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Depression: An Immuno-Inflammatory Cascade

Depresyon: Bir İmmüno-İnflamatuvar Döngü

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ABSTRACT

Major depressive disorder also known as clinical depression, unipolar depression or depression is associated with significant morbidity, mortality, high suicidal tendencies and deaths. Preclinical and clinical studies suggest that psychiatric illnesses like major depression are associated with inflammatory processes. While it is unlikely that major depression is a primary inflammatory disorder, there is now evidence to suggest that inflammation play a subtle role in the pathophysiology of major depression. The inflammation in depression cascade pin points to the origin from immune hyperactivity and thus a new theory that explains role of immune system mediated inflammation has been accepted and researched upon. widely. This theory states that depression is accompanied by altered immune function and activation of the inflammatory response system. This theory is strengthened form the fact that the current therapeutic options which mainly target neurotransmitters, are not effective in many patients and these patients has been found to be associated with elevated levels of inflammatory mediators specifically cytokines. It is reported more recently that other risk factors for depression, including psychosocial stress, psychological trauma, sleep disturbance and pain, also increases inflammatory processes. Thus the intervention in the immune system originated from inflammatory cytokines seems a therapeutically viable option in the field of depression research.

Key words : BDNF, cytokines, depression, inflammation, neurogenesis.

ÖZET

Klinik depresyon, unipolar depresyon veya depresyon olarakta bilinen major depresif bozukluk morbidite, mortalite, yüksek intihar eğilimi ve ölümle önemli ölçüde ilişkilidir. Preklinik ve klinik çalışmalar, major depresif bozukluk gibi psikiyatrik hastalıkların inflamasyon süreci ile ilişkili olduğunu

ifade etmektedir. Major depresif bozukluğun temelde bir inflamasyon hastalığı olması muhtemel olmamasına rağmen, inflamasyonun major depresif bozukluğun patofizyolojisinde az da olsa rol oynadığını ileri süren kanıtlar bulunmaktadır. Depresyon kaskatı dahilinde gelişen inflamasyon, immünitenin aşırı aktivitesinden orijinlendiğine işaret eder ve böylelikle immün sistem aracılı inflamasyonun rolünü açıklayan yeni bir teori kabul öngörülmüş olup araştırılmıştır. Bu teori depresyonun, değiştirilmiş immün fonksiyon ve inflamasyon cevap sistemi ile birlikte görüldüğünü belirtir. Bu teori temelde nörotransmitterleri hedefleyen mevcut terapotik seçeneklerin birçok hastada etkili olmadığı gerçeği ile güçlenmiştir ve bu hastalarda inflamasyon mediatörlerinin artan seviyeleri ile sitokinlerin spesifik olarak ilişkili olduğu bulunmuştur. Son zamanlarda psikososyal stres, psikolojik tramva, uyku bozukluğu ve ağrı gibi depresyonun diğer risk faktörlerinin de inflamasyon sürecini artırdığı bulunmuştur. Bu bağlamda inflamatuar sitokinlerden orijinlenen immün sistemdeki müdahalelerin depresyon araştırmaları alanında terapötik olarak uygulanabilecek bir seçenek olarak görülmektedir.
Anahtar kelimeler: BDNF, sitokinler, depresyon, inflamasyon, nörogenez.

Introduction

Current research mindset regards inflammation as the major cause of almost all pathologies and psychiatric illnesses are no exceptions. The present review aim to describe the role of inflammation in depression and how imbalanced immune status initiate this inflammatory cascade is deliberated.

Mood disorders account for a significant proportion of the global disease burden, surpassing that of cardiovascular and oncological pathologies[1]. Mood disorders are characterized by a pathological distortion of affect[2]. and behavior. They are the most common form of severe adult-onset psychiatric illnesses which will be the second most common cause of morbidity by 2020[3]. Mood disorders belong to two etiologically related[4] but uniquely treated psychiatric illnesses[5] major depressive disorder (MDD) and bipolar disorder (BPD). Although they both are clinically characterized by episodes of depression (e.g. lowered mood, loss of interest or pleasure, loss of energy etc.) yet BPD also have episodes of mania or hypomania (e.g. expanded self-esteem, increased distractibility, talkativeness) [6,7].

The people who sufferers from depression are at very high risk for suicide than the general population[8]. Yearly, almost a million lives are lost due to suicide, which translates to 3000 suicide deaths every day. 50-80% of older adults who die by suicide have been shown to have major depression as the underlying cause[9]. The percentage is projected to be higher among untreated patients. Depression has become a significant economic burden[10,11] associated with

substantial use of health care and management resources[3]. Depression is also a major cause of work absenteeism, loss of productivity, mortality and also may be a originative cause for anxiety and behavioral disorders as well as for substance abuse[12,13].

A persistent low mood, anhedonia, fatigue or low energy are the major features of depression and one of these core symptoms, or a combination, present on most days continuously for 2 weeks. Disturbed sleep with early morning wakening, loss of appetite, diurnal mood variation and reduced libido are the other biological symptoms that characterizes depression. Cognitive symptoms include hopelessness, helplessness, worthlessness, poor concentration, low-self esteem, guilt and suicidal ideation. Depression consists of seven or more of these symptoms once they become pervasive and significantly affect daily functioning. The aetiology includes stressful life events, personality, gender, illness, family history, personal support, loneliness as well as alcohol and drugs abuse. Although the pathophysiology of depression is poorly understood, it is thought to include changes in the expression of neurotransmitters, alterations to the hypothalamus-adrenal-pituitary (HPA) axis, genes and structural changes within the brain[14]. Psychosocial treatment can be successfully used to treat depression, but in severe cases of depression selective serotonin re-uptake inhibitors, selective norepinephrine re uptake inhibitors and other drugs are prescribed as well. Although in majority these are thought to be successful drugs but unfortunately, approximately 30% of depressed patients do not fully respond to these antidepressants[15]. Thus it is assumed and debated that whether the current approach fully meets the requirements of desired approach or we are missing some important mechanisms and factors in the cascade of depression which are detrimental.

Beside several areas the role of immune system is under scanner for a long time and the current theory advocates a multifaceted approach that targets both immune system and resultant inflammation. At present time, there is a circumstantial evidence suggesting that major depression is associated with dysregulation of the immune system[16]. Thus Immune system oriented and cytokine mediated inflammatory responses thus has become an intriguing approach for preventing the process before the production and release of these inflammatory mediators[17].

Cytokine Hypothesis and Depression

Beside the classical monoaminergic hypothesis of depression, several theories have been put forwarded to explain the pathogenesis of depression that include involvement of BDNF, neurogenesis, neurotrphic factors and mainly the role of neurotransmitters. One major theory

that advocates involvement of immune system and inflammation in depression has emerged as the most convincing theory. According to this theory immune system originated cytokines are the major factor resulting in the depressive syndrome and also for complicating the pathology further.

From historical perspective it was in 1957, a soluble factor that protected cells from viral infection was discovered by Isaacs and Lindenmann and was named interferon (IFN)[18]. This landmark finding set the stage for cytokine research and till now more than 90 cytokines and cytokine receptors have been identified and many are the foundations for current therapeutics for several ailments[19]. Thus cytokines has the fundamental role and importance in the pathologies of many disorders and there has been extensive worldwide research and development focused on inhibiting or antagonizing and enhancing or mimicking cytokine activity[20]. The cytokines refers to a bioactive cell secretion that belongs to a family of glycosylated or nonglycosylated polypeptides and proteins which are secreted although transiently yet it modulates the behavior of target cells[21].They belong to a complex and dynamic system, detrimental in numerous biological responses of human body[22]. Cytokines affect several important function and events in brain that includes regulation of sleep, cognition, behavior, food intake, body temperature and neuro-endocrine dysfunction[23]. According to cytokine hypothesis environmental stressors as well as organic inflammatory conditions trigger depression via inflammatory processes[24].

Indeed, systemic infections and stressful life events triggers activation of the peripheral immune system (required response of the body to cope with the adverse condition) however, when the activation of the immune system is prolonged because of a persistence and continuation of the adverse event cytokines and other immune modulators access the brain and affect different brain systems that play a role in enhancing vulnerability to depressive disorders[25,26]. Thus immune system oriented cytokine production seems to play an intriguing role in the beginning cascade of depression.

A number of immune components, pro inflammatory cells and other inflammatory mediators are multiplied in depressed patients[24] and the research in the past two decades have verified the fact and further gathered lots of proofs linking psychiatric illnesses to inflammatory processes[1]. Alterations in serum and CSF concentrations of a number of inflammatory markers, including cytokines, chemokines and acute phase reactant proteins, have been found in patients with depression and exist in the absence of comorbid medical illness[1,27]. It was found that the cytokines IFN-α and IL-2, used effectively as therapy for hepatitis C and cancer,

increase the risk for the development of depression[28,29]. Alterations in cytokine production have also been observed in animal models. In mice, mild chronic stress was associated with increased IL-1 and IL-2 production in concert with decreased NK cell activity and mitogen induced lympho proliferation[30]. Furthermore, therapies with tumor necrosis factor α (TNF-α) antibodies not only decrease symptoms of inflammatory diseases, but also symptoms of major depression[31]. Cytokine mRNA levels were also found when investigating peripheral blood cells. Indeed, higher mRNA levels of TNF-α, IL-1β, IL-6 and INF-α were found in the peripheral blood mononuclear Cells (PBMCs) of patients suffering from MDD[32] and an increased expression of cytokine mRNA levels in the leukocytes of drug free depressed patients as compared to controls was also seen[33] Taken together, it is likely that both peripheral and central inflammation are associated with MDD and anti-inflammatory drugs could ameliorate depressive symptoms in MDD patients[34].

Interestingly and importantly, the depressed patients who are non responders to antidepressant therapies or who are treatment resistant show higher plasma concentrations of several pro-inflammatory cytokines as compared to responders[35,36]. To add to the conclusions, cytokine expression in the leukocytes from depressed patients are reduced following escitalopram and nortriptyline treatment with a significant correlation between these changes and treatment response. Furthermore, the antidepressant sertraline (SSRI) decrease serum levels of proinflammatory cytokines (TNF-α,IL-2 and IL-12), whereas serum levels of anti-inflammatory cytokines were increased (IL-4,TGF-β1)) in a study conducted on depressed patients[37].

Cytokines, CNS Infiltration and Immune Sysytem

The immune system was first described to play an important role in the pathophysiology of depression in 1969[38]. A clear indication for the involvement of immune reactions in the depressed patients is the raised body temperature. Normally, the body temperature increases upon pathogenic invasion and returns to normal when the pathogen is removed. In depression, the body temperature remains elevated during the course[39] and it is hypothesized that maladaptive version of cytokine induced sickness turns into depression. This might occur when the intensity and/or duration of the innate immune response is exacerbated which finally turns into depression[40].

The immune system is thought to be critical for health and wellbeing, as it coordinate the body's response to physical injuries and infections. These injuries if are un-adrresed cause

illness or death. There are evidences that severity of depression have impacts on the immune defense mechanisms, through the activation or interaction with the cytokine network[41]. The findings that communication may occur between the immune and central nervous systems[42] led to the conclusion that depression may be influenced by immunological processes, just as psychological stressors have such an effect. While several potential routes of communication exist between the immune and central nervous systems, it has been suggested that cytokines, may act as immunotransmitters[43].

Normally, cytokines are expressed at very low levels in healthy brain tissue under but they can be rapidly induced and multiplied after a variety of stimuli. There are plethora of routes by which cytokines can access the brain, influence central neuronal chemistry and functions and cause behavioral changes, a coordinated set of psychological and physiological modifications that develop during the course of an infection[44] and that resemble depressive symptoms. One pathway may involve macrophage-like cells located in the circumventricular organs and the choroid plexus, which detect and respond to circulating pathogen associated molecular patterns by producing pro- inflammatory cytokines; these cytokines can then cross the Blood Brain Barrier (BBB) and affect neuronal function and microglia activation[26].

Although, the large size of cytokine molecules limits access to the brain, but they gain access where the barrier is less restrictive and permeable (e.g., the organum vasculosum laminaeterminalis), or via different transport system[45,46]. Furthermore, the integrity of the BBB may be compromised by various insults including stressors and pathological conditions (e.g., seizure)[47].In addition to infiltration from the periphery, cytokines are constitutively expressed in several brain sites, including circumventricular regions, hypothalamus, hippocampus, cerebellum, fore-brain regions, basal ganglia, as well as brainstem nuclei. Moreover, bioactivity of cytokines within brain may be provoked by various challenges, such as systemic or central bacterial endotoxin administration, and under neuropathological conditions, including brain injury, cerebral ischemia, and seizure[47,48].

Particularly, interleukin-1b (IL-1b)[45]and tumour necrosis factor-a (TNF-a) use carrier-mediated transport mechanisms that help to pump these cells into brain. Moreover, cytokines and stressors may increase BBB permeability by increasing the expression of vasoactive and inflammatory factors, such as cyclooxygenase-2 (COX-2 ; rate-limiting enzyme for the synthesis of the pyrogenic, prostaglandins and histamine at cerbrovascular sites. Additionally, stressors may influence the trafficking of cytokines into the brain parenchyma;as such challenges may also alter BBB permeability[49].

After gaining access to brain cytokines provoke a functional response by binding to specific receptors at hypothalamic and extra-hypothalamic brain regions[50] or by stimulating neurotransmitter functioning. Both IL-1 and TNF-a may have functions similar to classical neurotransmitters through their modulation of neuronal Ca^{2+} channels and activation of intra- cellular second-messenger systems[51]. The atrophic changes in hippocampus and frontal cortex might result from the increased levels of apoptosis following inflammatory responses[52,53]. In addition, anatomical changes such as neurotransmitter effects and vascular alterations in the brain might also be linked to chronic inflammation[52].

Cytokine Mediated Pathways Relevant to Depression

Cytokine interact at various levels and these events ultimately turns into a sickness behavior called depressive syndrome or depression. The various target sites for cytokines are summarized and discussed in the coming sections.

1. Effect on Neurogenesis

Cytokines alter brain functions by inhibiting or altering neurognesis. In a study systemic or intra-hippocampal administration of Lipopolusaccharides (LPS) reduces the formation of newborn neurons in the adult hippocampus, reveresed by indomethacin, a non steroidal anti-inflammatory drug, which act by inhibiting the synthesis of pro-inflammatory prostaglandins[54,55].

Neurogenesis in the hippocampus contribute to consolidation of memory and learning. Neurogenesis is the process by which new neurons are formed from neural progenitor cells and this process takes place in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. Both transplanted and endogenously generated neural stem cells are vital and important to CNS repair and functioning[56].

Neurogenesis maintain function and plasticity in response to extrinsic and intrinsic changes in brain. Abnormal neurogenesis is likely to exacerbate major neurological disorders like depression[57] while a pathogenic role for reduced neurogenesis in depression is unclear, there is now considerable experimental evidence that the generation of new neurons in the dentate gyrus is enhanced by antidepressant treatment[58].

Cytokines are vital to determine the inflammatory micro environment that ultimately affects differentiation, proliferation, migration and survival of neural stem/progenitor cells

(NSC/NPC)[56]. Monje et al reported that neuroinflammation inhibits neurogenesis and non-steroidal antiinflammatory drug restores neurogenesis[55]. Kaneko et al. found that IFNa suppressed neurogenesis in the dentate, and that IL-1b played an essential role in that suppression[59]. Stress induced reduction in hippocampal neurogenesis is also inhibited IL-1b receptor blockade and mice deficient in TNF receptor1 (responsible for neuronal damage) exhibit enhanced hippocampal neurogenesis[60]. These studies clarifies that somewhere cytokines mediate the neurogenesis and stress which is an important factor in depression pathology also causes progressive changes by manipulating rate and turnover of neurogenesis[61].

2. Stress, Immunity and Cytokines

Stress is the main factor responsible for depression that interacts with cytokines[62]. Stressors from different etiology activate immune cells in both the periphery and CNS to release cytokines that lead to biochemical changes and alterations in behavior that leads to this chronic illness[63].

The concept of an inter-relationship between the psychological state and immune status can be traced back to ancient history when AD Galen (200 AD) examined that melancholic women are susceptible to breast cancer than sanguine women[64]. Further in 1951, George Day, concluded that unhappiness is the major cause of lowered resistance tuberculosis patients[65].

Stressful events, are fundamental and decisive in the provocation of affective disorders[66] and may exacerbate pathologies that overstimulate immune system[67]. The findings that communication occur between the immune and CNS[68] led to the conclusion that depression is influenced by immunological processes, just as psychological stressors have such an effect.

Stressor, activates the hypothalamic–pituitary–adrenal (HPA) axis and/or the sympathetic nervous system (SNS) to help an organism to adapt physiologically to deal with a threat[69] and to maintain homeostasis. More broadly, psychological stress include the triggers and situations in which events or environment demands more than the ability of person to deliver. Stressors activate the sympathetic–adrenal–medullary (SAM) axis, as well as the HPA axis, and thereby influence the release of pituitary and adrenal hormones. For example, the catecholamines (adrenaline and noradrenaline), adreno-corticotropic hormone (ACTH), cortisol, growth hormone and prolactin all are influenced by negative events and negative emotions, and each of these hormones can induce quantitative and qualitative changes in immune activity. Furthermore, depression can substantially elevate cortisol levels which

provoke multiple adverse immunological events which strengthen the belief that a hyperactive HPA axis is associated with clinical depression[70].

The bidirectional communication between CNS and immune system is further become apparent as IL-1 influences the production of corticotropin releasing hormone (CRH) by the hypothalamus which affect the HPA axis and thereby trigger stress hormone levels, ultimately results in dysregulation of immune function[71].

All immune cells have receptors for one or more of the hormones which are linked with the HPA and SAM axes. Immune modulation by these hormones proceed through two pathways: directly, through binding of the hormone to its receptor at the surface of a cell; or by inducing dysregulation of the production of cytokines, such as interferon-γ (IFN-γ) etc. Cytokines like IFN-γ have many functions and affect different target cells so there are secondary effects of many stress hormones on the immune response[72,73]. Overactivity of the HPA axis in MDD causes hyper-cortisolemia which may either result in decreased expression of the glucocorticoid receptor (GR) or decrease functionality of the GR, both ultimately resulting in glucocorticoid resistance. Through these mechanisms, there is evidence for a role of proinflammatory cytokines such as TNF-α in glucocorticoid resistance. The peripheral immune cells does not respond to cortisol due to glucocorticoid resistance and the negative regulation on the immune response is lost which increase inflammation. Further glucocorticoid mechanisms are also linked to neurogenesis and it is thought that GR activation is necessary for its modulation by antidepressants drugs[74].

In chronic inflammation too, cytokines cause glucocorticoid receptor resistance in immunocytes and their cellular targets through the induction of the MAP kinases c-jun N-terminal kinase (JNK) and p38[75] help in progression ogf inflammatory cascade. Pro-inflammatory cytokines promote expression of the β isoform of the glucocorticoid receptorwhich is inactive but able to bind its ligand[76]. At the hypothalamic level, this glucocorticoid receptor resistance explain the reduced ability of glucocorticoids to down-regulate the production of CRH. At the level of peripheral and central innate immune cells, the normally inhibitory effect of glucocorticoids on cytokine production and action would no longer be operative, setting the condition for a feed-forward cascade that result in an ever increasing production of pro-inflammatory cytokines. This increased inflammatory response in the brain results in a decreased inhibitory feedback on CRH by glucocorticoids, thereby intensifying the stress-mediated immune over activity leading to cytokine infiltration response system[77].

In the normal situation, GCs keep check on inflammatory events by a negative feedback on the hypothalamus however GC resistance results in impaired negative feedback. As a result, the inflammatory processes which are normally under control of the HPA axis will get out of control. In this way, the impaired feedback regulated by GCs contributes to the development of the excessive inflammation seen in depression[78,79]. The glucocorticoid resistance hypothesis thus suggests that stress plays an important role in the eventual dysregulation of the immune system.

3. Cytokines and Neurotransmitters

As described earlier, cytokines reach the brain is via binding with their specific transporters, which are located on the BBB. Moreover, microglia cells in the brain produce cytokines receptors and thus amplify the inflammatory signals[80]. Once in the brain, cytokines alter and affect brain function in a variety of ways, including the modulation of neurotransmitter metabolism and neurotoxic mechanisms. For example, cytokines induce the enzyme Indoleamine 2,3 Dioxygenase (IDO), which breaks down the serotonin precursor tryptophan into kynurenine that, once converted into quinolinic acid, lead to neurotoxicity through the activation of the glutamatergic system[81].

Furthermore, cytokine induces changes in metabolism of the monoamines like dopamine, noradrenaline and serotonin[82]. IL-1β and TNF-α stimulate the gene expression of serotonin reuptake transporters[83] and IL-1β and IFN-γ stimulate enzymes such as indolamine-2,3-dioxygenase (IDO). The net result is reduced synthesis or increased breakdown of neurotransmitters, resulting in decreased tryptophan and serotonin (5-HT),which can cause depressive disorders[84].

Dopamine(DA) is another neurotransmitter implicated in MDD thought to be responsible for the symptoms of sickness behavior and anhedonia. There is a reduction in DA in the basal ganglia in MDD and this contribute to the blunted reaction to positive reinforces and abnormal response to negative feedback observed in depressed patients. As with 5-HT described previously, pro-inflammatory cytokines influence dopamine synthesis and reuptake[85].

Kynurenine is converted into kynurenic acid, an NMDA antagonist, which antagonizes α7nicotinic acetylcholine (ACh) receptors and can reduce striatal dopamine release. Dopamine reuptake is increased through phosphorylation of the dopamine transporter (DAT) by mitogen activated protein kinase kinase (MAPKK)[85]. NA is also thought to be involved in the

pathogenesis of depression however the role of inflammation in the reduction of NA has not yet been established in humans with MDD.

4. Cytokines and BDNF

Brain-derived neurotrophic factor BDNF protects the CNS from injury and other drastic events by inhibiting apoptosis and by stimulating sprouting and neuronal reorganization. Because of its relevance to the functioning of the CNS, BDNF has been implicated in the pathogenesis of different neuropsychiatric diseases, including depression[86]. Emerging evidence points to the impaired signaling of BDNF in the pathophysiology of major depression. BDNF is one of a series of small proteins that the brain uses, first-in its development and later in adulthood, to regulate nerve cell growth and function. Depressed patients exhibit low circulating levels of BDNF which may be reversed by the antidepressant treatment[87].

The BDNF hypothesis of depression postulates that stress reduces BDNF concentrations in limbic system structures and this underpins the central pathogenic process in depression, whilst anti-depressants restore BDNF concentrations and through this alleviate depressive symptoms. Inflammatory cytokines also influence BDNF receptor (TrkB) phosphorylation, there by further interfering with BDNF signaling. Consistent with these findings, the reversal of LPS induced apoptosis by antidepressants requires intact BDNF signaling. Levels of BDNF and its receptor, TRKB, are also reported to be down regulated in a region-specific manner, in the postmortem brains of subjects with major depression. In addition, antidepressants in rodent models lead to increased brain BDNF protein levels, while intra-hippocampal BDNF administration leads to diminished depressive-like behaviors. Recent work has also suggested that rapid antidepressant response following ketamine administration is mediated by BDNF signaling[88,89].

Chronic administration of several antidepressants, including selective serotonin reuptake inhibitors, increases BDNF expression in the hippocampus. Downregulation of BDNF could contribute to accelerate the atrophy of CA3 neurons, making these neurons more susceptible to other factors, such as adrenal glucocorticoids that are induced in response to repeated stress. A study realized by Bilbo et al.[90] showed that neonatal infection with E. coli decreased BDNF mRNA in the hippocampus area, CA1, CA3 and dentate gyrus, besides showing an increase of IL-1 mRNA in the CA1 region. These effects found may be related to BDNF[91]. In fact, cytokines interferes directly with BDNF signal transduction in cultured neurons in vitro by preventing its neuroprotective actions[92].

5. Cytokines and Cyclooxygenases

One of the important targets of pro-inflammatory cytokines is cyclooxygenase-2 (COX-2). COX-2 is an inducible enzyme that is unexpressed under normal conditions, but becomes expressed upon inflammation. Elevated neuronal levels of COX-2 were indeed found in the brain of depressed patients. The major function of COX-2 is the production of prostaglandins, amongst which prostaglandin E2 (PGE2)[93].The elevated levels of COX-2 in depression would suggest PGE2 levels to be elevated as well. Indeed, multiple studies reported elevated levels of PGE2 in the cerebrospinal fluid (CSF), serum and saliva of patients with major depression as well as rat models.

PGE2 is an important immune modulator, which is involved in the regulation of the balance between the Th1 and Th2. In chronic inflammation, PGE2 suppresses the aggressive cytotoxic (type 1) immunity, and promotes the less aggressive Th2 immunity, amongst others by inducing regulatory T-cells[94].With respect to depression, this would suggest that the increased levels of PGE2 would have beneficial effects. On the other hand, another resource indicates that PGE2 elevates levels of IL-6, which would suggest that the Th1 immunity would be elevated, which would further increase the harmful effects of neuroinflammation. This contradiction might be due to the fact that Kasper et al. describe the function of PGE2 early in the inflammatory process, where it promotes active inflammation, whereas Kalinski et al [94] studied chronic inflammation. However, it can be concluded that exact consequences of elevatedPGE2 levels for depression are not too clear and that further research to clarify these effects would be desirable.

6. Cytokines and NO

Another consequence of elevated levels of pro-inflammatory factors is an increased production of nitric oxide(NO).Nitric oxide is a free radical, which can induce apoptosis. In case of neuro-inflammation, increased levels of apoptosis following NO secretion constitute a serious risk for neurodegeneration. The main activators of NO are TNF- -α and TGF-β, which are present in higher levels in depressed patients. At the same time, depression is associated with decreases in IL-4 and IL-10, the factors that inhibit NO production. Based on this information, it would be expected that depression is associated with increased levels of NO. Indeed, elevated levels of NO were observed in the plasma of patients with major depression[93].

Conclusion

In response to acute stressors, numerous biological processes are activated, the function of which may be of adaptive significance. Stress mediated activity of HPA axis, Role of SNS is although well investigated yet the role of immune over activity and resultant inflammation seems inevitable and decisive in depression. Cytokine plays with neurotransmitters, NO, BDNF and interfere with neurogenesis and normal neurochemistry of brain. Thus screening immune activity and targeting cytokines in depression seems to be a required and much needed multifaceted approach.

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