published during the period 2008-2018.

Information sources and search methods:

A manual search in PubMed and Google scholar was conducted using the terms microbiota, effects, modulation, and hypothalamus-pituitary axis.

Study selection and data extraction:

The abstracts and full text [18] were screened independently by two reviewers, after removing the

irrelevant articles and duplication**,** the authors names, year, country, methods used and conclusions were reported. The results were then divided in to animals and human studied and discussed under the headings: Antibiotics, maternal immune activation, stress, probiotics, and diet effects.

RESULTS:

A total of 240 studies were identified through the database search. Thirty-three full-text articles were assessed for eligibility and 18 studies met the inclusion criteria for the systematic review. Figure 1. Depicted the different phases of the systematic review [PRISMA]. Tables 1&2 showed the animal and human studies respectively.

Figure 1 –The different phases of the systematic review[PRISMA flowchart].

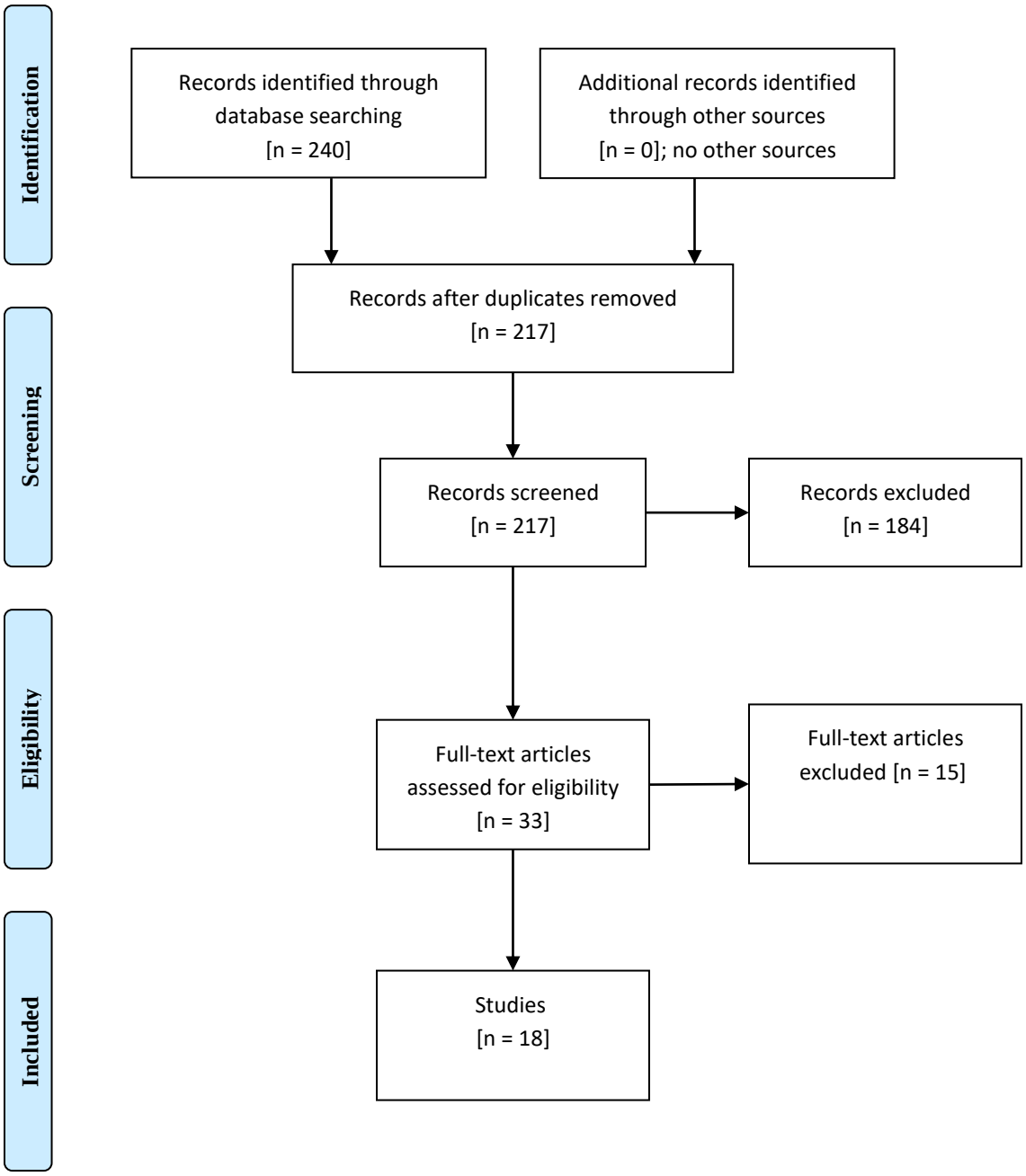

Table 1. Animal studies on the gut-hypothalamo-pituitary axis

Author	Year	Country	Methods	Conclusion
Gao et al.	2018	China	Piglets infused with antibiotics or saline in the ileum, then ileal and fecal microbiota, serum amino acids and neurotrans mitters, and hypothalamic transcriptomics were analyzed.	Antibiotics induced modulation of large intestinal microbiota altered aromatic amino acid profile and expression of neurotransmitters in the hypothalamus.
Morais et al.	2018	Ireland	Maternal immune activation mice [NIH Swiss, and C57BL6/J]	Social deficits occurred in both strains, although depression and anxiety more pronounced in NIH Swiss model and are associated with a marked alteration of gut-brain axis communication, namely the : the endocrine response to stress and gut permeability. Changes in vasopressin receptor 1a mRNA expression in the hypothalamus were also observed.
Agusti et al.	2018	Spain	Adult male wild-type C57BL-6 mice fed a standard diet or high fat diet, supplemented with either placebo or the bifidobacterial strain	Anhedonia, and exaggerated HPA response to acute physical and social stress were ameliorated with B. pseudocatenulatum CECT 7765, so it may play a role in depressive behavior comorbid with obesity via regulation of endocrine and immune mediators of the gut-brain axis.
Reyer et al.	2018	Germany	Full-sib pigs assigned to high and low efficient feed	Minerals, hormones, hypothalamic abundance of transcripts, and circulation of energy equivalents are promoted indicating host-microbiota interaction in efficient feeding
Vodička et al.	2018	Czech	Specific pathogen-free [SPF] and germ-free [GF] BALB/c mice subjected to stress	Microbiota attenuated the expression of Fkbp5, a gene in the pituitary andthe expression of genes encoding steroidogenesis in the adrenal gland shaping the response of peripheral tissues to stress
Noguera et al.	2018	Spain	Spain Corticosterone implants] in a wild avian species, the yellow-legged gull *Larusmichahellis*	*Mycoplasma* and *Microvirga* and beneficial Firmicutes reduced suggesting a role of stress in preventing infections.
Huo et al.	2017	China	Germ-free and specific pathogen-free mice divided in to 4 groups Chronic stress induced	Specific pathogen-free mice showed more anxiety-like behavior than counterparts under the same external stress. A significant difference was observed among germ free model regarding hormonal and receptors compared to Specific pathogen-free. Imbalance in HPA caused by intestinal microbiota could lead to anxiety-like behavior through neurotransmitters in the brain and could be a treatment target for stress disorders.
Bagarolli et al.	2017	Brazil	Swiss mice were submitted to a high-fat diet with probiotics or pair-feeding for 5 weeks	The huge alteration of microbiota, increased gut permeability, and hyperphgia observed in obese mice were reversed by probiotics. Furthermore, hypothalamic insulin and leptin resistance. were improved.

Zhuang et al.	2017	China	C57BL/6J obese mice	Arachidonic acid induce hypothalamus resistance to leptin, favor proinflammatory microbiota, decrease butaryte and serotonin production, aggravates steatohepatitis and hypothalamus inflammation. Thus inducing obesity through gut-liver-adipose-hypothalamus axis
Nilaweera et al.	2017	Ireland	C57BL/6 mice fed whey protein isolate	Reduced the hypothalamic expression of pro-opiomelanocortin gene and increased energy intake. *Firmicutes* microbiome were reduced
Abildgaard et al.	2017	Denmark	Male Sprague-Dawley rats were fed a control or high-fat diet, then treated with probiotics or vehicle	IFNγ, IL2 and IL4 increased at the expense of TNFα and IL6, hippocampal transcript levels of factors involved in HPA axis regulation were lowered in probiotics treated rats. The reverse happen among in high fat diet indicating the positive effects of probiotics in depression.
Burokas et al.	2017	Ireland	C57BL/6J male mice were administered fructo-oligosaccharides [FOS] and galacto-oligosaccharides [GOS] or combination, then exposed to psychological stress	Prebiotics [FOS&GOS] modified specific gene expression in the hippocampus and hypothalamus, increased short fatty acids acetate and propionate and reduced isobutyrate in the ceacum.corticosterone and proinflammatory markers of stress, depression, and anxiety were reduced suggesting a beneficial role of prebiotics in stress-related behavior.
Golubeva et al.	2015		Dawley pregnant dams were subjected to repeated restraint stress in late pregnancy.	The hypothalamic-pituitary-adrenal [HPA] axis response to stress was exaggerated, together with decreased Lactobacillus genus, accompanied by elevated abundance of the Oscillibacter
Crumeyrolle-Arias et al.	2014	France	Germfree and specific pathogen free rats subjected to stress, then examine for behavior responses to social interaction and open-field tests.	Germ free rats showed elevated corticotrophin releasing hormone mRNA expression in the hypothalamus and reduced glucocorticoid mRNA expression in the hippocampus indicating that absence of microbiota ex exacerbates the neuroendocrine and behavioral responses to acute stress .
Ait-Belgnaoui et al.	2012	France	Females rat subjected to stress , antibiotics, and L. farciminis administration.	L. farciminisdecreased, plasma ACTH and corticosterone, hypothalamic corticotrophin releasing hormone and pro-inflammatory cytokine expression induced by stress, while antibiotics prevented HPA axis stress response and increased expression of pro-inflammatory cytokines in the hypothalamus.

Table 2. Human studies on the gut-hypothalamo-pituitary axis

Author	Year	Country	Study	results	Comments
Kreutzer et al.	2017	Germany	Case-control, high fat diet	High-fat diet induces reduction of *Parasutterella sp.* in the gut, which is significantly correlated with mediobasal hypothalamus hyperintensity on MRI indicating inflammation but the number of neuron is equal suggesting a functional disturbance.	
Fernandez-Real et al.	2015	Spain	Case-control of obese and non-obese subjects, gut microbiota, brain microstructurs, and cognitive function were the outcomes	Specific microbiota-brain map was defined for obese subjects, Actinobacteria phylum was linked to cognitive test scores, and magnetic resonance imaging diffusion tensor imaging variables in the hypothalamus, thalamus, and amygdale indicating an effect of obesity on microbiota- brain microstructure and cross talk.	
Schmidt et al.	2015	UK	Healthy 52 volunteer given prebiotics	Morning cortisol suppressed suggesting a anxiolytic effect.	

DISCUSSION:

Gut microbiota can affect the hypothalamus through their effects on hormones, circulation products that can induce pro-inflammation [by reducing butyrate production and circulating serotonin], or through the modulation of the innate immune system [Zhuang]. Altered microbiota diversity may affect various organs including the hypothalamus-pituitary axis resulting in depression, anxiety, and high body mass index [6]. The microbiome can be affected by the animal environment including perinatal stress, type of delivery, hospital environment, diet, and antibiotic use [15]. In the following we discussed factors that influence gut microbiota and relate them to hypothalamus-pituitary axis

Factors affecting the gut microbiota and their reflection on the hypothalamus-pituitary axis [animal studies]:

Antibiotics effects:

Gao et al. [16] in his experimental study on Piglets found that antibiotics modulate interstinal microbiota and altered aromatic amino acid profile and neurotransmitters expression in the hypothalamus.

Maternal immune activation:

Morais et al. [17] studied maternal immune activation in mice and showed social deficit, anxiety and depression, and a marked alteration in the endocrine response to stress, changes in vasopressin receptor 1a mRNA expression in the hypothalamus , and gut permeability.

Studies on stress effects:

Ait-Belgnaoui et al. from France in 2012 [18] studies stress, antibiotics, and L. farciminis administration effects among rats and found that, L. farciminis reduced the hypothalamus-pituitary-adrenal response to stress and decreased pro-inflammation, while the antibiotics prevent stress response and increased the expression of pro-inflammatory cytokines in the hypothalamus.Crumeyrolle-Arias et al. [19] studied the effect of acute stress among germ free and specific pathogen free rats and found an increased Corticotrophin releasing hormone [CRH] mRNA in hypothalamus, and decreased glucocorticoid mRNA in hippocampus indicating an exacerbation of stress response. Golubeva et al. [20] studied the effects of repeated stress in late pregnancy among Dawley pregnant dams in Ireland and found the abundance of Oscillibacter, a reduction in Lactobacillus genus, and exaggerated HPA response to stress in offspring. Burokas et al. from Ireland [21] studies the effects of probiotics on stress and concluded: Prebiotics [FOS&GOS] modified specific gene expression in the hippocampus and hypothalamus, increased short fatty acids acetate and propionate and reduced isobutyrate in the ceacum.Corticosterone and proinflammatory markers of stress, depression, and anxiety were also reduced suggesting a beneficial role of prebiotics in stress-related behavior.Hou et al. from China [22] assessed the effect of chronic stress among germ free and specific pathogen free mice showed more anxiety among specific pathogen free with significant differences among germ free model regarding hormonal and receptors compared to Specific pathogen-free. The imbalance in HPA neurotransmitters caused by intestinal microbiota

could be targeted as an interventional therapy for stress disorders.Agusti_ et al. from Spain in their recent study [23] assessed the combined effects of stress and bifidobacterial strain and found that: Anhedonia, and exaggerated HPA response to acute physical and social stress were ameliorated with B. pseudocatenulatum CECT 7765, so it may play a role in depressive behavior comorbid with obesity via regulation of endocrine and immune mediators of the gut-brain axis.Noguera et al. [24] assessed the effect of corticosteroid implants in wild bird and reported a decrease in *Mycoplasma* and *Microvirga* species suggesting a role of stress in preventing infection through microbiota. A recently published study [25], showed that the gut microbiota modulates the peripheral response to stress through genes attenuation.

Studies on the effects of diet and probiotics:

Probiotcs:

The beneficial effects of probiotics on obesity in term of reversal of the huge alteration of microbiota, increased gut permeability, and hyperphgia were shown byBagarolli et al. [26] in their study conducted on Swiss mice in Brazil. Furthermore, hypothalamic insulin and leptin resistance. were improved.Abildgaard et al. [27] from Denmark studied male Sprague-Dawley rats and showed that, IFNγ, IL2 and IL4 [antinflammatorty markers] increased at the expense of TNFα and IL6 [pro-inflammatory] among probiotics treated rats, also hippocampal transcript levels of factors involved in HPA axis regulation were lowered in probiotics treated rats. The reverse happen among high fat diet rats indicating the positive effects of probiotics in depression.

Diet:

Nilaweera et al. [28] investigated the effects of whey protein isolate among mice and showed a reduction of hypothalamic expression of pro-opiomelanocortin gene and *Firmicutes* microbiome leading to high energy intake.Another study conducted among obese mice [29], showed that arachidonic acid induce hypothalamus resistance to leptin, favor proinflammatory microbiota, decrease butaryte and serotonin production, aggravates steatohepatitis and hypothalamus inflammation. Thus inducing obesity through gut-liver-adipose-hypothalamus axis. Reyer et al. [30] in their recent study on type of feeding concluded the promotion of minerals, hormones, hypothalamic abundance of transcripts, and circulation of energy equivalents indicating host-microbiota interaction in efficient feeding.

Humans studies:

A study published in the United Kingdom [31] showed that prebiotics suppressed morning cortisol response suggesting an anxiolytic effect of micobiota. Fernandez-Real et al. [32] conducted a case-control study among obese participants and defined a specific microbiota-brain map for obese subjects. The author found that, Actinobacteria phylum was linked to cognitive test scores, and magnetic resonance imaging diffusion tensor variables in the hypothalamus, thalamus, and amygdale indicating an effect of obesity on microbiota- brain microstructure and cross talk. Another case control study conducted by Kreutzer et al. [33] showed that, high-fat diet induces reduction of *Parasutterella sp.* in the gut, which is significantly correlated with mediobasal hypothalamus hyperintensity on MRI indicating inflammation but the number of neuron is equal suggesting a functional disturbance.

Conclusion: The microbiota disruption altered neurotransmitters and vasopressin receptor 1a mRNA expression in the hypothalamus, ameliorated the HPA response to acute stress, reduced insulin and leptin resistance, increased IFNγ, IL2 and IL4 at the expense of TNFα and IL6, modified specific gene expression, and induced inflammation in the hypothalamus.

Conflicts of interest: None to declare

Abbreviations:

HPA: Hypothalamus-pituitary axis
RNA: Ribonucleic acid
IFN: Interferon
IL: Interleukin
TNF: Tumor necrosis factor
CRH: Corticotrophin releasing hormone

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