Role of Interleukins in Major Depressive Disorder: Understanding the Pathophysiology and Biomarker Insight

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis/project titled "Role of Interleukins in Major Depressive Disorder: Understanding the Pathophysiology and Biomarker Insight" submitted by Sarder Mostakim Hasan (22146088) of Summer, 2025 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy.

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Abstract

Major Depressive Disorder (MDD) is a disease of complex biological origin, including much more than personality or a mere imbalance of neurotransmitters. More recently, there has been a growing appreciation that immune dysregulation, specifically interleukins, plays an important part in its pathophysiology. In addition to that, the function of these interleukins is not limited to neurotransmitter metabolism via the kynurenine pathway but may also affect neuroplasticity by means of activating the HPA axis due to decreased BDNF levels. Besides, interleukins can serve as markers of the severity and treatment efficacy of the disease. As for treatments based on targeting inflammation, they proved themselves very promising, especially when the disorder is treatment-resistant.

Keywords: *Major Depressive Disorder (MDD); Interleukins; Neuroinflammation; Cytokines; Biomarkers; HPA Axis*

Dedication

This thesis is dedicated to my beloved parents, who have always supported me through thick and thin, providing me with a lot of love and encouragement. It is due to their tireless efforts and continuous motivation that I was able to achieve what I did. In addition to this, this thesis is also dedicated to all the other students, my instructors, and my mentors, without whom I could not have done what I have accomplished. Their advice and mentorship have helped me shape my academic and professional life in a very positive manner. This thesis is also dedicated to all the people suffering from mental disorders, especially individuals struggling with Major Depressive Disorder.

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Chapter 1

Introduction

1.1 Background of Major Depressive Disorder

Major Depressive Disorder (MDD) is a widespread yet serious mental health disorder. Decreased interest in being active, persistent sadness, cognitive impairments and a wide variety of somatic symptoms is characterizing it with significant impact on public health and still the leading cause of disability worldwide (World Health Organization, 2021).

MDD impairs the regulation of emotions, cognition, and physiology, which can lead to functional impairment in daily life. People can feel hopeless and very tired, find it hard to concentrate, change their appetites or sleeping patterns, and think of hurting themselves in some way. These causes lead to a state of MDD that may be brought about by biological processes, psychological factors, environmental influences, and genomic vulnerability (Otte et al., 2016).

1.2 Constraints of Conventional Theories of Depression

In terms of history, the monoamine theory, which linked MDD with low concentrations of neurotransmitters such as dopamine, serotonin, and norepinephrine, provided only a primitive explanation for the condition. This theory, although it caused some conflict in my early practice life, was responsible for giving birth to SSRIs; however, it did not provide an accurate biochemical picture of the disease. But research into the monoamine theory also pointed out a number of its shortcomings: Many people fail to respond to antidepressants. Clinically important antidepressant therapies generally require weeks of administration for an effect to be seen. Decreasing monoamines in healthy individuals does not consistently induce depressive symptoms. Results imply that different biological cautions have MDD course and advancement (Miller, et al., 2009).

1.3 Emergence of the Inflammatory Hypothesis

Recent studies have drawn attention to the influence of the immune system on mental health. The inflammatory theory of depression states the low level chronic evolement & persistence of depressed symptoms. Several observations support this hypothesis, by finding an increased risk of inflammatory markers in MDD patients. People with chronic inflammatory diseases

are more likely to experience depression. Depression has been linked to pro-inflammatory cytokines. Findings indicate that the activity of interleukins are frequently elevated in patients suffering from depression, indicating an apparent connection between immune system and brain dysregulation (Dantzer et al., 2008).

1.4 Interleukins as Key Mediators in Depression

Interleukins, cytokines that aid in the regulation of inflammation and immune responses. They impact brain function through neuroimmune signaling and promote immune cell communication. Multiple interleukins have been associated with MDD. Interleukin-6 (IL-6) is associated with depression severity and to the importance of treatment resistance. Interleukin-1 beta (IL-1β) is linked to reduced neurogenesis and neural inflammation. Interleukin-18 (IL – 18) mediates stress-induced immune activation. Cytokine which may protect by reducing inflammation is mediated by IL-10 (Interleukin-10). Depression could potentially be influenced by these interleukins through neurotransmitter activity, hormone regulation, and brain connectivity (Otte et al., 2016).

1.5 Neuroimmune Interaction in Major Depressive Disorder

Interleukins affect brain function by crossing the blood-brain barrier and engaging microglial cells in the brain. Through modifying neurotransmitter systems including dopamine and serotonin, it affects the hypothalamic pituitary adrenal axis. Dantzer et al.(2008) states that hyperactive neuroinflammatory pathways may also disrupt stress response and adaptive ability when these processes are prolonged over time.

1.6 Rationale of the Study

Much has been learned over the past few decades about diagnosing and treating depression, but it still presents challenges. Some of this heterogeneity in MDD may point towards different biological subtypes, for example, systemic inflammation and cytokines.
Interleukins have emerged as prime candidates for recognizing the biological roots of sadness. Much of the focus now is on the discovery of new biomarkers for prognosis and diagnosis and developing targeted treatment plans.
Integration of immunological and psychiatric perspectives requires a similar detailed examination of interleukins in MDD. Determine whether interleukins are useful biomarkers and clarify their causal role in MDD. It may investigate the importance of particular interleukins in MDD. It will help to understand the pathways by which inflammation and

depression are connected. ILs can be considered as predictive & diagnostic biomarkers for its role of interleukin targeting in therapeutic effects and to investigate the therapeutic effects of interleukin targeting.

Chapter 2

Interleukins and the immune system

2.1 Overview of the Immune System

The immune system is a complex network of organs, cells and chemical signals working together to keep the internal environment stable (homeostasis) and protect from pathogens. It is principally divided into two elements (Abbas et al., 2021): the innate and the adaptive immune system. The mechanism can be fast even but it is not specific. On the contrary, to generate focused immune responses and maintain immunological memories, the highly sophisticated cell relies on lymphocytes, namely T- cell & B-cell (Abbas et al., 2021).

2.2 Cytokines: Definition and Classification

Cytokines are small, soluble proteins secreted by immune cells that allow them to communicate and coordinate their actions. They are also essential to regulating blood cell production, dampening inflammation and coordinating immune responses throughout the body.

Cytokines are in general classified into several groups, including:

- ILs, or interleukins
- TNFs — Tumour necrosis factors
- IFNs, or interferons
- Chemokines

Interleukins are especially important in immunology due to their roles across a range of functions, largely governing inflammation and immune activity (Dinarello, 2007).

2.3 Interleukins: Structure and Function

Interleukins are primarily secreted by leukocytes but can also be produced in endothelial cells. Interleukins attach to specific receptors on target cells to initiate intracellular signalling pathways that affect gene expression and cell functions. These molecules participate in physiology processes such as activation and differentiation of immune cells, regulation of inflammatory response, and coordination of both innate and adaptive immunity. Each of the forty plus interleukins which have been discovered so far serve a unique biological function.

Depending on its context interleukins may cause inflammation to develop or subside (Turner et al., 2014).

2.4 Pro-inflammatory and Anti-inflammatory Interleukins

Interleukins are classified based on whether they promote or inhibit inflammation.

2.4.1 Pro-inflammatory Interleukins

Pro-inflammatory interleukins drive immune activation and the inflammatory process. Interleukin-1 beta (IL-1β) induces fever, activates immune cells, and enhances inflammatory signaling. Interleukin-6 (IL-6) works on persistent inflammation and regulates acute-phase immune responses. Interleukin-18 (IL-18) elevates the production of interferon-gamma and augments immune defenses. Although these cytokines are necessary for host defence, dysregulation of them can lead to pathological inflammation (Dinarello, 2007).

2.4.2 Anti-inflammatory Interleukins

By reducing excessive immune responses, anti-inflammatory interleukins contribute to the resolution of inflammation. Two notable examples are Interleukin-4 (IL-4), which promotes the development of antibodies and helps to maintain immune system homeostasis. Many chronic illnesses exhibit imbalance between pro-inflammatory and anti-inflammatory interleukins (Miller et al., 2009).

2.5 Interleukin Signaling Pathways

Interleukins initiate intracellular signalling cascades. In the end, these pathways impact cell behaviour (O'Shea et al., 2015). Key interleukin signalling mechanisms include the system. Certain interleukins, such as IL-6. Genes that regulate inflammation and immunological responses are transcriptionally triggered when this pathway is activated (O'Shea et al., 2015). Immunological responses and cellular viability are triggered by interleukins.

2.6 Role of Interleukins in Neuroimmune Communication

Recent research highlights the role of interleukins in facilitating connection between the immune system and CNS. Interleukins impact brain function through multiple mechanisms like overcoming the BBB (blood-brain barrier), vagus nerve signalling activation, changing microglia activity.

Microglia amplify neuroinflammation by producing additional inflammatory mediators in response to interleukins (Dantzer et al., 2008). Neuroimmune interactions play a pivotal role

in psychiatric disorders, with persistent inflammation potentially modifying neurotransmitter pathways, hormonal regulation (Dantzer et al., 2008).

Chapter 3

Pathophysiology of MDD

3.1 Overview of the Pathophysiology of MDD

Major depressive disorder (MDD) is a complex disease that disrupts numerous biological measures. Various factors like genetic vulnerability, environmental stressors, neurochemical variables, hormonal irregularities and immune system activation are relevant in the evolution instead of stemming from a single origin (Otte et al., 2016). Depression has been increasingly recognized in recent studies as a complex, systemic disorder involving interconnected biological pathways around: Neurotransmitter systems HPA axis (regulation of neuroendocrine functioning) Brain inflammation Disease state viability and neuroplasticity The complexity surrounding the interrelations between these systems is key to the initiation, progression and relapse/recurrence of depressive episodes (Otte et al., 2016).

3.2 Neurotransmitter Dysregulation

3.2.1 Revisiting the Monoamine Hypothesis

Depression can be attributed to low amounts of monoamines required for the regulation of mood as well as reward and motivation according to the monoamine theory. However, while use of antidepressants associated with these neurotransmitter systems causes an improvement in symptoms among many patients suffering from major depressive disorders, the monoamine theory alone fails to account for the various intricacies of MDD. Latency of time before these drugs cause their effect shows that other factors, including changes in gene expression and neuroplasticity, play a role as well (Krishnan and Nestler, 2008).

3.2.2 Serotonin System

Serotonin has a major impact on sleep, emotional processing, and mood regulation. Reduced serotonergic activity has been associated with depressed state of mind, fear or even suicidal thoughts and actions.

By activating indoleamine 2,3-dioxygenase that redirects tryptophan from produce serotonin to the kynurenine pathway produces neurotoxic and inflammatory cytokines, inflammatory cytokines can modify serotonin metabolism (Dantzer et al., 2008).

3.2.3 Dopamine and Reward Dysfunction

Motivation and reward processing depend on dopamine. Decreased dopaminergic activity in MDD is linked to anhedonia, diminished drive or even decision-making impairment. Inflammatory mediators that reduce dopamine synthesis and release may contribute to this dysfunction (Felger & Miller, 2012).

3.3 Dysfunction of the HPA Axis

The HPA axis serves as the initial system for the body's stress response, managing the secretion of cortisol in adapting to stress.

3.3.1 Mechanism of HPA Axis Activation

The body uses negative feedback to keep this mechanism in check with the help of cortisol, but healthy people are likely unaffected. But in MDD prolonged stress keeps the HPA axis activated which stimulates impaired negative feedback mechanisms. That results in increased cortisol levels remaining consistently high. This syndrome is known as hypercortisolemia (Pariante & Lightman, 2008).

3.3.2 Impact of Increased Cortisol

Our brains can be damaged by high exposure to an increase in cortisol levels on the following: decreased volume of the hippocampus, impaired neuronal generation, cognitive dysfunction. On top of that, cortisol interacts with inflammatory pathways to aggravate the neurobiological changes linked to depression.

3.4 Neuroinflammation

3.4.1 Inflammatory Activation in MDD

One of the main advances in depression research is showing that neuroinflammation is a key component. Ps: Higher inflammatory marker levels e.g. interleukins and other cytokines are often noted in people with MDD.

Chronic inflammation is due to the following reasons like stress in the mind or an infection. These inflammatory responses might also influence behaviour and brain functioning and may be impacted by these inflammatory reactions (Miller et al., 2009).

3.4.2 Microglia's Function

Microglia are the main immune cells of the central nervous system (CNS). When activated, they release reactive oxygen species (ROS), pro-inflammatory cytokines and various neurotoxic agents. Within MDD, upregulation of microglial activation may happen with amplified neuroinflammatory signalling and disruption of synapses and damage to neurons. This mechanism, at least in part, accounts for the brain anatomical and functional changes associated with depression (Dantzer et al., 2008).

3.4.3 Behavioural Alterations Caused by Cytokines

Pro-inflammatory cytokines can cause behavioural alterations that resemble signs of depression, such as weariness, anhedonia, diminished appetite, social disengagement etc. Sickness behaviour is a phenomenon that lends credence to the connection between depression and immunological activation.

3.5 Impaired Neuroplasticity and Neurogenesis

3.5.1 Brain-Derived Neurotrophic Factor (BDNF)

Neuroplasticity is the brain's ability to adjust and reorder synapses. Brain derived neurotrophic factor (BDNF) is an important protein involved in neuronal growth and synaptic plasticity. Within MDD, enhanced BDNF release occurs with defective neurogenesis of the hippocampus. These changes are associated with dysregulated affect and impaired cognition (Krishan & Nestler, 2008).

3.5.2 Stress and Inflammation's Impact on Neuroplasticity

Neuroplasticity is adversely affected by long-term stress and inflammation by lowering the expression of BDNF which elevated oxidative stress while encouraging the death of neurons. These processes are significantly influenced by interleukins, especially pro-inflammatory ones, which connect immunological activation to structural alterations in the brain.

3.6 Microbiota and the Gut-Brain Axis

Recent studies indicate that depression might be linked to. Microbiota interact with the immune system and influence brain function by the production of neurotransmitters, control

of inflammatory responses, alteration of the hypothalamic pituitary adrenal axis elevation. That shifts to the greater inflammation and depressive symptoms. (Cryan & Dinan, 2012).

3.7 Integration of Pathophysiological Mechanisms

The pathophysiology of MDD is best envisioned as the result of dynamic interactions between multiple interconnected systems. Inflammation has an effect on neurotransmitter metabolism. Stress responses get exaggerated as a result of disruption to the HPA axis. Neuroplasticity must be ignited for brain function. Gut bacteria affect Immune and neural pathways.

Chapter 4

Role of Interleukins in MDD

4.1 Overview

Psychoneuroimmunology perspective in the pathophysiology of MDD Interleukin signalingAmong the most significant signaling molecules of the immune system, interleukins have recently been shown to influence behavior and brain function (including emotion regulation) (18). There is emerging evidence that changes in interleukin production associate closely with depressive disorders (Miller et al., 2009).

Patients with MDD have a common finding of chronic, low-grade inflammation as indicated by increased concentrations of interleukin. These inflammatory dysfunctions are believed to relatively influence significant neurobiological mechanisms including neurotransmitter metabolic process, hormonal adjustment and synaptic plasticity (Miller et al., 2009). The following sections summarize discussions of some interleukins involved in the pathophysiology of MDD.

4.2 Interleukin-1 Beta (IL-1β)

4.2.1 Biological Function

Activated macrophages and microglia are the main producers. It is essential for starting inflammatory reactions, raising fever, and stimulating cells. By binding to IL-1 receptors, it activates intracellular pathways which control production of those genes (Dinarello, 2009).

4.2.2 Major Depressive Disorder and IL-1β

Multiple studies demonstrate that MDD patients present elevated levels of IL-1β in their peripheral and brain fluids. High levels of IL-1β impacts severity of depressive symptoms and impaired cognitive function along with resistance to the therapy.

One such pro-inflammatory cytokine, IL-1β, is of utmost importance and acts to modulate stress on the brain. Chronic stress induces immune responses that increase IL-1β production and adversely impacts brain function (Dantzer et al., 2008).

4.2.3 Depression Mechanisms of Action

IL-1β is causatively linked to depression in several ways:

a) Neurogenesis Inhibition

IL-1β inhibits neurogenesis. This is relevant given that a decrease in hippocampus neurogenesis characterises depression.

b) The HPA Axis Activation

Upon activation, cortisol production increases due to the stimulation of CRH release by IL-1β. The long-term increase of cortisol increases the symptoms of depression.

c) Changes in Neurotransmitters

Due to the kynurenine pathway, where IL-1β regulates serotonin catabolism and reduces the availability of serotonin while increasing the production of neurotoxic metabolites.

4.3 Mechanisms of Action in Depression

a) Impact on Neurotransmitters

IL-6 modulates release and reuptake of monoamine neurotransmitters including serotonin, dopamine and norepinephrine.

b) HPA Axis Dysregulation

Chronic production of IL-6 stimulates the HPA axis, leading to altered response to stress due to persistent high cortisol levels but regular low stress.

c) Synaptic Plasticity

The effect of IL-6 on synaptic plasticity leads to the impairment of neuronal connectivity.

d) Behavioral Effects

In experimental delivery; IL-6 elicits motivation withdrawal (and social) tests.

4.4 Interleukin-18 (IL-18)

4.4.1 Biological Function

Interleukin-18 is a cytokine that stimulates inflammation. By boosting inflammatory activities and inducing the generation of interferon-gamma (IFN-γ), it contributes to both innate and adaptive immune responses..

4.4.2 Correlation

IL-18 increased in individuals with Major Depressive Disorder (MDD) and may correlate with: Stress-induced immune activation. Severity of depressive symptoms Coexisting

inflammatory disorders IL-18 holds particular significance in relation to chronic stress, which is risky for developing depression.

4.4.3 Mechanisms of Action in Depression

a) Stress Response Modulation

Data are based on chronic stress-induced IL-18.

b) Interaction with Other Cytokines

Of these, IL-18 has been shown to interact with each of these cytokines and amplify the magnitude of inflammatory responses (Koo et al. 2016), further deteriorating neurobiological dysfunction.

c) Neurotoxicity

Increased levels of IL-18 can promote neuronal injury via enhanced oxidative stress and inflammatory signalling.

4.5 Interleukin-10 (IL-10)

4.5.1 IL-10 in Major Depressive Disorder

In contrast to pro-inflammatory cytokines, IL-10 levels are frequently lower. Decreased IL-10 levels correlate with increased inflammation, more severe symptoms and worse treatment outcomes. A characteristic aspect of depression portraits in between pro-inflammatory and anti-inflammatory cytokines (Otte et al., 2016).

4.5.2 Mechanisms of Action in Depression

a) Regulation of Inflammation

IL-10 antagonizes pro-inflammatory signaling pathways and restores the immune balance.

b) Neuroprotective Effects

IL-10 protects neurons from inflammatory damage and supports neurogenesis.

c) Modulation of Microglial Activity

IL-10 suppresses microglial activation, reducing neuroinflammation and preventing neuronal injury.

4.6 Cytokine Imbalance in MDD

A key feature of MDD is the imbalance between pro-inflammatory and anti-inflammatory interleukins. This results in chronic systemic inflammation, increased oxidative stress and disruption of neural circuits.

4.7 Clinical Evidence Supporting the Role of Interleukins

4.7.1 Observational Studies

Numerous reports have demonstrated high levels of IL-6 and IL-1β in patients with MDD compared to healthy controls.

4.7.2 Longitudinal Studies

Prospective studies suggest that increased cytokine levels may tell the onset of depression, indicating a potential causal relationship.

4.7.3 Treatment Studies

Antidepressant treatment has further supported their role in depression.

Chapter 5

Mechanisms Linking Interleukins To Major Depressive Disorder

5.1 Introduction

While Chapter 4 was dedicated to exploring the role of each interleukin individually with respect to MDD, elucidating the physiological influence that these (and other) cytokines play in function will certainly require a more thorough investigation over specific biological pathways. There are critical mediators that impact neurochemical, neuroendocrine and neuroplastic processes to induce changes in silencing and quiescing networks from upstream areas in the CNS. Interleukin mediated depression is characterized mainly by: alteration of monoamine neurotransmission, disruption of neurogenesis and neuroplasticity, participation in gut–brain axis, and potentiation of oxidative stress and excitotoxicity.

5.2 Interleukins and Monoamine Neurotransmission

5.2.1 Mechanism

Processing serotonin Tryptophan Metabolic pathway linking interleukins to depression Pro-inflammatory interleukins IL-1β and IL-6 activate the enzyme indoleamine 2,3-dioxygenase (IDO). It has been shown to cause this change by decreased serotonin, increased neurotoxic metabolite production, not limited to quinolinic acid and greater excitotoxic glutamatergic restricted predominance of quinolinic (Dantzer et al, 2008).

5.2.2 Effects on Dopamine and Norepinephrine

Interleukins also affect monoamine pathways:

Dopamine: Cytokines inhibit the formation of dopamine, a cofactor necessary for making dopamine.

Norepinephrine: Cytokine signaling leads to changes in norepinephrine release and turnover, impacting attention and arousal (Felger & Miller, 2012).

5.3 Activation of the Hypothalamic Pituitary Adrenal (HPA) Axis

5.3.1 Cytokine-Induced HPA Axis Stimulation

Interleukins are key players in the activation of the HPA axis. On the other hand, pro-inflammatory cytokines cause the release of CRH by stimulating the hypothalamus. This involves a cascade of hormonal reactions, where CRH causes the pituitary gland to release cortisol. Due to this, there is an increase in the levels of cortisol, especially during chronic inflammation states (Pariante & Lightman, 2008).

5.3.2 Glucocorticoid Resistance

In MDD, prolonged exposure and production of cytokines leads to glucocorticoid resistance. As a result, inflammation exists even with elevated levels of cortisol and chronic stress responses are maintained. Thus driving the cycle of inflammation and endocrine dysfunction that exacerbates depressive symptoms (Miller et al., 2009).

5.4 Interleukins and Neuroplasticity

5.4.1 Inhibition of Neurogenesis

Hippocampal neurogenesis Neurogenesis, especially in the hippocampus, is a key process involved in mood and cognitive functions. Interleukins have an adverse effect on this process via inhibition of neural progenitor cell expansion, increasing apoptosis meaning programmed cell death and inhibiting neuronal differentiation.

One example is that it acts in directly inhibiting neurogenesis in the hippocampus, contributing to structural alterations in the brain seen in depression (Koo & Duman, 2008).

5.4.2 Reduction of Brain-Derived Neurotrophic Factor (BDNF)

Reduced BDNF expression is caused by high levels of pro-inflammatory interleukins. This reduction leads to impaired synaptic connectivity, reduced neuronal resilience, increased vulnerability to stress, reduction of BDNF is believed to be most of the main mechanisms behind depression that leads to brain impairment (Krishnan & Nestler 2008).

5.5 Microglial Activation and Neuroinflammation

5.5.1 Role of Microglia

Microglial cells act as the main immune cells in the CNS, being crucial for maintaining neural homeostasis. In normal conditions, microglia support neuronal health and promote synaptic reorganization. But at higher levels of interleukins: Activation of microglia They

release more pro inflammatory cytokines. This results in chronic neuroinflammation (Dantzer et al., 2008).

5.5.2 Synaptic Dysfunction

Activated microglia can indirectly disrupt synaptic function by: Excessive pruning of synapses. Altering the release of neurotransmitters. Causing damage to neuronal structures. These changes lead to dysfunction and disturbance.

5.6 Oxidative Stress and Excitotoxicity

5.6.1 Oxidative Stress

Release of interleukins stimulates the production of reactive oxygen species (ROS) causing

oxidative stress. This condition results in damage to cellular moieties including lipids, proteins and DNA. Moreover it results in mitochondrial dysfunction and impaired neuronal energy metabolism. Depression has been strongly linked to oxidative stress (Maes et al., 2011).

5.6.2 Glutamate Excitotoxicity

Activation of the kynurenine pathway after inflammation results in greater production of quinolinic acid, leading to NMDA receptor overstimulation. This results in:

Excessive calcium influx into neurons, neuronal injury and death, impaired synaptic function.

Excitotoxicity is a key mechanistic link between inflammation and neurodegeneration, in depression.

5.7 Gut Brain Axis and Interleukins

5.7.1 Role of Gut Microbiota

The intestinal microbiota is a critical player in the control of immune and inflammatory responses. Imbalance in gut bacteria, called dysbiosis, leads to greater illness that enable an activation of the immune system and subsequently promote interleukin production.

5.7.2 Interaction Between Immune and Neural Systems

Interleukins produced as a result of gut inflammation can influence brain function through circulation in the bloodstream and penetration of the blood brain barrier. This interaction

contributes to neuroinflammation and the manifestation of depressive symptoms (Cryan & Dinan, 2012).

5.8 Integrated Model of Interleukin-Mediated Depression

The mechanisms described above are highly interconnected and form a complex network: Interleukins alter neurotransmitter systems. They activate the HPA axis and disrupt stress regulation. They impair neurogenesis and synaptic plasticity. They promote oxidative stress and neurotoxicity. They interact with the gut brain axis. Together, these processes cause neural dysfunction, ultimately leading to depressive symptoms.

Chapter 6

Biomarker Insights Of Interleukins In Major Depressive Disorder

6.1 Introduction

The discovery of objective biomarkers for the diagnosis of MDD has emerged as a foremost priority in psychiatric research. The heterogeneity of MDD, and the lack of objective diagnostic tests, has resulted in a clinical diagnosis based largely on clinical assessment and consensus-based subjective reporting of symptoms.

Their role as major inflammatory mediators renders interleukins as highly evaluated biomarker candidates in MDD. Abnormal profile of interleukins among patients with depression, indicating a possible clinical utility. In this chapter, we discuss the potential role of interleukins as diagnostic, prognostic and predictive biomarkers in people with MDD.

6.2 Concept of Biomarkers in Psychiatry

6.2.1 Definition of Biomarkers

A biomarker is defined as a measurable and quantifiable indicator of a biological state, progression of disease, or response to therapeutic intervention. Biomarkers in psychiatry can be derived from the following sources: blood (e.g., cytokines, hormones), cerebrospinal fluid (CSF), imaging techniques, genetic and epigenetic markers. An ideal biomarker for major depressive disorder (MDD) would have high sensitivity, specificity, measurability, and generalizability to different populations; clinical applicability would also be important. However, due to the complex nature of psychiatric disorders, a single marker is unlikely to do the job; panels comprising multiple biomarkers may instead need to form risk assessment signatures (Strimbu & Tavel 2010).

6.3 Interleukins as Diagnostic Biomarkers

6.3.1 Elevated Pro inflammatory Interleukins

Individuals with MDD have significantly higher circulating levels of IL-6 compared to healthy controls. Elevated IL-6 levels are associated with both acute and chronic depressive states (Haapakoski et al., 2015). Similarly, IL-1β has been linked to symptom severity and cognitive dysfunction, while IL-18 is associated with stress-related immune activation.

6.3.2 Reduced Anti-Inflammatory Interleukins

Conversely, IL-10 tends to be lower in individuals suffering from depression. This discrepancy between interleukins leads to a chronic inflammatory condition. The proportion of IL-6 to IL-10 has been suggested as a possible diagnostic indicator of a person's overall inflammatory condition.

6.3.3 Peripheral vs Central Measurements

Interleukin levels can be measured in peripheral blood or cerebrospinal fluid. While peripheral measurements are more practical, they may not fully reflect central nervous system activity. However, evidence suggests that peripheral cytokine levels correlate with central inflammation, supporting their use as accessible biomarkers (Dowlati et al., 2010).

6.4 Interleukins as Prognostic Biomarkers

6.4.1 Predicting Disease Onset

Interleukins can predict the future development of depression. For example: Individuals with high baseline IL-6 levels are at increased risk of developing MDD. Chronic inflammation may precede the onset of depressive symptoms. This suggests that interleukins may serve as early warning indicators for individuals at risk (Valkanova et al., 2013).

6.4.2 Association with Disease Severity

High levels of pro-inflammatory interleukins are associated with more severe depressive symptoms, including greater emotional distress, increased fatigue and cognitive impairment IL-6, in particular, has been shown to correlate strongly.

6.4.3 Risk of Recurrence

Recurrent episodes of major depression are associated with persistent inflammation. Increased interleukins reflect a condition of chronic inflammation which probably makes patients more vulnerable to relapse. Interleukines

6.5 Interleukins as Predictive Biomarkers for Treatment Response

6.5.1 Antidepressant Response

Blood levels of interleukin may help infer the antidepressant treatment response. We know that individuals with lower baseline inflammation respond better to conventional

antidepressants, studies show this. Treatment resistance is associated with increased levels of IL-6 and IL-1β. It suggests that they may disrupt the antidepressive activity (Uher et al., 2014).

6.5.2 Personalized Treatment Approaches

The identification of inflammatory subtypes of depression has led the field toward the concept of precision psychiatry, where treatment is determined on an individual basis to fit biological characteristics. Analysis of cytokine profiles could be used to direct drug choice.

6.5.3 Monitoring Treatment Progress

Symptom relief is often accompanied by a decrease in pro-inflammatory cytokines. In this sense, interleukins are useful not only for prediction but also for monitoring treatment results.

6.6 C-Reactive Protein (CRP) and Its Relationship with Interleukins

CRP (C-reactive protein), although not an interleukin, is closely associated with interleukin properties like IL-6 to induce liver CRP synthesis. CRP is commonly used as a clinical marker of inflammation. Effects of ineffective treatment With respect to interleukins (Miller et al., 2009), CRP is of interest, with a chronic nature and an easily measurable blood parameter. Symptomatic severity increased.

6.7 Challenges and Limitations

There are promising results; however, there are some challenges for clinical application of ILs as biomarkers.

6.7.1 Lack of Specificity

Inflammation in depression Inflammatory markers are certainly not specific to depression either as they are elevated during infections and other autoimmune diseases.

6.7.2 Variability

The interleukins can be influenced by the primary aspects like age, gender, lifestyle (dietary habits, physical activity level), and coexisting health problems.

6.7.3 Methodological Differences

These methods lead to inconsistent results between different studies.

6.7.4 Need for Multi-marker Approaches

It is highly improbable that one biomarker alone can describe the complexity of MDD. Combining interleukins with other biological and clinical markers may improve a diagnoses accuracy.

6.8 Future Perspectives

Future directions for study include the development of standardized measurement methods, definition of biomarker sets, integration of biomarkers with clinical and genetic information, creation of affordable diagnostic devices, technological progress, such as artificial intelligence and systems biology, could improve the clinical application of interleukins.

Chapter 7

Therapeutic Implications Of Interleukins In Major Depressive Disorder

7.1 Introduction

The role of inflammation as an important player in the development of Major Depressive Disorder (MDD) opens up a whole new avenue for therapy. Conventional drug therapy for MDD mainly focuses on monoamines; but unfortunately, the majority of patients do not respond favorably to such therapies.

Interleukin's role in the pathology of MDD implies that new approaches may be considered based on inflammation. In this chapter the therapeutic potential of interleukin modulation (i.e., anti-inflammatory agent, cytokine inhibitors and novel personalized methods in depression models as well), will be discussed.

7.2 Limitations of Conventional Antidepressant Therapies

Antidepressant medications come with a significant downside: only 60-70% of patients are adequately controlled on therapy. It takes an average of 2-6 weeks for the effects of these medications to take place. Adverse effects may negatively impact on patients' compliance with the therapeutic regimen. They may be less valuable for inflammatory driven depression. This has underlined the urgent demand for additional approaches that do not just correct neurotransmitter imbalances or offset psychopathology, but alleviate the underlying biological processes driving these problems (Rush et al., 2006).

7.3 Anti-Inflammatory Agents in Depression Treatment

7.3.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Aspirin, celecoxib and other non-steroidal anti-inflammatory drugs (NSAIDs) were the first explored as potential adjuncts to antidepressants based on their COX inhibition and anti-inflammatory action. The adjunctive use of NSAIDs might improve antidepressant effects in clinical studies. COX-2 inhibitors such as Celecoxib have been found to exhibit promising effects on depressive symptoms. However, there are risks associated with long-term NSAIDs use including gastrointestinal and cardiovascular (Köhler et al., 2014).

7.3.2 Cytokine Inhibitors

There are more targeted treatments for cytokines; this can be either a single or family of pro-inflammatory, in particular interleukins that directly target the depression related to inflammation. Such as anti-IL-6 therapies that could alleviate depressive symptoms in patients with increased inflammation. Moreover it reduces neuroinflammation. These agents, though developed for autoimmune diseases, have been shown to also improve mood (Raison et al., 2013).

7.3.3 Minocycline

Minocycline is an anti-inflammatory antibiotic that has been investigated as a treatment in depression. Clinical trials have demonstrated that it reduces neuroinflammation and improves treatment response in combination with antidepressants.

7.4 Immunomodulatory and Biological Therapies

7.4.1 Monoclonal Antibodies

Monoclonal antibodies targeting cytokines are increasingly being explored for their therapeutic potential in psychiatric disorders. For example chronic inflammatory diseases. Anti-IL-6 antibodies may help reduce inflammation-driven depressive symptoms. These therapies offer a targeted approach but are currently limited by high cost and potential side effects.

7.4.2 Interferon-Induced Depression as a Model

Interferon-alpha is used to treat specific viral infections and cancers. It causes depressive symptoms in certain patients. Apart from these antidepressants may also treat or prevent interferon induced depression (Dantzer et al., 2008).

7.5 Role of Lifestyle and Non-Pharmacological Interventions

7.5.1 Exercise

Doing regular exercise to help in reducing inflammation. As a result of exercise: Increased emotion-positive effects Neuroplasticity and conversion of new neurons Decreased systemic inflammation A properly-balanced weight-reduction plan can have an effect on how much irritation takes place. Emerging research says that diets high in Omega-3 fatty acids Whole grains are related to lower inflammatory markers as well decreased likelihood of depression.

Interventions such as cognitive behavioral therapy (CBT) can affect inflammation pathways indirectly through stress reduction and improved coping mechanisms.

7.6 Personalized Medicine and Precision Psychiatry

7.6.1 Inflammatory Subtypes of Depression

It has been found that MDD does not have just one form but consists of multiple types, some of which include an inflammatory subtype characterized by higher cytokine concentrations. These multiple types allow for: Targeted treatments Improved outcomes Reduced guessing when prescribing

7.6.2 Therapy Informed by Biomarkers

High levels of Interleukin can be very useful in determining the course of treatment for an individual. For example, people with high IL-6 should be given treatment focused on decreasing their inflammation. On the other hand, individuals with low inflammation would probably react positively to conventional anti-depressants. This approach marks the shift towards personalized medicine in psychiatry (Miller et al., 2009).

7.7 Future Therapeutic Directions

Possible future areas for investigation may include selective cytokine blockers. A combination of treatments for neurotransmitter dysfunction and inflammation is being applied. Biological drugs may be introduced in patients with resistant depression with the application of artificial intelligence in treatment selection. The study of the signaling mechanism of interleukins will cause less adverse reactions.

7.8 Challenges and Considerations

Several developments need to be performed in recent times. Like the high cost of biological therapies is concerning. There are several risks of immunosuppression and limited long-term safety data.

Chapter 8

Discussion

8.1 Introduction

MDD can be considered a multifactorial disease and, as such, its patho-physiology is highly complex and heterogeneous. As far as the literature has traditionally concentrated on the mysterious condition of neurotrans-mitter imbalance, recent years have seen a much wider approach with new insights being added about neuroendocrine, immune, and neuroplasticity systems. It appears that, in particular, interest in inter-leukins and disturbances in immune response have grown considerably among others.

The role of interleukins in MDD has been considered in our thesis from biological properties to possible treatments. This chapter will sum up relevant and additional findings as well as provide their interpre-tation.

8.2 Integration of Findings Across Chapters

8.2.1 Interleukins as Central Mediators

The thesis was based on the assumption that interleukins are one of the components involved in the mechanisms of MDD. These results support previous ones and the immunological signature of MDD is represented by an increase in proinflammatory cytokines as well as a decrease in anti-inflammatory cytokines, such as IL-10. This discrepancy may be regarded as an inflammatory disorder.

It has been reported that it contributes to the development of changes in the nervous system underlying depressive manifestations and is not a result of depression (Miller et al., 2009).

8.2.2 Interconnection of Biological Systems

The current study demonstrates one of the critical concepts about the biological processes associated with MDD; namely, their interrelatedness. For instance, interleukins link with immune response activation, neurotransmitter imbalance, HPA axis dysfunction, neuroplasticity impairment.Activation of the kynurenine pathway together with the HPA axis

dysfunction leads to a reduction in BDNF. These processes demonstrate the complexity of MDD and cannot be explained using reductionist approaches.

8.3 Interleukins and the Inflammatory Subtype of Depression

8.3.1 Evidence for an Inflammatory Subtype

In fact, there is a biological sub-type distinguished by inflammation. This group tends to be associated with high levels of interleukin 6 and interleukin 1beta along with high symptom severity.

This idea of having an inflammatory sub-type of depression is essential for further understanding of this condition since it indicates that there may not be one mechanism for developing depression.

8.3.2 Clinical Implications

The presence of an inflammatory subtype implies the necessity of individualized treatment regimens. Individuals showing higher IL levels may be more responsive to anti-inflammatory treatments or immunotherapy, whereas patients not experiencing inflammation may exhibit improved response to conventional antidepressants.

Nonetheless, additional studies are required to validate criteria for defining such a subtype in a medical setting.

8.4 Interleukins as Biomarkers: Strengths and Limitations

8.4.1 Strengths

There is evidence that the use of interleukins in diagnosing MDD may be justified because of the following facts: The regular increase of IL-6 and IL-1β can be seen in patients suffering from depression. The ability of interleukins to predict the development of the disorder in prospective studies may also be mentioned.

8.4.2 Limitations

Even though these markers have some value, there are certain limitations that need to be kept in mind: Non-Specificity of Interleukins Interleukins are not specific to depression and may be elevated in other diseases as well (for example, infections, autoimmune disorders, metabolic diseases). Individual Biological Differences The levels of cytokines vary widely between individuals, based on factors such as age, gender, the time of day, and individual

lifestyles – factors that can influence the utility of these markers as biological indicators. Differences in approaches used in various research methodologies using different research designs can explain the differences in results between them.

8.4.3 Need for Multi-Biomarker Approaches

Given all these constraints, the likelihood of one interleukin alone being a definitive biomarker for MDD appears highly unlikely. A combination of several biomarkers such as cytokines, neuroendocrine indicators, and even genetics may serve the purpose better.

8.5 Mechanistic Insights and Their Implications

8.5.1 Neurotransmitter Alterations

The association between interleukins and neurotransmitter systems plays an essential role in explaining the nature of depression. Interleukins activate the production of toxins that damage neurons and decrease the amount of serotonin. This finding contradicts the traditional theory of depression because it indicates that the alteration in neurotransmitters could be a consequence of the immune system's activation rather than the cause of depression.

8.5.2 Dysregulation of the HPA Axis

Interleukins being involved in the activation of the HPA axis provides further explanation on how it works. Chronic inflammation causes increased secretion of cortisol, leading to glucocorticoid resistance, thus affecting the stress mechanism. This explains why people suffering from stress are at higher risk of developing depression.

8.5.3 Neuroplasticity and Structural Brain Changes

The reduction of BDNF levels and neurogenesis due to increased interleukin levels cause changes in the brain structure, particularly in the hippocampus and prefrontal cortex. Such changes are associated with impaired cognition, mood swings, and greater vulnerability to stress, highlighting the importance of inflammation in the prolonged course of the disease.

8.6 Therapeutic Considerations and Future Research Directions

8.6.1 Treatments Targeting Inflammation

The discovery that interleukins play an important role in MDD can thus serve as a good reason to use anti-inflammatory medications. The clinical trials using anti-inflammatory drugs or cytokine inhibitors, including NSAIDs and minocycline; clinical antidepressant have demonstrated a reduction in depression levels, particularly in cases where there is high inflammation. However, due to adverse effects and individual differences, these drugs have to be used carefully.

8.6.2 Precision Psychiatry

Use of biomarker information in treatment decisions would constitute a huge leap forward for the development of precision psychiatry. If biological techniques allow for the identification of particular subgroups of depression patients, doctors ought to be able to personalize treatment approaches for each individual case to achieve greater efficacy while minimizing any unnecessary side effects from ineffective treatment. Interleukins would definitely have a prominent part in this progression towards their increased usefulness in medical practice. Possible areas for future research include: Cytokine inhibitors Specific pathways in signaling, like JAK-STAT, combination therapy to address both inflammation and neurotransmitter disorders.

8.7 Challenges in Translating Research into Clinical Practice

Although there have been many advancements in this regard, a number of obstacles still need to be addressed before the results of research can be applied clinically. Unavailability of standard methods for the determination of cytokines and expensive treatment options such as biological drugs. Issues of ethics involving immune modulations and clinical trials on a large scale.

8.8 Strengths and Limitations of the Review

8.8.1 Strengths

- Full combination of views on immunological and psychological aspects
- Use of different interleukins and their methods of action
- Attention to biological and clinical consequences.

8.8.2 Limitations

- Use of previously published data that is prone to bias
- Lack of long-term and large-scale studies

- Different study samples and techniques used

8.9 Overall Interpretation

The results of the current study indicate that the conceptualization of Major Depressive Disorder needs to undergo a paradigm shift. Major depressive disorder is seen as an illness that entails systemic inflammation and dysfunctional immunity. The central importance of interleukins in the mechanism of this condition is due to their action on different systems in the body, such as neurotransmission, hormonal regulation, and neuroplasticity.

8.10 Conclusion of Discussion

In conclusion, despite the difficulties in using interleukins in the study of MDD, it is crucial for further development of depression treatment to implement the discoveries from the field of immunology into psychiatric science in order to change the way we diagnose and treat depression.

Chapter 9

Conclusion

9.1 Summary of Key Findings

MDD (Major Depressive Disorder) is a multi-component psychiatric condition characterized by genetic, neurochemical, environmental and immunological features. This thesis has mainly focused on interleukins as one of the important immunological aspects of MDD pathophysiology, diagnostics and treatment. The literature review indicates that increased production of pro-inflammatory cytokines (interleukins and inflammation) together with decreased anti-inflammatory cytokines, for example, IL-10, suggests upregulated immunity as one of the main factors in the development of depression. Cytokines affect neurotransmitter activity and neuroplasticity, and, hence, affect depressive symptoms. Mechanisms involving Interleukins play the following roles in MDD: Activation of kynurenine pathway leading to decreased serotonin level. Increased secretion of glucocorticoids caused by activation of the HPA axis, deficiency of neurogenesis and neuroplasticity, especially in the hippocampus and prefrontal cortex. These pathophysiological mechanisms help explain different clinical manifestations of MDD. Potential biomarkers like interleukins are promising as biomarkers of MDD. In MDD patients, IL-6 and IL-1β concentration levels are increased; besides, measuring IL-6 and IL-1β concentrations in peripheral blood helps to diagnose and predict the course of MDD and treatment-resistant forms. The application of the approach is limited because of variations and lack of specific measurements.

Implications in Therapy Treatment strategies that take into account inflammatory signaling offer an innovative way of managing depression. Inflammatory blockers like NSAIDs and minocycline can enhance depressive conditions, especially in those individuals who carry substantial inflammatory loads. Monoclonal antibodies against cytokines can facilitate very precise approaches. Additionally, lifestyle modification and psychological treatments can have secondary effects on inflammation. The idea of inflammatory mechanisms underlying depression emphasizes the importance of using precision strategies in treating the disease

Biomarker guided therapy (profile of interleukins, for instance) can raise the efficacy rates while reducing exposure to unsuccessful therapy methods.

9.2 Significance of the Study

In other words, this thesis sheds light on an emerging trend in the connection between immunological issues and depression with particular attention paid to the vital role of interleukins in this connection. In summary, there are several main controversies that emerged in relation to this thesis: Merging fields of immunology and psychiatry. The article demonstrates how knowledge gained in these fields can be integrated into research on MDD as well as in relation to diagnostics and treatment of this condition. It should be noted that even though there are no currently available diagnostic methods and treatments based on target interleukins yet, the results are encouraging enough to develop them for inflammatory depression and even resistant depression. This thesis found knowledge gaps and argued why certain steps should be made for further research, specifically, standardization of biomarker tests.

9.3 Limitations

Despite its contributions, this research suffers from certain weaknesses including: Dependence On Past Literature As a review thesis, it depends on past literature, which varies in design and target subjects. The results obtained from these studies can be affected due to variation among studies1: the variations include the technique used to determine the interleukin, samples used either serum or cerebrospinal fluid, and subjects included. Despite the known effect of interleukin, not much has been achieved in translating this knowledge into standardized applications in diagnoses or treatments. Lack of Focus Although this thesis concentrates only on the interleukin, other immune mediators like the TNF-α have not been considered.

9.4 Future Directions

Future directions that researchers may explore in this context are: Longitudinal Studies The performance of prospective cohort studies to study cause-effect relationships between cytokine levels and the occurrence of depression and its severity and recurrence. Standardizing the methodology used for measuring cytokines, keeping into account factors like the influence of the circadian cycle, age, gender, and comorbidity. Therapies Conducting trials of cytokine inhibitors as potential depression treatments in patients with an

inflammatory subtype. Combinations between the interleukins and other biomarkers to help diagnose depression and predict response to therapy. Incorporation of AI-based analytical methods in the analysis of high-dimensional data sets with complex phenotypes to devise personalized depression treatment plans.

9.5 Concluding Remarks

Interleukins have proved to be essential players in the pathophysiology of MDD. It means a lot of progress in understanding mechanisms underlying this condition. It appears that it was not simply an indication of inflammation, but rather a part of mechanisms involved in it. Thus, it allows us to present a holistic picture of the variety of depressive symptoms through the effects on neurotransmission, endocrine system and neuroplasticity. Although implementation of such knowledge in everyday practice requires certain efforts, it holds great promise regarding biomarkers and drug targets in depression treatment. With the help of the immunological background of the disease, this thesis strives for a holistic approach to MDD and for a shift towards personalized therapy. Finally, the results demonstrate that depression is far from being merely a psychological problem, but also an immunological disorder. Therefore, the novel approach based on interleukins as targets for treatment of MDD non-responders is proposed.

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