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Immunology of Major Depression

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Abstract
High levels of several proinflammatory components of the immune system, such as interleukin-6, C-reactive protein, tumor necrosis factor (TNF)-α, or neopterin in patients suffering from major depression (MD) point to the involvement of an inflammatory process in the pathophysiology of MD. The direct and indirect effects of cytokines on neurotransmitter storage and release – mediated by microglia cells and astrocytes – are discussed. The tryptophan/kynurenine metabolism is one of the indirect mechanisms because the enzyme indoleamine 2,3-dioxygenase – a key enzyme of this metabolism in the central nervous system – is driven by pro- and anti-inflammatory cytokines and degrades serotonin. Moreover, neuroactive kynurenines such as kynurenic acid and quinolinic acid act on the glutamatergic neurotransmission as N-methyl-D-aspartate antagonists and agonists, respectively. Alterations of the serotonergic, noradrenergic and glutamatergic neurotransmission have been shown with low-level neuroinflammation and may be involved in symptom generation. Epidemiological and clinical studies show a role for inflammation as a risk factor for MD. A large-scale epidemiological study in MD clearly demonstrates that severe infections and autoimmune disorders are lifetime risk factors for MD. The vulnerability-stress-inflammation model matches with this view as stress may increase proinflammatory cytokines and even contribute to a lasting proinflammatory state. Further support comes from the therapeutic benefit of anti-inflammatory medications such as the cyclo-oxygenase-2 inhibitors, TNF-α antagonists and others, and the anti-inflammatory and immunomodulatory intrinsic effects of antidepressants.

Introduction

Activation of the inflammatory response system in major depression (MD) is well documented [1–5]. Two recent meta-analyses clearly showed elevated interleukin (IL)-6 levels in patients with MD [6, 7]. However, the findings of the two meta-analyses differed regarding levels of the inflammatory markers C-reactive protein (CRP), IL-1, IL-1RA and tumor necrosis factor (TNF)-α. In general, the inflammatory response system appears to be activated, but the levels of the different markers vary across studies. MD is a disorder often triggered by stress. It has been shown that – often based on genetic disposition – early-life stress or separation stress are associated with an increase of proinflammatory cytokines leading to an activation of the immune system and proinflammatory prostaglandins. Prostaglandin E2 (PGE2) is an important mediator of inflammation [8]. Increased PGE2 in the saliva, serum and cerebrospinal fluid (CSF) of depressed patients has been described previously [9–12]. The enzyme cyclooxygenase-2 (COX-2) is involved in the function of PGE2 in the inflammatory pathway. In the brain, the activation of microglia cells and astrocytes is crucial, because proinflammatory molecules are produced and released in

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the brain. The interactions between the immune system and neurotransmitters, the tryptophan/kynurenine system, and the glutamatergic neurotransmission are further links between stress, depression and the immune system. Accordingly, anti-inflammatory therapy, e.g. with the COX-2 inhibitor celecoxib, is effective in depression.

The roles of microglial cells and astrocytes as mediators of inflammation in the brain are discussed, as is the influence of a disturbed blood-brain barrier (BBB) in facilitating the invasion of inflammatory molecules and immune cells, including monocytes, T and B cells.

The Cellular Basis of Inflammation in the Central Nervous System

Microglia cells and astrocytes have been shown to play a central role in regulating neuroinflammation [13, 14]. Astrocytes comprise approximately 80% of brain cells and are the most abundant type of glial cells in the central nervous system (CNS), while microglial cells represent about 15% of brain cells. Astrocytes have a strategic location: they are in close contact with CNS resident cells (neurons, microglia, oligodendrocytes and other astrocytes) and are part of the immune and inflammatory systems in the CNS. Among the cytokines, TNF-α, interferon (IFN)-γ, IL-1 and IL-6 are the main astrocytic activators [14]. Astrocytes are strongly involved in increased BBB permeability, endothelial cell activation, monocyte and microglia activation, and B cell survival and differentiation. Astrocytes produce and release a series of chemokines and are thus involved in the recruitment of monocytes and macrophages, dendritic cells and T and B cells in the CNS.

Astrocytes, however, also store and release neurotransmitters [15]. For example, an important function of astrocytes is the regulation and storage of glutamate, which is actively transported into astrocytes [16]. Therefore, astrocytes play a role not only as immune regulators and hosts of kynurenine metabolism, but also in the bioavailability of neurotransmitters including glutamate, the most abundant neurotransmitter, which is involved in psychiatric disorders such as MD.

BBB Disturbance in MD

By far the most studies of biological parameters, including immune parameters in MD, have examined components of blood cells and serum, although the CSF reflects disturbances in the CNS much better. During acute inflammation, immune cells invade the CNS parenchyma through the disturbed BBB, i.e. through the endothelium of the small vessels and the tight junctions of astrocytes around the vessels. This invasion is mediated by cytokines, chemokines, adhesion molecules and other mediators of inflammation. Signs of inflammation in the CNS are a disturbance of the BBB, increased immunoglobulins and, especially in acute inflammatory states, an increase in the cell number in the CSF.

Analysis of the CSF is the gold standard for diagnosing CNS inflammatory disorders [17, 18]. The rough method of 'routine' analysis of CSF parameters, however, only discovers gross changes in the CSF. More subtle changes in the CSF of MD patients may occur in a higher percentage of patients. Pathological changes in the CSF were observed in a subgroup of around 25–30% of patients suffering from MD [19–21]. These changes included an increased production of IgG and an increased BBB permeability, as is found in inflammatory states. Recent studies with the advanced CSF methodology have confirmed and extended these previous studies in that about 15% of cases with therapy-resistant depression provide evidence of low-grade classical neuroinflammation, about 25% provide evidence of blood-CSF barrier dysfunction [22] and, with some overlap to these pathological findings, about 30% of patients demonstrate inflammatory activation patterns on CSF cells [23]. In addition, more than 30% showed, with little overlap to the other findings, considerably increased CSF-neopterin, likely indicating some immune-inflammatory condition [24].

The Model of 'Sickness Behavior' for Depression

An animal model for MD is 'sickness behavior', i.e. the behavioral, vegetative, cognitive and emotional reaction of an organism to infection and inflammation [25, 26]. In humans, the involvement of cytokines in the regulation of sickness behavior has been studied by administering the bacterial endotoxin lipopolysaccharide, LPS, to healthy volunteers [27]. The levels of anxiety, depression and cognitive impairment were found to be related to the levels of circulating cytokines [27, 28].

The Proinflammatory Immune State in MD

A high blood level of CRP is a common marker for an inflammatory process. Higher than normal CRP levels have been repeatedly observed in depression, for example

in severely depressed inpatients [29], and high CRP levels have been found to be associated with the severity of depression [30]. Higher CRP levels were also observed in remitted patients after a depressive state, in both men [31, 32] and women [33, 34]. In a sample of older healthy persons, CRP levels (and IL-6 levels) were predictive of cognitive symptoms of depression 12 years later [35].

Characteristics of immune activation in MD include increased numbers of circulating lymphocytes and phagocytic cells, upregulated serum levels of markers of immune activation (neopterin, soluble IL-2 receptors), higher serum concentrations of positive acute-phase proteins, APPs, coupled with reduced levels of negative APPs, and increased release of proinflammatory cytokines, such as IL-1β, IL-2, TNF-α and IL-6 through activated macrophages, and IFN-α through activated T cells [3, 36–41] (table 1). Increased numbers of peripheral mononuclear cells in MD have been described by different research groups [42–44]. In accordance with the findings of increased monocytes and macrophages, an increased level of neopterin has also been described [45–48]. The role of cellular immunity, cytokines, the innate and the adaptive immune system in depression has been recently reviewed [49, 50].

Table 1. Candidates for immune markers related to major depression

Disease-related markers	Markers for antidepressant response	Markers for response to immune-related therapy
IL-6	IL-6	IL-6
TNF-α	Quinolinic acid	CRP
CRP	TNF-α	TNF-α
Neopterin		TNFR1
		TNFR2
		Kynurenine/tryptophan

Infections and Autoimmune Disorders as Risk Factors for MD

Results of a very interesting population-based Danish register study support the view that an infection or an autoimmune disease significantly increases the risk of later developing a depressive disorder. This population-based prospective cohort study of 78 million person-years includes 3.6 million registered people (born between 1945 and 1996). The follow-up was documented from 1977 to 2010. All individuals with the diagnosis of an affective disorder according to ICD-8, ICD-9 or ICD-10 were included in case they had had at least one hospital contact as an in- or outpatient due to affective disorder (including bipolar disorder). Every hospital contact due to an autoimmune disorder or infection (excluding HIV/AIDS) prior to psychiatric diagnosis was recorded and >91,000 affective disorder cases were identified, of which ~30,000 were diagnosed with infection and >4,000 were diagnosed with autoimmune disease.

Hospitalization for infection significantly increased the risk of later mood disorder by 62% (incident rate ratio, IRR, 1.62), while hospitalization for autoimmune disease significantly increased the risk of later mood disorder by 45% (IRR 1.45). The interaction of both risk factors increased the risk to IRR 2.35. The risks were higher for hepatitis infection (IRR 2.82) compared to sepsis or CNS infections. The risk of mood disorder increased with the proximity to the infection, with the highest risk within the first year (IRR 2.70) [51].

Inflammation Influences the Metabolism of Serotonin and Noradrenalin in Depression

Overwhelming evidence collected over the last 40 years suggests that disturbances in serotonergic and noradrenergic neurotransmission are crucial factors in the pathogenesis of MD [52, 53]. Although the pathogenesis of the disturbed serotonergic and noradrenergic mechanisms is still unclear, the involvement of the proinflammatory immune state might be crucial. The proinflammatory cytokine IL-1β increases the metabolism of serotonin and noradrenalin within the hypothalamus, prefrontal cortex, hippocampus and amygdala [54–59]. Similar but less pronounced effects on central monoamine activity after stimulation with LPS or poly:IC have been observed for several mediators such as IL-6 and TNF-α [59, 60].

Similarly, administration of the proinflammatory cytokine IFN-α is associated with reduced levels of serotonin in the prefrontal cortex [61]. Accordingly, symptoms of depression have been observed in many patients treated with IFN-α [62, 63].

Moreover, two indirect pathways of the tryptophan/kynurenine metabolism contribute to the induction of symptoms of depression by proinflammatory cytokines: (1) the increased metabolism of serotonin and (2) the increased production of N-methyl-D-aspartate (NMDA) agonists, i.e. glutamatergic products of kynurenine metabolism, after activation of the enzyme indoleamine 2,3-dioxygenase (IDO) by proinflammatory cytokines [64, 65]. Proinflammatory molecules such as PGE2 or TNF-α, however, induce the increase of IDO activity synergistically with IFN [66–68].

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Increased activity of the glutamatergic system in the peripheral blood of depressive patients has been repeatedly shown [69–71], although this result could not be replicated by all groups [72]. The inconsistency of the findings, however, might be due to methodological problems [73]. Support for increased glutamatergic activity in depression comes from magnetic resonance spectroscopy: elevated glutamate levels were found in the occipital cortex of unmedicated subjects with MD [74]. Furthermore, NMDA antagonists such as MK-801 [75, 76], ketamine [77], memantine [78], amantadine [79, 80] and others [73] have exhibited antidepressant effects in humans. The partial NMDA receptor agonist D-cycloserine demonstrated antidepressant effects at high doses [81].

Several mechanisms can cause depressive states: (1) a direct influence of proinflammatory cytokines on serotonin and noradrenalin metabolism [60, 82, 83]; (2) an imbalance of the type 1 and type 2 immune responses leading to increased tryptophan and serotonin metabolism by activation of IDO in the CNS [84, 85]; (3) a decreased availability of tryptophan and serotonin [47], and (4) a disturbance of kynurenine metabolism, with an imbalance in favor of the production of the NMDA receptor agonist quinolinic acid [85, 86].

CNS Volume Loss in Neuroimaging Studies – A Consequence of an Inflammatory Process?

A loss of brain volume has been observed in MD. Male patients with a first episode of MD had significantly smaller hippocampal total and grey matter volumes than healthy male comparison subjects [87]. In a long-term study a significantly higher decline of volume in several CNS regions compared to healthy controls was observed [88]. The pathophysiology of this volume loss is unclear. Glial reductions have been consistently found in brain circuits known to be involved in mood disorders, such as the limbic and prefrontal cortex [89–93]. Recent studies have shown that the number of astrocytes is reduced in patients suffering from MD [94–96], although the data are not fully consistent [97].

COX-2 Inhibition as an Example for an Anti-Inflammatory Therapeutic Approach in MD

COX-2 inhibitors influence the CNS serotonergic system, either directly or via CNS immune mechanisms. In a rat model, treatment with rofecoxib was followed by an increase of serotonin in the frontal and the temporoparietal cortex [98]. Therefore, COX-2 inhibitors would be expected to show a clinical antidepressant effect. In the depression animal model of the bulbectomized rat, a decrease in hypothalamic cytokine levels and a change in behavior have been observed after chronic celecoxib treatment [99]. In another animal model of depression, however, the mixed COX-1/COX-2 inhibitor acetylsalicylic acid showed an additional antidepressant effect by accelerating the antidepressant effect of fluoxetine [100]. A significant therapeutic effect of the COX-2 inhibitor celecoxib in MD was also found in a randomized, double-blind pilot add-on study of reboxetine and celecoxib versus reboxetine versus placebo [101]. Interestingly, the ratio of kynurenine to tryptophan, which represents the activity of the proinflammatory cytokine-driven enzyme IDO, predicted the antidepressant response to the celecoxib therapy. Patients with a high activity of IDO, i.e. a high proinflammatory activity, responded better to celecoxib [Müller et al., submitted]. Another randomized, double-blind study in 50 depressed patients suffering from MD also showed a significantly better outcome with the COX-2 inhibitor celecoxib plus fluoxetine than with fluoxetine alone [102, 103]. This finding was recently replicated using the combination of sertraline and celecoxib in 40 depressed patients [103]. Interestingly, the blood levels of IL-6 predicted the antidepressant response both in the sertraline (plus placebo) group and in the celecoxib (plus sertraline) group.

The anti-TNF-α antibody infliximab, which blocks the interaction of TNF-α with cell-surface receptors and was developed for the therapy of inflammatory joint disorders and psoriasis, showed a highly significant effect on symptoms of depression in psoriasis patients [104]. In a placebo-controlled add-on study using infliximab, however, an overall antidepressant effect could not be shown in a study of treatment-resistant depressed patients. Three infusions of infliximab or placebo were given in a 12-week trial (n = 60) in partly medication-free (n = 23) nonresponders to antidepressant therapy. No overall better outcome of infliximab versus placebo could be shown. There was, however, a significant interaction between treatment, time and baseline CRP (≤5 mg/l): patients with higher baseline CRP had a higher response rate to infliximab (62%) versus placebo (33%). Moreover, the baseline concentrations of TNF-α, sTNFR1 and sTNFR2 were significantly higher in infliximab responders ($p \leq 0.01$). Additionally, infliximab responders exhibited a significantly higher decrease of CRP ($p \leq 0.01$) than nonresponders [105]. Interestingly, there are also preliminary

findings that the angiotensin II AT1 receptor blockade has anti-inflammatory effects in the CNS and ameliorates stress, anxiety and CNS inflammation [106, 107].

Inflammatory Pathogenesis in MD and Schizophrenia – The End of the Kraepelinian Dichotomy?

The Kraepelinian dichotomy of schizophrenia and affective disorder has been discussed for many years. Several findings of modern biological psychiatry show an overlap of both disorders and genetic researchers postulate, in particular, that new diagnostic classifications which have greater biological validity will in the future allow the selection of treatments based on the underlying pathogenesis [108]. With respect to the mechanisms of inflammation, different patterns of type 1 and type 2 immune activation seem to be associated with schizophrenia versus MD [109]. The large table of immune and inflammatory genes involved makes it plausible that various types of immune balance may be involved. Differences in immune activation may have different impacts on the IDO activation and the tryptophan/kynurenine metabolism, which then may result in increased production of kynurenic acid in schizophrenia and increased quinolinic acid levels in depression. Such differences may be associated with an imbalance in the glutamatergic neurotransmission, contributing to an exaggerated NMDA activity in depression and NMDA antagonism in schizophrenia. Moreover, differential activation of microglia cells and astrocytes in schizophrenia and depression may be an additional mechanism to increased production of PGE2 and increased expression of COX-2.

Although there is strong evidence for the view that the interactions of the immune system, IDO, serotonergic system and glutamatergic neurotransmission play a key role in schizophrenia and depression, several gaps, for example the roles of genetics, disease course, sex, different psychopathological states, etc., have to be bridged by further intense research. Moreover, COX-2 inhibition is only one example of possible therapeutic mechanisms acting on these mechanisms. Also, the effects of COX-2 inhibition in the CNS as well as the different components of the inflammatory system, the kynurenine metabolism and the glutamatergic neurotransmission need further careful scientific evaluation.

Moreover, similar pathological influences may lead to different psychopathological states due to different localizations of the pathological processes in the CNS. Neuropathological and neuroimaging studies show that – albeit with a broad range of overlap – different brain regions are involved in schizophrenia (e.g. the hippocampus [110, 111]) and depression (e.g. the habenula [112, 113]).

Despite some common pathways, different final pathways may lead to different syndromes of schizophrenia and depression. Inflammation, including low-grade inflammation, is a general pathway of the body representing a response to a lot of different noxae and pathogens. Despite some overlap, which is apparent between pathophysiological mechanisms identified in schizophrenia and affective disorders, the differential mechanisms are also of major interest. Similar phenomena, overlap and some specificity are found in medicine in general, and not only in psychiatry. To develop preventive strategies in high-risk individuals and patients [114], such refined understanding is of immense interest.

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