Literature Review

Inflammation in Depression

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Abstract

There is growing evidence of a relationship between inflammation and psychiatric illness. Increased inflammation has been observed in a significant subgroup of patients with mood disorders. The inflammatory hypothesis is one of the most prevalent topics concerning depression. To understand the bidirectional relationship between inflammation and depression, which one process can drive the other and ultimately production of more effective depression treatments. We reviewed several studies from the international database Pubmed Central, textbook, review paper, comment, and editorial, to evaluate contemporary concepts concerning inflammation and their relationship to various depressive disorders. Pro-inflammatory cytokines have been found to influence the progression and severity of depressive disorders in different populations. Anti-inflammatory treatment of depression may have adjuvant properties with current depression medications. There is significant evidence that inflammatory processes influence the development and progression of depression. Future studies with larger arrays of cytokine profiles aided by neuroimaging may provide more sensitive and specific diagnostics modes in determining depression aetiology and guide individual therapies.
Introduction

Depression is a severe disease and will burden the world’s top health global problems in the next 2030. Depression is estimated to affect nearly 350 million people worldwide. Based on the Indonesia Basic Health Research in 2018, the prevalence of mental-emotional disorders in Indonesia reached 6.1%.[1,2] Depression often occurs alongside chronic medical diseases related to inflammatory processes such as cancer, diabetes mellitus, stroke, brain tumours, and coronary heart disease.[3] Depression worsens prognosis, decreases life quality, shortens life expectancy, especially in illnesses that cause pain, disability, or social isolation, which leads to fatigue, self-doubt, and hopelessness.[2,4,5] The disorder is chronic progressive, has a high relapse rate and a low remission rate. Therefore, a new approach is needed to treat depression.[6,7]

The neurobiological approach concludes that depression is associated with brain neurotransmitter deficiencies, namely serotonin (5-HT), norepinephrine (NE), and dopamine (DA).[6,8,9] Some results show a correlation between inflammatory processes and depression. Specific inflammatory mediators are thought to play a significant role in influencing behaviour, symptoms, and circuit changes in the brain of people with depression. It is actively supported by some findings that stated that the third of people with depression showed an increase in inflammatory mediators even without medical illness.[10,11] People with depression showed higher levels of inflammatory mediators. However, there are limited reviews on how inflammatory mechanisms can cause depression, how depression cause inflammation, or even simultaneously. This review is created to provide an overview of the reciprocal mechanisms between depression and inflammation comprehensively.[2,12]

Stress and Inflammation

Psychosocial stress leads to an increase of hypothalamic pituitary adrenal (HPA) axis activity. Its characterized by an increase in corticotropin-releasing hormone (CRH) in cerebrospinal fluid (CSS). CRH increases episodes of adrenocorticotropic hormone secretion (ACTH) hypersecretion, increasing cortisol (hypercortisolemia) release. Cortisol is useful to maintain life to regulate sleep, appetite, kidney function, and immune system. Elevated cortisol levels should stimulate a negative feedback mechanism like the hypothalamus suppresses CRH secretion. It then sends a message to the pituitary to lower ACTH production and is passed back to the adrenals to reduce cortisol production. In chronic stressful conditions, the autoregulation system or negative feedback function does not work. HPA axis hyperactivity causes depression during psychosocial stress and has a greater risk of self-harm, ideas, or suicidal behaviour.[12] The largest expression of glucocorticoid receptors in the brain is in the hippocampus (HC). The prefrontal cortex makes this area highly sensitive to stress-trigger stimuli leading to indirect microglia effects in this region.[16,17]

Stressful life experiences in childhood are associated with an increase in pro-inflammatory cytokines associated with a high risk of mental illness in adulthood (two-hit hypothesis). The hypothesis states that early stress in life makes microglial cells priming in the central nervous system (CNS) generates an excessive increase in microglia activity that impact onto adulthood stress. This cause brain changes and become the development basis of mental disorders in the future. Microglia are myeloid cells as the primary form of the immune response in the CNS. These cells modulate neural function during inflammatory responses and brain plasticity in order to quickly respond small changes in the brain.[18,19] In a healthy environment, most microglia morphology have long and thin branches, allowing microglia to look for harmful agents (resting morphology). When a stressor detected, these cells turn into enlarged soma, fewer branches and processes (amoeboid morphology).[17]

Depression and Inflammation

Some studies suggest a link between pro-inflammatory cytokines and depressive symptoms through the immune-to-brain communication pathway. Pro-inflammatory peripheral cytokines can affect the brain’s immune system, HPA axis, and neurotransmitters synthesis, thereby triggering behaviour changes resembling depression.[18] Some data indicate that a person experiencing depression also experiences inflammation characterized by increased C-reactive protein levels (CRP) > 3 mg / L compared to non-inflammatory individuals with CRP levels of < 1 mg / L. This increase is associated with anhedonia and psychomotor retardation.[10,22]

Systemic inflammation induced by cytokines can modulate behavioural changes such as sleep disorders, anorexia, weight loss, fatigue, cognitive impairment, and psychomotor deceleration. This syndrome is referred as sickness syndrome with an image that resembles depression-like behaviour. Psychomotor symptoms were significantly more predominant in
Infection and tissue damage can increase the production of pro-inflammatory cytokines such as IL-6 by microglia and endothelial cells in the brain. A research showed that the activation of cell-mediated inflammation (CMI) by platelet-activating factors (PAF) has a role in depressive symptoms. Depressed patients significantly show higher levels of mitochondrial oxidative damage than people who do not experience mental disorders. Mitochondrial dysfunction results in cells not functioning properly. This phenomenon can occur due to decreased activity of mitochondrial enzymes, increased reactive oxygen species (ROS), decreased expression of mitochondrial deoxyribonucleic acid genes (mtDNA) that encode transcription, dysregulated signal calcium that decreases the production of adenosine triphosphate (ATP). Infection and tissue damage can increase the production of cytokines both in CNS and in peripherals. Cytokine has a large enough molecular size and is hydrophilic. Thus, it is difficult to penetrate the blood-brain barrier (BBB) under normal conditions. BBB is composed of microvascular endothelial cells surrounded by a primary membrane consisting of pericytes and astrocytes. Peripheral cytokines can be connected to the cerebrum through brain immune communication pathways through sensory fibres stimulation of vagus nerves. Besides, central and peripheral inflammatory communication occurs due to the absence of passive diffusion in some BBB regions and active transport of cytokine through activation of the central noradrenergic system. Peripheral cytokines can also activate neural afferents that stimulate the production of interleukin-6 (IL-6) by microglia and endothelial cells in the brain. A research data showed that pro-inflammatory cytokines such as TNFα, IL-1β, IL-6, interferon (IFN)-γ have a role in depressive pathophysiology. The presence of pro-inflammatory cytokines, including IFNs, IL-1β, TNF, are associated with depression. A research data showed that the activation of cell-mediated inflammation (CMI) and brain pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and plasma CRP proteins in inflammatory pathways affected by platelet-activating factors (PAF) has a role in depressive pathophysiology. Pro-inflammatory cytokines decrease the synthesis of monoamine neurotransmitters 5HT, DA and NE. These cytokines increase the expression and function of presynaptic reuptake pumps (transporters) by lowering extracellular levels. It is done by activating mitogen-activated protein kinase (MAPK) pathways and lowering enzymatic co-factors such as tetrahydrobiopterin (BH4). Activation of microglia and infiltration of monocyte and macrophage in the brain activates Indoleamine 2,3 Dioxygenase (IDO) enzymes. The enzyme that increases the metabolism of tryptophan (TRP), a precursor to the primary amino acid 5-HT, converted into a kynurenine metabolite, thus lowering levels of 5-HT and causing depression symptoms. Activated microglia then convert kynurenine metabolites into neurotoxic serotoninergic metabolites called quinolinic acid (QUIN). Moreover, increased QUIN levels are found in microglia, specifically in the anterior cingulate cortex (ACC) area in depressed patients who committed suicide. Pro-inflammatory cytokines also affect the neurotransmitters' levels which influence motivation, reward, and anhedonia in corticostriatal circuits in basal ganglia, ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC). It also affects symptoms of anxiety, arousal, and fear in the amygdala, hippocampus (HC), dACC, and insula areas. Indirect measurement of BH4 activity through phenylalanine to tyrosine ratio is associated with DA concentration in CSS, affecting depressive symptoms.

Mechanism of Neuroendocrine
Pro-inflammatory cytokines inflect the glucocorticoid insensitivity which resulting in HPA axis hyperactivity. Pro-inflammatory cytokines IL-1, IL-6, TNF-α IFN-α increase the inflammatory response that affects the function of glucocorticoid receptors (GRs) and induce gene expression and CRF. It stimulates ACTH and increases glucocorticoid secretion. HPA axis hyperactivity stimulates the cytokine production again. There is a complex positive feedback loop where psychosocial stress increases cytokine levels and induces HPA axis and glucocorticoid resistance characterized by increased cortisol levels and positive dexamethasone suppression test (DST). HPA axis hyperactivity produces catecholamine NE and increases the production of pro-inflammatory cytokines. Hypercortisolemia stops cell cycles, especially in HC. Dendrite retraction decreased neurogenesis in the dentate gyrus, and breakdown of microglia cells can occur, especially in HC areas. As a result, HC cells die, reducing HC volume that plays a role in memory, learning, attention, and emotional function. Memory impairment is found when the patient suffers from depression but can persist until the patient recovers.

Mechanism of Oxidative Stress
Pro-inflammatory cytokines decrease the levels of BH4, an enzyme co-factor for the synthesis of monoamine neurotransmitters.
Neurotransmitters. Nitric oxide synthase (NOS) can induce oxidative stress and produce nitric oxide (NO). Pro-inflammatory cytokines increase oxidative stress in HC. Astrocytes also experience function changes in depression. Pro-inflammatory cytokine stimulates the IDO enzyme and triggers the release of neurotoxic metabolites, including 3-hydroxykynurenine, kynurenine acid, or QUIN. It causes oxidative stress that contributes to depression symptoms. The release of glutamate induces reactive oxygen species (ROS) and reactive nitrogen species (RNS). The O&NS pathway results from cytotoxic action imbalances of ROS and RNS that can interfere with cellular signaling and cause cell damage. Dysregulation of O&S pathways also contributes to the depression onset. Antioxidants, both exogenous and endogenous, can counteract the effects of ROS/RNS-induced toxicity. In depression, there is an increase in levels of oxidative stress markers in DNA damage and a decrease in serum levels of total antioxidant capacity. The administration of antidepressants is thought to help restore the stability of pro-oxidant and antioxidants. [2,25]

Mechanism of Neuroplasticity
Neuroplasticity is the brain and nervous system’s ability to reorganize itself both structurally and functionally as a result of environmental input. [13] The CNS consists of two main cell types: neurons and glial cells. Glial cells include microglia and astrocytes. Microglia are the primary producers of immune cells in the brain, and their activation is an early marker of the brain environmental changes through the mechanism of astrogliosis. Astrocytes and microglia are components of natural immunity that contribute in the pathophysiology of depression. Examining depressed patients using positron emission tomography (PET) in the prefrontal cortex, anterior cingulate cortex, and insulae indicates increased microglial activity and inflammation in the brain. [10] Microglia and astrocytes are activated by peripheral inflammation through immune brain communication through IDO enzymes that convert TRP metabolism to kynurenic acid, picolinic acid, and quinolinic acid (QUIN), all of which are important N-methyl-D-aspartate (NMDAR) receptor agonists. Induces the release of glutamate and inhibits glutamate reuptake by astrocytes resulting in excessive glutamate leading to depression. Activated microglia convert kynurenine to QUIN, which binds to NMDAR and reduces the number of astrocytes. Excessive glutamate then triggers a decrease in brain-derived neurotrophic factor (BDNF) levels and triggers excitotoxicity, especially in HC's gyrus dentata area. It will affect neuronal integrity, including neurogenesis, long-term potentiation, and dendritic sprouting, which significantly impacting learning and memory functions. Pro-inflammatory cytokines have an effect on cognitive function and emotions that result in cognitive dysfunction in depression. Factors that take place in nerve cell growth are neurotrophins, brain-derived neurotrophic factors (BDNF), nerve growth factors (NGF) which have a major role in the differentiation and growth of brain neurons in various form. BDNF take an essential role in neurogenesis, neuron plasticity, and synapse growth. In the developed brain (adults), it functions as a survival factor for microglia in protecting against damage. Repeated stressors cause a decrease in BDNF expression, resulting in neuronal cell death, especially in the HC region. [23]

Depression Treatment

The Role of Antidepressants Against Inflammation
Most depressed patients require antidepressant medications (70-80% of patients respond to antidepressant treatment). Monoamine neurotransmitters (5-HT, NE, and DA) are targets of antidepressant drugs. The selection of antidepressants can including increased IL-1, CRP, and monocyte chemoattractant protein-1. The researchers also found that depressed patients have significantly higher levels of TNF-α than normal populations. Systematic review and meta-analysis reported that the concentration levels of CRP and IL-6 are associated with the appearance of depressive symptoms. [3] Experimental studies using infliximab (TNF-α antagonist) plus antidepressants compared to placebo with antidepressants showed that at CRP, plasma concentration levels of more than five mg/L turned out to show an anti-inflammatory effects as well as improvements in sickness symptoms and core depression. In contrast, CRP plasma concentration levels less than five mg/L, placebo and antidepressant groups have better effects in lowering depressive symptoms. [24]

A research of NSAIDs consisting of COX-2 and non-selective COX inhibitors are widely conducted to observe the effects of antidepressants on the drugs. The results vary widely. Some studies have antidepressant effects on anti-inflammatory drugs, but others do not have any effect. The difference in these results is influenced by factors including the type and dosage of antidepressants used, the type of anti-inflammatory (either selective COX-2 inhibitors or non-selective COX inhibitor NSAIDs), the study design, the age of the respondent, the degree weight of the depressive symptoms, and the absence of comorbidities. Non-steroidal anti-inflammatory drugs (NSAIDs)
have antidepressant effects in the brain through their ability to lower the pro-inflammatory cytokine mediator both centrally and peripherally. COX-1 plays a predominant role in the activation of microglia as a pro-inflammatory cytokine in the brain. While celecoxib, a selective COX-2 NSAIDs inhibitor, has a therapeutic effect when used in addition to antidepressant therapy. Selective COX-2 inhibitors of NSAIDs significantly decrease IL-6 levels and Hamilton Rating Scale for Depression (HAM-D) scores, especially when administered together with antidepressants of the SSRI (sertraline) group. Some anti-inflammatory drugs such as NSAIDs, omega-3 fatty acids, and cytokine antagonists are thought to have antidepressant effects. Therefore, they can be considered for depression treatment. However, some studies mentioned the risk of threatening side effects due to anti-inflammatory administration in people with depression. Experimental study of aspirin (non-selective COX inhibitor NSAIDs) 160 mg/day combined with citalopram (antidepressant group SSRI) 20mg/day obtained a results 8 out of 10 people showed anxiety and akathisia, three patients due to anxiety and anxiety, two patients have had suicide attempts, this combination is considered unsafe by researchers rate. The combination of sertraline (antidepressant SSRI group) 200 mg/day and celecoxib (selective COX-2 start from the SSRI group regarding to the very mild side effects and the safety limits are wide. There is evidence that serotonin plays a predominant role in regulating HPA axis activity. Antidepressant therapeutic activity is obtained due to its ability to inhibit the reuptake of monoamine neurotransmitters (5-HT, NE, and DA), thus normalizing the number of monoamine neurotransmitters available inside the brain. It will improve the HPA axis, prevent and repair neuron damage, stimulate neurogenesis through BDNF induction, improve dendrite retraction, which then initiates improvements in depressive symptoms and improved cognitive function. HPA axis improvement will decrease the production of pro-inflammatory cytokines. The administration of SSRI therapy is significantly able to decrease the pro-inflammatory cytokine levels, namely IL-1β, TNF-α, and IL-6, as well as anti-inflammatory cytokine IL-10. [18].

The Role of Psychotherapy Against Inflammation

Psychotherapy is indicated to provide warmth, empathy, understanding, and optimism. Patients are helped to perform catharsis, identify a "single cognitive triad" (a distorted perceptions include a person's negative interpretation of life experiences, self-devaluation, and cause of depression), identify precipitation factors, and directionally solve external problems. The result of a systematic review by Ping Zhang et al. in cancer patients stated that most of the cancer patients experienced psychological disorders such as chronic stress, anxiety, stress, depression, and social isolation. Cognitive Behaviour Therapy (CBT) is a form of psychotherapy that can be given to cancer patients with psychological disorders. It has been demonstrated that CBT makes cancer patients able to get through the stressful experience of being diagnosed with cancer. This therapy also transforms their point of view, from a threat to a challenge. CBT lowers stress and negative emotions and improves HPA axis balance, sympathetic nervous system, and immune system. CBT consistently increases the levels and activity of natural killer cells (NK cells), part of innate immunity, which is the first defence mechanism against tumour cells and infections. Usually, NK cells level in cancer patients is low, and increase when it is related to improve immune function, prevent tumor enhancement, and metastases. Furthermore, CBT also increases IL-2 and IFN-γ levels that induce NK cells to perform anti-tumor activities. IL-4 levels also increase, which serves to inhibit the growth of breast cancer. Improvement in IL 2, IL 4, and IFN-γ have positive effects on cancer patients' immune function and prognosis. [25]

Anti-Inflammatory Role For Depression

Clinical research has shown a link between the concentration of pro-inflammatory cytokines (specifically IL-1β, IL-6, and TNF-α) and CMI with depressive symptoms. Compared to normal populations, depressed patients showed an increase in inflammatory mediators concentration both peripherally and in CSS, inhibitor NSAIDs) 2 dd 200 mg for six weeks showed a more significant decrease in IL-6 and a decrease in HAM-D value than compared to placebo. The combination of celecoxib 400 mg/day and fluoxetine (antidepressant group SSRI) 40 mg/day in 6 weeks showed better results in treating depression than a single administration of fluoxetine.[2]

The differences in the study results, makes it hard to justify if the entire case of depression is considered as an inflammatory disease and should take an anti-inflammatory treatment. A wide range of research results suggests that only a certain subgroup of depressed sufferers received benefits of a decrease in depressive symptoms due to anti-inflammatory drugs. Inflammation is not the only cause of depression. [23]

Conclusion

Depression is associated with a deficiency of the brain neurotransmitter monoamine (5-HT, NE, DA) and HPA axis neuroendocrine function dysregulation. Some studies have shown a link between pro-inflammatory cytokines concentration
specifically IL-1β, IL-6, and TNF-α) and CMI with symptoms of depression through immune-to-brain communication pathways. Peripheral pro-inflammatory cytokine can affect the immune system in the brain, HPA axis, function, and synesthete neurotransmitters, thereby triggering behavioural changes of depression. There are four mechanisms to underlie inflammatory and depressive relationships; mechanisms of neurotransmission, neuroendocrine, neuroplasticity, and oxidative stress.[26]

Antidepressant therapeutic activity is able to inhibit the reuptake of monoamine neurotransmitters (5-HT, NE, and DA) into the presynaptic terminal nerve. Thus, normalizing the amount of monoamine neurotransmitter available inside the brain. It will improve HPA axis settings, prevent and repair neuron damage, stimulate neurogenesis through BDNF induction, improve dendrite retraction, then initiates improvements in symptoms of depression and improved the cognitive function. [3] The administration of antidepressant drug (SSRI) significantly decreases the pro-inflammatory cytokine levels of IL-1β, TNF-α, and IL-6, as well as the anti-inflammatory cytokine IL-10. Systematic review and meta-analysis results in cancer patients showed that CBT psychotherapy could lower stress levels and negative emotions, improved the HPA axis regulation, sympathetic nervous system, and immune system. Psychotherapy CBT consistently increases the levels and activity of NK cells, IL-2 IL 4, and IFN-γ which have a positive effect on immune function. [25]

Some anti-inflammatory drugs are thought to have antidepressant effects and considered for the depression treatment, although the risk of side effects has not been removed. Research on the anti-inflammatory drug NSAIDs consisting of COX-2 and non-selective COX inhibitors are widely conducted to observe the effects of antidepressants on these drugs. Only a certain subgroup of depression patient benefits a decrease in depressive symptoms with the addition of anti-inflammatory drugs. [27], [28].

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