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Psychoneuroimmunology of Depression and its Relation to the Gut-Brain Axis: Literature Review

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Abstract---*Background: Psychoneuroimmunology (PNI) or also called psychoneuroendocrinology is the study of how psychological, neural, and immunological processes interact and influence human health and behavior. It is known that psychosocial factors contribute to the development of many diseases and that the immune system plays an important role in this relationship. Likewise, immune system signals in the brain affect mood, cognitive function, and behavior. Method: Literature review through scientific sources from books and journals related to the psychoneuroimmunology of depression and its relationship with the gut-brain axis. Discussion: Several studies have shown that patients with severe mental disorders including depression are affected by various changes in the gut microbiota and increased intestinal permeability. The gut microbiota can activate the Hypothalamic-Pituitary-Adrenal (HPA) axis through some mediators that cross the blood-brain barrier and include antigens, microbes, cytokines, and prostaglandins. Some bacterias release neurotransmitters that can interact directly with the vagus nerve. Hypothalamic-Pituitary-Adrenal axis activation can influence gut microbiota and gut permeability. An imbalance in intestinal flora can reduce protective properties, and increase neurotoxins and inflammatory mediators, causing nerve damage from the synaptic cleft which causes depression. Conclusion: There is an interrelated relationship between the psychoneuroimmunology of depression and the gut-brain axis. Imbalances in the gut flora lead to immune activation and dysfunction in the gut-brain axis, contributing to neuropsychiatric disorders including depression.*

Keywords---*depression, gut-brain Axis, microbiota, psychoneuroimmunology, psychosocial.*

Introduction

Psychoneuroimmunology (PNI) or also called psychoneuroendocrinology is the study of how psychological, neural, and immunological processes interact and influence human health and behavior. It is known that psychosocial factors contribute to the development of many diseases and that the immune system plays an important role in this relationship. Likewise, immune system signals in the brain affect mood, cognitive function, and behavior. This two-way path became the focus of the PNI (Alessi & Bennett, 2020).

In the early days before Christ, the Greeks viewed mental illness as the result of an imbalance in the body's fluids. Years later, Plato proposed that an imbalance in mind, body, and mentality can cause emotional distress; and later in the 18th and 19th centuries, the idea emerged that painful life experiences especially during childhood could

have negative effects on the human psyche that persist into adulthood and potentially touch every aspect of a person's social and emotional life (Alessi & Bennett, 2020; Halaris et al., 1975).

Modern psychopathology has made substantial progress in focusing researchers' attention on the more biologically plausible mechanisms that may underlie mental illness. A wide variety of roles are considered, including those involving social, psychological, neural, immunological, genetic, and genomic processes. Integrating complex systems and different levels of analysis to achieve a more coherent and coherent perspective on the underlying pathophysiology of mental illness is no easy task (Homan, 2020; Halaris et al., 2019).

One of the most fundamental underpinnings of PNI involves the discovery that components of the immune system involved in inflammation are influenced not only by factors such as viruses and bacteria present in the body but also by signals and events that occur in the external social and physical environment. Such an effect is inconsistent with the classical model of the immune system, which suggests that inflammation is regulated largely by internal interactions that occur from the upper abdomen down and do not involve the brain. However, it is now widely recognized that socio-environmental processes, including psychological stress, can substantially increase inflammatory activity as well as increase a person's risk of various health problems and are associated with a poor prognosis (Homan, 2020; Halaris et al., 2019).

Immune System in Psychoneuroimmunology

Psychoneuroimmunology provides a framework for understanding the shared relationship between immune dysfunction and mental illness. Research on psychological modulation of the immune system began in the 1970s with the discovery that the immune system could be classically conditioned in animal models as well as in humans. It is now well established that the brain and immune system communicate in a two-way manner, connected mainly through the autonomic nervous system and neuroendocrine signalling from the hypothalamic–pituitary–adrenal (HPA) axis. Peripheral cytokines affect the central nervous system by modulating neurotransmitter metabolism, activating the HPA axis and afferent vagal nerves or directly crossing the highly permeable blood-brain barrier (Misiak et al., 2020).

HPA axis dysregulation observed in many mental illnesses as well as autoimmune disorders implicates the role of a disorganized stress response system in immune and mental health. Cortisol, a hormone product of the HPA axis, is thought to be anti-inflammatory and usually suppresses the heightened immune response that occurs under conditions of acute stress. However, when repeatedly activated by chronic stress, the body's stress response system is considered disorganized and insensitive to its feedback mechanisms, contributing to a low-grade inflammatory response. Thus, chronic stress and increased stress reactivity may directly contribute to systemic inflammation and immune dysfunction. A study in animals showed that stress causes depressive behavior and an increase in the number of cytokines, whereas, in humans, psychological stress often triggers episodes of mood disorders. An estimated 80% of first-onset major depressive episodes are preceded by a major life stressor, making stress a significant risk factor for developing depression (Misiak et al., 2020).

Stress and Allostatic Load

Stress can be interpreted as a threat to a person's psychological or physiological integrity. When stress occurs, acute catecholamines and cortisol are released from the spinal cord and suprarenal cortex. This physiological response plays a short-term protective role, although if stress is chronically maintained or in the case of dysregulation of hormonal secretions it can be detrimental to the organism. This is an aspect covered by the allostatic load model. Organisms tend to seek a balance between regulatory physiological systems (homeostasis) using adaptive responses (allostasis) involving the sympathetic and neuroendocrine nervous systems, especially the HPA axis. When chronic stress is present and allostatic load exceeds a limit, chronic dysregulation of allostatic mediators occurs along with cellular responses that have been associated with different medical conditions including mental illness (unipolar depression, bipolar disorder and schizophrenia), neurodegenerative diseases (cognitive impairment) or endocrine metabolic disorders. (obesity and metabolic syndrome) (Slavich, 2020).

Different factors play a role in the response to stress and the capacity to tolerate allostatic loads. These factors include personal experience, genetics, and behavior. When the brain perceives an experience as stressful, physiological and behavioral responses are triggered, including the participation of the immune system, which initiates the processes of allostasis and adaptation. Accumulation of allostasis, excessive exposure to cellular stress, and endocrinological and immunological mediators will lead to disease development. The allostatic load has been associated with different mental conditions, including burn-out syndrome or chronic fatigue, as well as parameters

associated with ageing such as cardiovascular risk and cognitive impairment (Slavich, 2020; Madison & Kiecolt-Glaser, 2019).

The fundamental goal of the human immune system is to keep the body biologically safe and protected from foreign pathogens. The immune system plays an important role in promoting health and survival, especially during physical injury or infection. This system has two interconnected branches known as humoral immunity and cellular immunity, these branches work together to provide short and long-term protection for humans against pathogens that can enter the body through open body cavities (eg nose or mouth). or through wounds incurred during fights or social conflicts (Homan, 2020; Halaris et al., 2019; Kohut, 2019).

Humoral Immunity

Humoral immunity represents a highly conserved and rapid first-line defence of the body against tissue damage and microbial infection. Humoral immune system responses are mediated by humoral immune cells (eg, monocytes/macrophages and dendritic cells) that circulate throughout the body and use invariant receptors to detect a wide variety of pathogens that have the potential to cause biological damage if left untreated. Once these cells identify an injury or infection, they initiate a complex inflammatory process that helps resist infection and promotes healing and recovery (Slavich, 2020).

Cellular Immunity

When the defences of the humoral immune system are insufficient to overcome a biological threat, a second branch of the immune system, cellular immunity, is called into action. In contrast to humoral immunity, which is non-specific and does not provide long-term protection for the host, cellular immunity involves the proliferation of microbial-specific white blood cells (i.e. lymphocytes) that attempt to neutralize or eliminate a particular microbe based on immunological memory of previously responding to a particular pathogen or antigen. Whereas humoral immune responses act quickly, within minutes or hours, cellular immune responses take days to develop (Slavich, 2020; Soria et al., 2018).

In contrast to humoral immunity, cellular immunity is initiated by antigen-presenting cells (APCs), such as macrophages or dendritic cells, which help the immune system distinguish between the host's cells (i.e., "self") and cells of invading bacteria or viruses (i.e., "not himself" or "stranger"). These antigen-presenting cells (APC) are attracted to the center of the body where they process and attack antigens. After the foreign antigen is ingested and processed, APCs then migrate from the site of infection to local lymph nodes, where they present antigen peptides to T helper (Th) cells, resulting in the release of various cytokines, including interleukin-2 (IL-2), interleukin-4. (IL-4), interleukin-5 (IL-5), and interferon-gamma (IFN- γ), which help promote and control cellular immune responses (Slavich, 2020; Vempati & Reddy, 2019).

Inflammatory Cytokines

Cytokines are key mediators of the inflammatory response and coordinate humoral and cellular immune system reactions against pathogens. Given their central role in stress physiology and in shaping mental health, however, cytokines deserve more attention. Cytokines are the major biological endpoints of immune system activity currently being assessed in biobehavioral research on stress and mental health (Feng et al., 2020; Delaney et al., 2019; Fond et al., 2020).

Cytokines are released from several different types of immune cells, including monocytes/macrophages, dendritic cells, and neutrophils, and their main function is to coordinate cell-to-cell communication during physical injury or infection. However, cytokines can also alter neurochemical and neuroendocrine processes that have far-reaching effects on human physiology and behavior. Cytokines can thus be considered to function like neurotransmitters and hormones insofar as they mediate physiological responses, depend on receptor-ligand interactions and have self (autocrine), local (paracrine), and distal (endocrine) effects. In general, cytokines can be categorized as those primarily involved in humoral immunity (eg, tumour necrosis factor- α [TNF- α], interleukin-1 [IL-1], interleukin-6 [IL-6], interleukin-8 [IL -8], and interleukin-10 [IL-10]), and cellular immunity (eg, IFN- γ , IL-2, IL-4, and IL-5), and those that enhance inflammatory activity (ie, reset/ reset) called pro-inflammatory cytokines, and activities that reduce inflammatory activity (downregulate) called anti-inflammatory cytokines (Feng et al., 2020; Delaney et al., 2019; Fond et al., 2020).

Hundreds of cytokines have been identified to date, some of which have been studied extensively by immunologists and others that are still unexplored. But in the context of psychology and psychiatry, the situation is very different. Currently, only a small number of cytokines have been studied consistently across stress and mental health research. These cytokines are primarily IL-1, IL-6, and TNF- α .¹⁷ (Ma et al., 2020).

Finally, at the neurocognitive and behavioral level, cytokines communicate with the central nervous system to induce a constellation of behaviors known as sickness behaviors. These behaviors include increased pain and sensitivity to threats, anhedonia, fatigue, psychomotor retardation, and withdrawal from social behavior. This behavior serves several functions and is intended, for example, to draw attention to potential injury (i.e., pain sensitivity), raise individual awareness of potential threats in the social and physical environment (i.e., sensitivity to threats), help individuals recover and recover from the likelihood of injury (ie, anhedonia, fatigue), and reducing the likelihood of infected individuals developing more severe disorders (ie, psychomotor retardation, social behavior withdrawal).

Combined, these effects help increase a person's chances of surviving an injury or physical threat. At the same time, it should be noted that its neurocognitive and behavioral consequences are very similar to some of the symptoms of anxiety and depression, suggesting that inflammation may play a role in anxiety and depressive disorders.

The immune system can mount a rapid and effective inflammatory response to physical injury or the first sign of a pathogen is essential for overcoming infection, repairing tissue damage, and increasing survival. Unfortunately, what can save us in the short term, can also kill us in the long term. This is because persistently increased inflammatory activity can lead to oxidative stress, partly driven by the production of cytokines that increase free radicals originating from reactive oxygen intermediate (ROI), which can directly oxidize and also interfere with DNA repair mechanisms (Ma et al., 2020; Miller & Goldsmith, 2019).

For example, the proinflammatory cytokine TNF- α promotes ROI formation by neutrophils and other cells in the body, stimulating nitric oxide expression in inflammatory and epithelial cells. These interactions can lead to DNA mutations, and genomic instability, and ultimately increase the risk of many health problems that have an inflammatory component. Consequently, although inflammation was previously thought to be involved only in a few disorders, such as cardiovascular disease and certain cancers, it is now recognized that chronic inflammation is involved in several mental illnesses, such as post-traumatic stress disorder (PTSD) and depression, and that it plays a role in the emergence, exacerbation, or the development of various physical conditions, including asthma, rheumatoid arthritis, diabetes, obesity, atherosclerosis, ovarian and breast cancer, and Alzheimer's disease (Ma et al., 2020; Miller & Goldsmith, 2019).

A beneficial inflammatory response occurs quickly in response to an obvious physical or biological threat and then dissipates once the threat is gone. One of the factors that can substantially change the response of the immune system and prolong the period of inflammation is psychological stress (Müller, 2018; Najjar et al., 2018).

Regulation of the Center for Inflammatory Activity

The human inflammatory response is a highly complex and tightly regulated process, influenced by a variety of physiological events that occur throughout the exterior of the body. However, systemic inflammatory activity is also regulated by processes occurring in the brain, including neurocognitive representations of the surrounding social and physical environment. These neuroinflammatory pathways are critical for survival because they allow the immune system to mobilize and redistribute immune cells not only after physical injury or infection occurs, but before physical attack can increase an individual's risk of developing disease-related infectious pathogens (Kalinkovich et al., 2020; Kelsven et al., 2020).

However, perhaps what is most important to understand is that the immunological response to a socio-environmental problem represents the body's attempt to deploy its resources in dealing with a specific biological threat that is most likely to exist in a different environment. Psychological stress, such as that involving social conflict or rejection, increase a person's risk for physical harm. Psychological stress experienced by individuals in their current environment is most likely to increase the expression of proinflammatory immune response genes, fighting bacteria and other extracellular pathogens that may be exposed during a physical injury. This response is accompanied by reciprocal downregulation of antiviral immune response genes that target intracellular pathogens such as viruses that spread in social situations. This term refers to the proinflammatory increase of the human basal gene expression profile (that is, the basal transcriptome) as a conserved transcriptional response to adversity (CTRA) (Miller & Goldsmith, 2019; Müller, 2018).

The fundamental principle of CTRA involves the ability of the immune system to activate host defence programs in response to new socio-environmental difficulties. The immune system cannot directly detect social threats in the

surrounding environment, so it relies on the brain, which can alert the peripheral immune system to threats via several separate pathways. Two of the major pathways are the sympathetic nervous system and the HPA axis (Miller & Goldsmith, 2019; Müller, 2018).

Sympathetic Nervous System

The sympathetic nervous system can influence the production of proinflammatory cytokines by releasing the neurotransmitter norepinephrine to peripheral tissues, primary and secondary lymphoid organs, and all other major organ systems, including vascular and perivascular tissues. Once released, norepinephrine modulates immune response gene transcription through stimulation of β -adrenergic receptors and possibly α -adrenergic signalling. This adrenergic signalling cascade suppresses the transcription of antiviral interferon type I genes and increases the transcription of proinflammatory immune response genes IL-1, TNF, and IL-6, leading to increased systemic inflammatory activity and decreased antiviral activity. Therefore, ultimately, the sympathetic nervous system plays a central role in coordinating CTRA, which directs humoral immune system responses between proinflammatory and antiviral phenotypes (Miller & Goldsmith, 2019; Müller, 2018; Najjar et al., 2018).

Hypothalamic-Pituitary-Adrenal Axis

The Hypothalamic-Pituitary-Adrenal (HPA) axis also regulates the activity of proinflammatory cytokines in the periphery of the body. It is thought that activation of the HPA axis suppresses the transcription of proinflammatory and antiviral immune response genes by stimulating the release of the glucocorticoid cortisol which is one of the most potent anti-inflammatory substances in the body. However, cortisol can also increase inflammation. Cortisol enables the catecholamines epinephrine and norepinephrine to enhance immune system activity, facilitates the mobilization of immune cells to injured tissues, and can also enhance the inflammatory response to immunological challenges. In addition, prolonged increases in cortisol can lead to a phenomenon called glucocorticoid insensitivity or glucocorticoid resistance, which occurs when immune cells become less sensitive to the anti-inflammatory effects of glucocorticoids, thereby causing an increase in HPA axis activity (as opposed to a decrease) in inflammation (Misiak et al., 2020).

Major Depression

Several studies have shown that older adults (40-60 years) who have mood-related mental illnesses such as depression and anxiety disorders have significantly higher salivary cortisol levels. The most systematic evidence linking impaired immune system function to mental status is in the context of major depression (Fond et al., 2020).

The social signal transduction theory of depression describes the complete range of social, psychological, and biological mechanisms that link the experience of social stress to the risk of depression (Kertiasih et al., 2023). According to this theory, social stressors that increase the organism's risk of physical threats, such as those involving social conflict, isolation, rejection, and exclusion, are represented by the nervous system that processes the affective and interoceptive aspects of physical and social pain, including the anterior insula and dorsal anterior Cingulate Cortex (dACC). This area projects signals to lower-level brain areas, including the hypothalamus and brainstem autonomic control centers, which modulate the activity of the HPA axis and the peripheral nervous system—resulting in the production of cortisol, epinephrine, norepinephrine, and acetylcholine—which in turn influences systemic inflammatory activity. Whereas cortisol and acetylcholine normally suppress (but can also increase) inflammatory activity, both epinephrine and norepinephrine promote inflammation by inducing the activation of the intracellular transcription factor NF- κ B and Activator Protein-1 (AP-1), which regulate the expression of proinflammatory immune response genes, including IL-1 β , IL-6, IL-8, and TNF (Feng et al., 2020; Delaney et al., 2019; Fond et al., 2020).

Expression of these genes ultimately leads to the production of proinflammatory cytokines that cause depressive symptoms such as sad mood, anhedonia, fatigue, psychomotor retardation, and withdrawal from social behavior, in addition to other cognitive, affective, and somatic phenomena that often coexist with depression, namely, increased alertness, increased anxiety, and pain sensitivity. The central nervous system can also influence peripheral inflammation through efferent vagus nerve activity which downregulates inflammation by suppressing TNF gene transcription (Miller & Goldsmith, 2019).

Ultimately, the biological responses that emerge in response to emerging problems are critical to survival in preparing the body for physical injury and infection, should they occur. However, in today's social environment,

these social signal transduction pathways are most often activated not by impending physical danger, but by contemporary social threats, including those that are purely symbolic, anticipated, or imagined. Socio-environmental conditions trigger biological responses that may lead to an increase in the proinflammatory phenotype which is hypothesized to be a key phenomenon driving the pathogenesis and relapse of depression, as well as the overlap of depression with several somatic conditions including asthma, rheumatoid arthritis, chronic pain, metabolic syndrome, cardiovascular disease, obesity, and neurodegeneration (Vempati & Reddy, 2019; Miller & Goldsmith, 2019).

A causal role for inflammation in depression was first demonstrated by the observation that treatment of proinflammatory cytokines (eg, IFN- α) for Hepatitis C induces major depressive episodes in up to half of patients. Cytokines, chemical messengers of the immune system, are responsible for experiencing "sickness behaviors" such as lethargy and loss of appetite that usually accompany inflammation and adaptation to acute illness. Several clinical studies have shown that cytokines (eg, IL-6 and IL-1 β) and other inflammatory biomarkers (eg, CRP) are increased in depressed patients in the absence of physical illness (Ma et al., 2020; Miller & Goldsmith, 2019).

Depression and other mood disorders almost always involve memory impairment. Memory is a function of the hippocampus, a brain region rich in glucocorticoid receptors. Chronically elevated cortisol levels, resulting from chronic stress, have been shown to decrease hippocampal volume and lead to the loss of neurons, which inevitably impairs memory. As expected, decreased hippocampal volume occurs in individuals with long-term depression and increased cortisol may be a contributing factor (Madison & Kiecolt-Glaser, 2019).

Chronic stress decreases brain-derived neurotrophic factor (BDNF) expression in limbic brain structures that control memory and mood and may offer one explanation for how chronic stress decreases hippocampal volume. Brain-Derived Neurotrophic Factor (BDNF) is a protein that supports the growth and differentiation of new neurons in the central and peripheral nervous system, most active in the hippocampus and frontal cortex areas of the brain, which control memory and mood. In a study that attempted to find a link between chronic stress, BDNF, and depression, sows were repeatedly tethered for 1.5 to 4.5 years to create stressful situations. The frontal cortex and hippocampus were analyzed after slaughter and revealed a decrease in BDNF protein levels as well as an increase in cortisol levels and adrenal weight. This effect was more pronounced in sows subjected to tethering for a longer duration, indicating that chronic stress progressively depletes levels of the protein BDNF, resulting in the degeneration of neurons in brain areas responsible for memory and mood (Slavich, 2020).

Gut-Brain Axis

The gut-brain axis is involved in the gut microbiota, neuroendocrine (hypothalamic-pituitary-adrenal axis), immune (cytokines and chemokines) and nervous systems, including the autonomic and enteric nervous systems. The gut microbiota communicates with the brain and maintains body homeostasis through this system. The gut-brain axis is a two-way communication system involving the brain and intestinal tract (Kelly et al., 2021).

The gut microbiota was found to communicate with the brain through several different mechanisms including through the production of neurotransmitters, modulation of neurotransmitter catabolism, innervation via the vagus nerve, or activation of the HPA axis. There are a total of six pathways that can be influenced by the gut-brain axis (Misiak et al., 2020; Madison & Kiecolt-Glaser, 2019).

Broadly speaking, it can be described that an imbalance in the gut microbiota can cause abnormal brain development, increased harmful substances in the body, decreased protective factors and damaged routine pathways to the brain. All these things then become a chain that causes an increase in inflammatory reactions in the body. Starting with the intestinal mucosal tract, then the blood-brain barrier resulting in the activation of microglia. This activation has an impact on the death of brain nerve cells, disruption of neurotransmitters which ends in a decrease in cognitive function, and positive or negative symptoms (Yuan et al., 2019).

Diet and Psychoneuroimmunology

Humans and gut bacteria have developed various ways to communicate and regulate one another. Psychological stress and depression tend to encourage excessive consumption of unhealthy foods, which affect the growth of gut bacteria. In addition, stress and depression can reshape the composition of gut bacteria in a similar (non-variable) way through stress hormones, and inflammation, and cause gut autonomic changes. Gut bacteria then release metabolites, toxins, and neurohormones that can alter eating behavior and mood. Several species of bacteria can encourage disordered eating. Gut bacteria may also regulate the stress response and increase the risk of depression, which may be attenuated by probiotic supplementation (Misiak et al., 2020; Madison & Kiecolt-Glaser, 2019; Kelly et al., 2021).

Stress can affect health through its impact on gut bacteria. The autonomic and circulatory systems carry distress signals to the gut. In addition, new bone marrow-mediated pathways were discovered, highlighting the role of immune cells as messengers conveying psychological stress to the gut. The increased inflammation that often accompanies stress and depression promotes the growth of pathogenic bacteria that promote dysbiosis and the development of leaky gut (Misiak et al., 2020; Madison & Kiecolt-Glaser, 2019; Kelly et al., 2021).

Both chronic and acute stressors can shift gut bacteria across multiple areas and habitats—both within the (lumen) and gut lining (mucosal lining). Several studies have demonstrated differences in gut microbiota composition and function in individuals with major depressive disorder, compared with healthy controls. Some data suggest that proinflammatory species may predominate at the expense of health function-promoting species in depressed individuals. Stress and depression can increase the permeability of the gut barrier. As a result, the 'leaky gut' allows bacteria to seep into the circulation, producing an inflammatory response (Misiak et al., 2020; Madison & Kiecolt-Glaser, 2019; Kelly et al., 2021).

Diet and stress regulate the gut microbiota. Available evidence suggests a two-way relationship between stress/mood, diet, and gut microbiota, which in turn forms a vicious cycle. This mind-body, human-bacteria helps explain the link between immunity and chronic disease. Today the top-down pathway from human behavior and mood to the gut microbiota is better understood (Madison & Kiecolt-Glaser, 2019).

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