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Inflammatory theory of depression

Piotr Gałecki, Monika Talarowska

Department of Adult Psychiatry, Medical University of Lodz

Summary

Brain diseases are one of the most socially and economically burdening diseases in Europe. Among all brain diseases, more than 60% of social and economic costs are generated by mental disorders (mainly depressive disorders and anxiety disorders). Recurrent depressive disorders have been a significant civilizational problem in recent times. Among the biological and psychological theories explaining the causes of depression, the hypothesis involving an active inflammatory process taking place in a human organism is becoming increasingly important. The following are considered inflammation markers: inflammatory enzymes (e.g., manganese superoxide dismutase (MnSOD), myeloperoxidase (MPO), inducible nitric oxide synthase), proinflammatory and anti-inflammatory cytokines, and the phenomenon of oxidative stress. Through the kynurenine pathway, these factors lead to a deficit in serotonin and melatonin, which is considered one of the main reasons of depression. We can consider depression to be a chronic cold of the organism, which develops in response to the action of greater or smaller everyday stressors. This paper presents results of recent studies regarding this matter.

Key words: depression, inflammation theory, cognition, emotions

Introduction

Brain diseases are some of the most socially and economically burdening diseases in Europe. Approximately 800 trillion euros are spent annually on the fight with the consequences of these diseases [1]. In 2010, 179 million citizens of Europe suffered from the said ailments; six years earlier, in 2004, there were only 127 million people affected by them. The figures mentioned above indicate an increase of incidence by more than 30% within just six years [2]. Among all brain diseases, more than 60%

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of social and economic costs are generated by mental disorders, mainly depressive disorders and anxiety disorders [2].

Annual prevalence of depression in the population of adults oscillates between 6% and 12%, while among people over the age of 65 it varies from 5% to even 30% according to various sources [3]. Based on the estimates of the World Health Organization (WHO), 350 million people around the world show symptoms of depression, while depressive disorders represent nearly 4.3% of the global burden of all diseases [3]. The risk of occurrence of the so-called major depression during lifetime is estimated at the level of 8–12%. Depression often accompanies other somatic diseases as a symptom. It means that approximately 10% of all adults (which corresponds to 100 million cases) show signs of depression during one year. Women suffer from depression twice as often as men [4].

The contribution of broadly understood inflammatory factors in the etiology of depressive disorders does not bring about doubts any longer [5]. This study presents reports regarding contemporary research studies in this matter.

Inflammatory theory – basic facts

Research studies conducted within the last ten years have confirmed that both physical and psychological (emotional) stress increases the likelihood of occurrence of mental disorders (including depressive disorders) [6] owing to the action of a series of hormonal and biochemical mechanisms [7], as well as epigenetic mechanisms, which has been recently confirmed [8]. It should be remembered that markers of active inflammatory process are one of the factors that severely alter BBB [9].

The kynurenine pathway

Hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA) and dysregulation of the immune system are the source of irregularities in the activity of the kynurenine pathway. Its basic role in a healthy organism is to transform tryptophan into two essential compounds engaged in mood regulation, i.e., serotonin and melatonin [10]. Based on the kynurenine pathway hypothesis of depression etiology, inflammatory factors cause excessive activation of indoleamine-2,3-dioxygenase (IDO), an enzyme present in microglia, astrocytes and neurons [11]. This enzyme catabolizes tryptophan, the source of serotonin, into kynurenine (KYN), a neurotoxic substrate which increases the risk of neurodegenerative and neurotoxic processes. In this way, IDO reduces the amount of tryptophan available for the production of serotonin [11], which is directly linked with the etiology of depression.

Inflammatory markers in depression

Enzymes of inflammation

Manganese superoxide dismutase (MnSOD), myeloperoxidase (MPO), and inducible nitric oxide synthase (iNOS) are among the enzymes of inflammation which take part in the etiology of recurrent depressive disorders (RDD) [12]. Not only do the compounds take part in an inflammatory reaction, but they are also actively engaged in the production of free radicals, as well as damage proteins, fatty acids and cellular DNA. This leads to brain damage both through neurogenesis deterioration as well as intensification of neurodegenerative processes [13].

Gałecki et al. [14] indicated that manganese superoxide dismutase gene polymorphism (Ala-9Val and Ile-58Thr) in the patients with RDD is associated with the occurrence of depressive symptoms. Madrigal et al. [15] described increased iNOS expression within the hippocampus and the cerebral cortex as a consequence of experienced stress, while Gałecki et al. [16] indicated increased iNOS expression at the mRNA level in the people affected by recurrent depressive disorders. Kim et al. [17] demonstrated an elevated level of nitric oxide (NO) in a group of 39 patients with RDD after a suicide attempt before examination commencement. The authors described substantially higher concentration of NO in the plasma in the group mentioned above as compared with the individuals suffering from RDD who did not attempt to commit suicide based on an interview, and as compared with healthy subjects.

Increased expression of MPO at the mRNA level in the group of patients affected by recurrent depressive disorders (n = 181), as compared with the group of healthy subjects, was described by Gałecki et al. [18]. Moreover, the same team, analyzing G-463A single nucleotide polymorphism (SNP) of the MPO gene, showed the differences in the distribution of genotypes and the frequency of alleles between the group of patients with RDD and healthy subjects [18]. The G-463G homozygote and the – 463G allele occur significantly more frequently in RDD. This confirms the correlation between the presence of the G-463G genotype and the – 463G allele and the risk of depression development.

The results recorded by our team in the last several years were confirmed in a meta-analysis performed by Köhler et al. [19].

Oxidative/nitrosative stress

Oxidative stress is a state associated with an increased activity of reactive oxygen species (ROS). It develops as a consequence of disorders in the balance between production and elimination of toxic derivatives of oxygen (a growing level of free radicals and products of their reaction dominates over the ability of their decomposition). A significant disorder of the balance between the system of oxidizing agents and antioxidants may lead to irreversible changes in the organism and be conducive to tissue damage in different pathological states [20]. Reactive oxygen species, produced in excessive amounts, play an important role in the mechanism of a chronic inflammatory reaction. Their accumulation stimulates the activity of protective systems [20].

The brain is particularly susceptible to oxidative damage. This results from the fact that it utilizes substantial amounts of oxygen and from the presence of a prominent level of lipids in its cells, including non-saturated fatty acids which free radicals easily react with. Moreover, some regions of a human brain contain substantial amounts of metal ions, especially Fe^{3+}, Cu^{2+} and Zn^{2+}, which is conducive to the production of ROS. Additionally, lower concentrations of antioxidants, as compared with other organs, are found in the tissues of the central nervous system [21]. Cells of the hippocampus in the CA1 region (Sommer's sector) and the CA4 region (Bratz's sector), cells in the dorsolateral region of the striatum, and neurons of the third and fifth layer of cerebral cortex are most sensitive to damage [20].

In our recent papers, we also indicated deteriorated efficiency of operational memory, declarative memory and verbal fluency in the patients suffering from depression in connection with increased expression of MDA (malondialdehyde) [22], NO [23], and thiol protein groups (TPGs) [24], and with reduced total antioxidant status (TAS) [25].

Proinflammatory and anti-inflammatory cytokines

Research conducted in recent years has confirmed that depressive disorders, in the absence of somatic comorbidity, are linked with an increase of central and peripheral concentration of many proinflammatory cytokines, including mainly tumor necrosis factor α (TNF-α) and interleukins (ILs). In compliance with the "theory of cytokine-induced depression" by Maes, inflammatory factors play a crucial role in the occurrence of symptoms of the illness [26].

Changes in the metabolism of biogenic monoamines, i.e., dopamine, noradrenaline and serotonin, in mesencephalic nuclei, are mentioned as potential ways of cytokines' impact on the etiology of depression [27]. Moreover, cytokines lead to excessive secretion of cortisol – directly by means of stimulating the HPA axis and indirectly by modifying the sensitivity of glucocorticoid receptors [27].

A particular role in the etiology of RDD is assigned to two proinflammatory interleukins (IL-1 and IL-6) as well as IL-10, which is one of anti-inflammatory interleukins [28]. In our research [29] we did not find any difference in the concentration of IL-1, IL-6 and IL-10 in the patients with the first episode of depression and treated due to RDD, which suggests that dysregulation of the level of proinflammatory cytokines is a constant feature during depression.

On the other hand, TNF-α induces excessive reuptake of monoamines, stimulates pathologic hyperactivity of the HPA axis, and increases the activity of IDO, hence reduces substantially the production of serotonin [30]. TNF-α and interleukins, both at the central and peripheral levels, are associated with the cognitive deterioration of the affected individuals [31]. A clear increase in the level of proinflammatory cytokines in response to a stress stimulus within the area of the prefrontal cortex and in the region of the hippocampus is observed during experiments on an animal model [31]. Additionally, overproduction of TNF-α may upset the system of melatonin production, which leads to circadian rhythm disorders [32].

HPA axis

In terms of pathophysiology, depressive disorders resemble chronic stress. Disorders of the HPA axis are observed in 50–75% of patients with diagnosed depression. The following symptoms are diagnosed: increased concentration of glucocorticoids in plasma, urine and cerebrospinal fluid, changes in the daily profile of glucocorticoid secretion with more frequent and longer periods of secretion, increased secretion of glucocorticoids in response to ACTH, an increase in the volume of hypophysis and adrenal glands [33].

The hippocampus is a structure of the brain which is particularly susceptible to stress-induced functional changes and dysregulation of the HPA axis. In such cases, a drop in the expression of the brain-derived neurotrophic factor (BDNF), deterioration of long-term potentiation (LTP), and inhibition of neurogenesis in the dentate gyrus (DG) are observed. A gradual reduction of hippocampal volume as a result of successive episodes of depression is observed [34].

Corticosteroids have a strong negative impact not only on the region of the hippocampus and the amygdala, but also on the functioning of the prefrontal cortex. In the patients with a tendency to dwelling upon unpleasant events the level of cortisol is higher than in a comparative group of healthy subjects and among people with diagnosed depression who do not mention any ruminations [35].

Somatic comorbidity

Symptoms of depression in the groups of patients treated somatically often remain unrecognized and untreated. However, results of multicentre meta-analyses indicate that the presence of depressive symptoms correlates with the deterioration of general well-being of patients, poorer therapeutic response to treatment of the somatic disease, and increases the likelihood of repeated hospitalization due to deteriorated somatic status of the patient [36].

Both depression and a range of civilization diseases (hypertension, coronary artery disease, diabetes, and even dementia) have the same immunological background. An increase in the activity of the immune system and the unfavorable metabolic conversions described above are observed in each of the diseases mentioned above [37]. Cardiovascular diseases, respiratory diseases, metabolic disorders and autoimmune diseases are not only the risk factors of a depressive episode, but they are also considered to be drug-resistance factors of depression and some of the significant causes of recurrence of deteriorated mood episodes. Wiltink et al. [38] demonstrated that a diagnosis of depression is often associated with dyslipidemia, coronary heart disease, diabetes, and even increases the risk of a heart attack.

This phenomenon has yet another underestimated aspect. Due to the occurrence of symptoms of depressive disorders (anhedonia, dejection, pessimism, resignation, deteriorated cognitive functioning), patients stop treating the basic disease (diabetes, cardiovascular disease), which leads to a diagnostic and therapeutic vicious circle in the longer term, and has a negative impact on the quality of life of the affected individuals [39].

Inflammation and cognitive functions

Cognitive dysfunctions during RDD have been described in research for several years now and do not bring about doubts any longer. Deficits may be selective and mild or generalized and significantly intensified [40, 41]. Typical symptoms include: psychomotor retardation, reduced effectiveness of memory processes and the ability of learning unfamiliar information, weakening of attention, deterioration of visuospatial abilities and visual-motor coordination, verbal fluency, as well as the so-called executive functions (among other, problems with inhibiting reactions, planning and solving problems) [40].

In the case of each episode of depression, even the mild one, the efficiency of cognitive functions is reduced. This phenomenon is observed regardless of whether we deal with depression only or with accompanying somatic comorbidity as well. This is what happens, for example, in the case of individuals diagnosed with diabetes, COPD or hypertension [42, 43].

Excessive generation of ROS, insufficient antioxidant activity of the organism's defense mechanisms and central inflammatory reactions, play a substantial role not only in the etiology of RDD, but also in the pathogenesis of many neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis or strokes. The importance of the said factors in the formation of mild cognitive abnormalities is also emphasized [44].

Inflammatory markers and emotions

Recent years have shown that axial symptoms of depression are caused by disorders of emotions regulation, dysfunctions in the reward system and deficits of cognitive processes [45]. Examples of mutual relationships between the cognitive sphere and the emotional one in recurrent depressive disorders include repeated ruminations in the affected patients (which indicate a tendency to long-lasting dwelling upon negative emotions together with their importance and actual or predictable consequences) [46], as well as deficits in the scope of social cognition [47]. The term "social cognition" refers to an ability to receive, identify and interpret stimuli that are socially significant (emotional expression of the face, tone of voice).

The same regions of the brain, particularly sensitive to the consequences of defense mechanism deterioration, i.e., the frontal and medial part of the cingulate gyrus, the dorsolateral and ventromedial area of the prefrontal cortex, the anterior part of the insula and the amygdala, are responsible for deficits in both the emotional and cognitive aspects [48]. In the functional model of depression, hyperactivity in the limbic area (the amygdala, hippocampus, anterior cingulate cortex) is not sufficiently controlled by the medial cortex of the frontal lobe in response to emotional stimuli of a negative charge. On the other hand, positive stimuli cause excessive inhibition in the frontal cortex. Reduced activity of the amygdala in response to positive information is linked with symptoms of anhedonia [49].

Recapitulation

Activation of the immune system is the common denominator for a series of civilization diseases and depressive disorders. The risk of a depressive episode in the individuals affected by these diseases should be considered at every stage of diagnosis and treatment. Therefore, we can consider depression to be a chronic cold of the organism, which develops in response to the action of greater or smaller stressors accompanying everyday life. The personality component is also significant [50] (Figure 1).

It is still undecided how depression should be treated. Selective serotonin reuptake inhibitors (SSRI) as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) are one of the most commonly applied drugs in the world during pharmacotherapy of recurrent depressive disorders [51]. The underestimated anti-inflammatory and

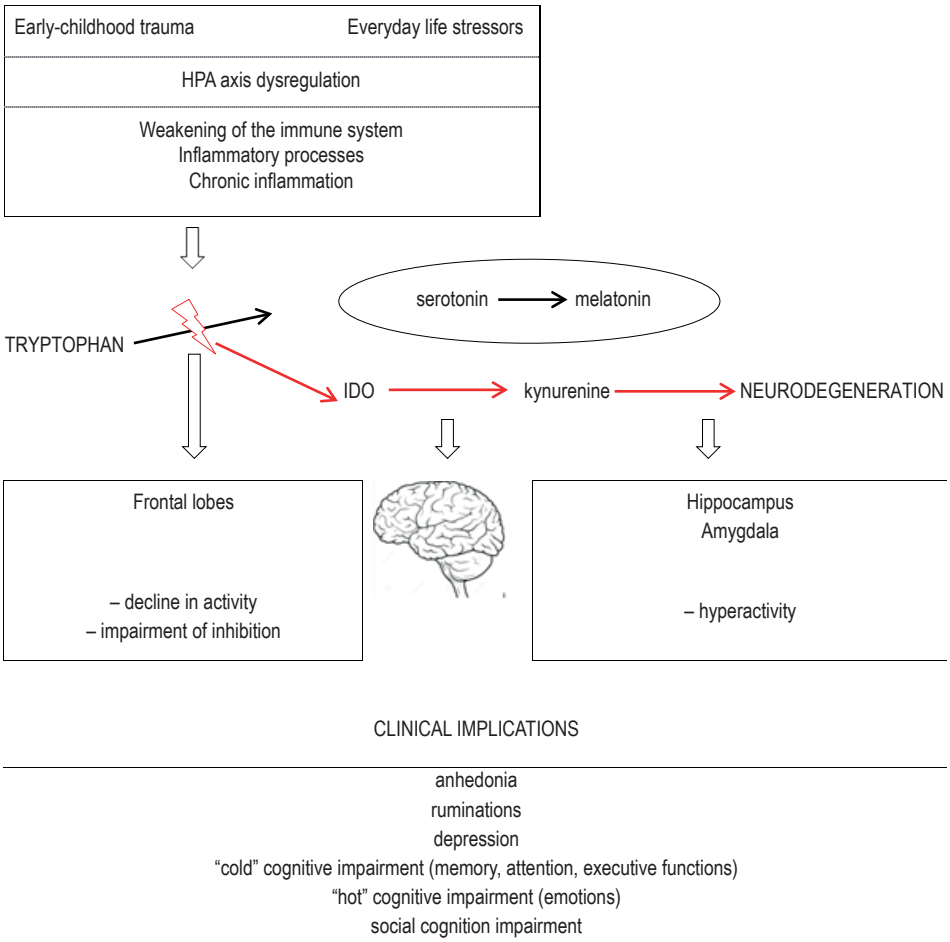

Figure 1. **Neurodevelopmental theory of depression [as cited in 50]**

anti-oxidative effect may be one of the potential mechanisms of action of the aforementioned preparations.

It seems that anti-inflammatory products should be the future in the therapy of depressive disorders and civilization diseases. The research by Souza et al. [52] indicates that the application of non-steroidal anti-inflammatory drugs and cytokine-based formulas offering anti-inflammatory action may be an effective alternative in the treatment of depression. Certainly, it is appropriate to take into consideration somatic comorbidity as a significant factor affecting treatment efficacy when deciding about the type of antidepressant pharmacotherapy to be administered.

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Address: Monika Talarowska
Department of Adult Psychiatry
Medical University of Lodz
91-229 Łódź, Aleksandrowska Street 159
e-mail: talarowskamonika@wp.pl