Anti-Inflammatory Drugs in Psychiatry

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Abstract: Nervous and immune system interact through many different messenger substances such as neurotransmitters, cytokines or neuropeptides. For instance, neuropeptides are capable of affecting the metabolism of cells belonging to the immune system. Conversely, cytokines such as tumor necrosis factor (TNF)-α, interferon (IFN)-α and IFN-γ, contribute to the receptor resistance of neuropeptides, reduce the availibility of amino acids which are needed for the synthesis of neurotransmitters or show neurotoxic effects. Other cytokines like granulocyte-colony stimulating factor (G-CSF) may be highly attractive candidates for the treatment of neurodegenerative conditions.

Cytokines are decisively involved in the pathophysiology of psychiatric disorders such as depression, schizophrenia or anorexia nervosa as well as in neurological, respectively neurodegenerative diseases like Parkinson's or Alzheimer's.

This connection between the immune system and the pathogenesis of psychiatric disorders leads to the concept that immunomodulatory drugs which are already in use for various diseases related to the immune system may also be efficient in the treatment of psychiatric disorders.

This article is supposed to give an overview over the current concepts and possibilities since hopefully these hypotheses lead to new therapeutical strategies for psychiatric patients in the future.

Keywords: Schizophrenia, narcolepsy, depression, dementia, anorexia nervosa, TNF-α, IFN-α, IFN-γ, G-CSF.

INTRODUCTION

Innate and Adaptive Immune System

The human immune system is divided into two major components: the innate immune system and the adaptive immune system. The innate immune system provides an immediate, but non-specific response. Natural killer cells, mast cells, eosinophils, basophils, and the phagocytic cells including macrophages, neutrophils and dendritic cells belong to the innate immune system. They are able to immediately identify and eliminate pathogens and influence the response of the adaptive immune system through the production of cytokines and the modulation of the cytokine system [1]. Interferon (IFN)-α, for example is a cytokine of the innate immune system which plays an essential role in antiviral innate immunity [2] by directly inhibiting viral replication in infected cells [3] and subsequently triggering adaptive T cell-mediated immunity of the adaptive immune system [4, 5].

The adaptive immune system allows for a stronger and more specific immune response as well as immunological memory [6]. The cells of the adaptive immune system are lymphocytes of which B cells and T cells are the major types [7].

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B Cells

B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response. Both B cells and T cells carry receptor molecules that recognize specific targets. Important B cells are plasma cells which secrete antibodies, B lymphocytes as their precursor cells and B memory cells. The B cell antigen-specific receptor is an antibody molecule on the B cell surface, and recognizes whole pathogens without any need for antigen processing [7].

T Cells

T cells can be distinguished from other lymphocyte types, such as B cells and natural killer cells by the presence of the T cell receptor (TCR). With some exceptions, T cells recognize targets only after having been processed and presented in combination with a so called major histocompatibility complex (MHC) molecule. Several different subsets of T cells have been discovered: Helper T cells (Th), cytotoxic T cells, memory T cells, regulatory T cells (Treg), natural killer T cells and γδ T cells.

As Th cells and Tregs act as regulators of the immune response and therefore modulate the production of cytokines, the messengers of the immune system, these cells are of specific interest for the interaction between the immune and the central nervous system (CNS).

Depending on their cytokine production pattern Th cells are divided into two subgroups: Th1 cells secreting mainly the type 1 cytokines interleukin (IL)-2, IFN-γ and tumor

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necrosis factor-α (TNF-α). Important cytokines produced by the Th2 cell line are IL-4, IL-5 and IL-10. Type 1 and type 2 cytokines antagonize each other. Type 1 cytokines mainly activate the cell mediated immune response against viruses and bacteria, whilst type 2 cytokines support B cell maturation and the humoral immune response against arthropods and helminths [8]. As a pathophysiological and unwanted reaction, type 2 cytokines can contribute to allergic reactions such as skin reactions to the mood stabilizers carbamazepine and lamotrigine [9].

Recently, a subset of T helper cells, the Th17 cells, which produce IL-17 was discovered. They are considered developmentally distinct from Th1 and Th2 cells and are thought to play a key role in autoimmune disease [10, 11]. Specifically, they are thought to play a role in tissue injury in these conditions [12]. The natural role of Th17 cells is suggested by studies which have demonstrated preferential induction of IL-17 in cases of host infection with various bacterial and fungal species. IL-17 is involved in the recruitment, activation and migration of neutrophils. These cells also secrete IL-21 and IL-22 [13].

Cytokines

As mentioned before, signal molecules for the communication between immune cells are the cytokines. Those are most useful in clinical and experimental practice classified into type 1 and type 2 cytokines. However, this classification does not cover all kinds of cytokines.

Cytokines are not only produced in the peripheral blood and the lymphatic organs but also in the CNS, for example by astrocytes and cells of the microglia [14, 15]. Cytokines produced within the CNS include IL-1, IL-6, IFN-γ and TNF-α. Increased concentrations of IL-1, IL-6 and TNF-α are found in injured brain areals, infections, stroke and cerebral inflammatory and neurodegenerative diseases and can lead to apoptotic processes as well as reduction of synaptical functions and hippocampal neurogenesis [8]. Microglia are activated in most pathological conditions of the CNS and play an important role in sensing and propagating inflammatory signals in response to activation of the peripheral innate immune system [16].

Influence of Cytokines on Neurotransmission and Nerve Cell Integrity

Additionally to the type 1 and 2 cytokines we already mentioned the cytokines of the innate immune response of which IFN-α is an example with antiviral and antiproliferative activities. IFN-α is therefore used to treat infectious diseases and cancer [17, 18]. Although an effective therapy, IFN-α induces high rates of behavioral disturbance, including depression, which develops to a clinically significant degree in 30% to 50% of IFN-α-treated patients [19]. And it could be shown that a peripherally administered cytokine can activate a CNS inflammatory response in humans that interacts with serotonin metabolism, which is associated with depression [20].

Granulocyte colony-stimulating factor (G-CSF) is another cytokine not to be easily assignable to type 1 or 2 cytokines. It is produced by a number of different tissues to stimulate the bone marrow to produce granulocytes and stem cells. It also stimulates the survival, proliferation, differentiation, and function of neutrophil precursors and mature neutrophils. In recent years, a novel spectrum of activities of G-CSF in the CNS has been uncovered. G-CSF and its receptor are expressed by neurons in many brain regions, and are upregulated upon experimental stroke. In neurons, G-CSF acts anti-apoptotically by activating several protective pathways. *In vivo*, G-CSF decreases infarct volumes in acute stroke models in rodents. Moreover, G-CSF stimulates neuronal differentiation of adult neural stem cells in the brain, and improves long-term recovery in more chronic stroke models. Thus, G-CSF may be a highly attractive candidate for the treatment of neurodegenerative conditions [21].

Chronic inflammation is often associated with clinical depression [22, 23]. Recent studies have focused on potential mechanisms that might link inflammation-induced depression to tryptophan metabolism, particularly in the brain, where a reduction in the bioavailability of tryptophan could affect serotoninergic neurotransmission and play a synergistic role in the induction of depressive symptoms [24]. A pivotal protein that has recently been shown to be required for development of inflammation-induced depressive-like behavior is indoleamine 2,3-dioxygenase (IDO), the first rate-limiting tryptophan-degrading enzyme in the kynurenine pathway [25]. Activation of this enzyme by type 1 cytokines and INF-α leads to an increase in the kynurenine/tryptophan ratio in plasma and the generation of neuroactive mediators, including 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN) [26]. High levels of 3-HK and QUIN induce neuronal damage *via* oxidative stress [27] and overstimulation of N-methyl-d-aspartate (NMDA) receptors [26, 28].

In animal studies, inhibition of IDO abrogates depressive-like behaviors induced by acute [29] or chronic inflammation [30]. IFN-γ is the predominant cytokine implicated in the induction of IDO [31]. However, subsequent studies have identified IFN-γ-independent pathways, including TNF-α and lipopolysaccharide (LPS), which are capable of inducing IDO activity [32].

It has additionally been shown that LPS induces IDO expression *via* an IFN-γ-independent mechanism that depends upon activation of c-Jun-N-terminal kinase (JNK) of the microglia. And it has been suggested that an inhibition of the JNK pathway may provide a new therapy for inflammatory depression [33].

IMMUNOLOGY OF PSYCHIATRIC DISORDERS

Several psychiatric disorders are reported to be associated with alterations of the cytokine system. In this article, hypotheses regarding associations of major depression, schizophrenia, narcolepsy, Alzheimer's disease (AD) and anorexia nervosa (AN) with immunological pathogenetic concepts are demonstrated. Additionally, one should keep in mind that in addition to AD and narcolepsy cytokine alterations, especially changes regarding the TNF-α system, are involved in the pathogenesis of other neurodegenerative disorders such as multiple sclerosis (MS) or Parkinson's disease (PD) [34].

Depression

Major depression is an affective disorder (or mood disorder) and the most common psyciatric disease. Typical symptoms are sadness, reduced interests and activity, mnestic deficits, sleep and weight changes. Depression has a high global prevalence even in comparison to all diseases in general. The global prevalence differs between 6% and 16% according to race, age, gender, and social factors like education, marital status or income. Compared to men the prevalence of women is twice as high [35].

Modern neurobiological methods have revealed pathophysiological mechanism associated with depression. The monoamine hypothesis, which was advocated in the 1950s, emphasizes that the deficiency of monoamine neurotransmitters, for example serotonin, brings about depressive symptoms. This theory played an important role in promoting the development of new antidepressants and it is underlined by genetic findings of polymorphisms of serotonin transporter gene associated with depression. Neuroendocrine studies have revealed the hypothalamo-pituitary-adrenocortical (HPA) axis dysfunctions in depressive patients and increased activity of HPA axis are considered as state marker of depression [36]. Several findings indicate an influence of pro-inflammatory cytokines such as IL-1, TNF-α, IFN-α and IFN-γ on serotonin metabolism as well as on the HPA axis.

Alterations in plasma cytokine levels have repeatedly been found in patients suffering from affective disorders [37, 38], and evidence suggests that cytokines may be involved in the development of depression [39].

It has been postulated that the activation of the cytokine system might play a causative role in the depression-related activation of the HPA system [40], and experimental studies applying immune stimulation in humans [41] as well as in rodents [3] showed that immune stimulation induces depression-like signs and symptoms supporting the view that inflammatory cytokines are causally involved in behavioral alterations of patients with depressive disorders.

In contrast, Schuld *et al*. reported data suggesting that chronic HPA system overactivity in depressed patients suppresses the production of inflammatory cytokines [42]. In another study on the mutual influence of the HPA system and the TNF-α system in depressed patients without inflammatory diseases, TNF-α levels were inversely associated with the adrenocorticotropic hormone (ACTH) response to the combined dexamethasone/corticotropin-releasing hormone (dex/CRH) test and it was concluded that elevated HPA axis activity in acute depression suppresses TNF-α system activity [43]. Therefore, the activated HPA axis in depressed patients seems to suppress the activity of the cytokine system.

As pro-inflammatory cytokines and serotonergic homeostasis have both been implicated in the pathophysiology of major psychiatric disorders, Zhu *et al*. hypothesized that cytokines might also activate neuronal serotonin transporters [44]. This idea would underline the theory of a serotonin deficiency during depression and the pharmacodynamic mechanism of selective serotonin reuptake inhibitors (SSRI) in the treatment of depression, because SSRIs lead to recovery from depression *via* deactivation of serotonin transporters. Indeed, Zhu *et al*. found that IL-1 and TNF-α stimulated serotonin uptake in both a rat embryonic raphe cell line and in mouse midbrain and striatal synaptosomes. These results provided evidence that pro-inflammatory cytokines can acutely regulate neuronal serotonin transporter activity. A mitogen-activated protein kinase may be involved in this mechanism [44].

Pro-inflammatory cytokines such as IL-1, IFN-α, IFN-γ and TNF-α affect the tryptophan metabolism directly or indirectly by stimulating the IDO which leads to a peripheral depletion of tryptophan [45]. And the aromatic amino acid tryptophan functions as precursor for the monoamine neurotransmitter serotonin in the brain.

Therefore, we can hypothesize three mechanisms how cytokines may lead to depression or depressive symptoms: the activation of the HPA axis, the activation of neuronal serotonin transporters and the stimulation of the IDO which leads to tryptophan depletion. To date, it is not clear which of these mechanisms plays the main role in the pathophysiological connection between cytokines and depression.

Several data from *ex vivo* studies suggest that antidepressants suppress pro-inflammatory cytokine production; and it was hypothesized that this suppression may be result in an improvement of depressive symptoms [46].

An immunomodulatory treatment approach is cyclooxygenase-2 (COX-2) inhibitors [47]. In a double-blind, randomized and placebo-controlled study Müller *et al*. could show a significant better improvement of symptoms in depressive patients after six weeks under therapy with reboxetine and celecoxib as add-on than under therapy with reboxetine alone [48]. Furthermore, celecoxib shows beneficial aspects in the treatment of bipolar disorders regarding both depressive and manic episodes [49, 50].

Another possibility of immunological treatment of depression involves the concept of TNF-α blockage. For example, Tyring *et al.* assessed the effect of etanercept on symptoms of depression associated with psoriasis. 618 patients with moderate to severe psoriasis received double-blind treatment with placebo or 50 mg twice-weekly etanercept. In this study, greater proportions of patients receiving etanercept had at least a 50% improvement in the depression measurement questionnaires Hamilton Depression Rating Scale or Beck depression inventory at the endpoint of the study; patients treated with etanercept also had significant and clinically meaningful improvements in fatigue. The improvements in symptoms of depression were less correlated with objective measures of skin clearance or joint pain. The authors concluded that etanercept treatment might relieve symptoms of depression associated with this chronic disease psoriasis [51].

Schizophrenia

Schizophrenia is a severe mental disorder characterized by abnormalities of the perception. It is associated with acoustic and visual halluzinations, paranoid delusion and disorganized speech and behavior. The global lifetime prevalence is around 4% [52].

As in depression, immunological aspects regarding the pathogenesis of schizophrenia play an important role.

Among genetic influences complications during pregnancy and perinatal infections increase the vulnarability for later onset of psychotic diseases such as schizophrenia. Infections and traumata are capable of inducing changes of the cytokine system which again influences the growth of neurons and glia cells. Mothers, whose children suffer from schizophrenia in adolescence, showed a significant increase of IL-8 plasma levels during the second trimenon [53]. Some other studies showed the relation between sexual transmitted diseases, other infectious diseases like toxoplasmosis, or diseases caused of pathogens like herpes or influenza virus during pregnancy and the higher risk for the child to develop schizophrenia later on [54-57]. Infections of the CNS also increase the risk for later schizophrenia [58].

Patients suffering from schizophrenia have a reduced in-vitro production of IL-2 and decreased plasma levels of IFN-γ caused by their reduced type 1 immune response. Unlikely, the type 2 response is activated: cytokines of the type 2 immune response are elevated, e.g. IL-6 plasma levels or IL-4 cerebral spinal fluid levels [59]. The increase of IL-10 levels within the cerebral spinal fluid of schizophrenic patients seems to be associated with the severity of the psychotic symptoms [60].

The functional consequences to which the imbalance of the type 1 and type 2 immune response leads are described in a review about immunological aspects in schizophrenia by Müller *et al*. [61]: on the one hand, the imbalance is carried forward to important key enzymes of the tryptophan-kynurenin metabolism – the IDO and the tryptophan-2,3-dioxygenase (TDO). In contrast, astrocytes are activated and microglia degenerates. Astrocytes are the main source of kynurenic acid, however, the cells of the microglia are able to catabolize intermediates of the tryptophan-kynurenin metabolism to quinoline acid. Finally the described imbalance leads to an accumulation of kynurenic acid, an endogenous antagonist of the NMDA and nicotine-acetylcholin receptor, in the CNS [62]. Increased plasma levels of kynurenic acid are described in the cerebral spinal fluid [63] and prefrontal cortex [64] of schizophrenic patients.

Via the NDMA-antagonism kynurenic acid has an activating influence to important dopaminergic regions of the brain regarding schizophrenia. The antagonism on nicotinergic acetylcholine receptors is discussed to be associated with cognitive deficits.

In reference to the described imbalance of the type 1 and type 2 immune response, drugs with the ability of adjusting this imbalance are of special interest. There is evidence that COX-2 inhibitors reduce the level of kynurenic acid [65, 47]. A therapeutical effect, respectively cognitive improvements, could be shown in a randomized double-blind study using the COX-2 inhibitor celecoxib as add-on to risperidone [66], whereupon it is not quite clear if the reason for this result may be due to a COX-2 independent mechanism [67]. Besides, a direct anti-inflammatory effect of risperidone itself is described by Kato *et al*. [68].

However, there are newer studies that try to disprove the theory of Müller *et al.* [69] or the influence of celecoxib to the cytokine system [70].

Altogether the exact immunological pathomechanism of schizophrenia is not known yet, but there is evidence of an involvement of immunologogical processes in the developement and characteristics of schizophrenia. Probably the influence of many different factors like antipsychotic drugs, disease progression (chronic residuum or exacerbation), immunological status of the patient and many more complicate the developement of a consistent theory regarding the role of the cytokine and therefore immune system in schizophrenia.

Narkolepsy

Narcolepsy is a disabling sleep disorder characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucination, and sleep paralysis [71]. Worldwide about three million people are affected. With a prevalence of 0.04% it is rare, even among the sleeping disorders [72].

Since the discovery of the extremely close association of narcolepsy and the human leukocyte antigen HLA-DR2 [73] it has been suggested that the immune system might play a pathogenic role, because it is known that HLA haplotypes are linked to a number of autoimmune diseases [74]. In human narcoleptics, a dramatic reduction in the number of hypocretin neurons could be observed [75]. Because of the association of narcolepsy with HLA-DR2, it was hypothesized that the loss of these neurons might be caused by an autoimmune process [76].

Furthermore, a small number of studies suggest that certain cytokine-producing genes may predispose to narcolepsy. Hohjoh *et al*. [77] conducted an association study of the TNF-R p75 polymorphisms with human narcolepsy and found that the 196 R allele was significantly more frequent in narcoleptic patients suggesting that this allele is associated with the susceptibility to narcolepsy.

In a sample of 30 narcoleptic patients in comparison to 120 gender- and age-matched and 101 gender-, body mass index (BMI)- and age-matched randomly selected normal controls, sTNF-R p75 levels were consistently elevated in the narcoleptic patients, even if compared to gender-, BMI- and age-matched counterparts. It was concluded that narcoleptic patients show increased plasma levels of sTNF-R p75 suggesting a functional alteration of the TNF-α cytokine system and further corroborating a possible pathogenic role of the immune system in this sleep disorder [78]. One possible hypothesis would be that the activation of the TNF-α system and a sTNF-R p75-mediated activation of cells of the immune system would lead to an autoimmune destruction of hypocretin neurons, which seems to be strongly associated with the development of narcolepsy. This destruction may involve Ths, cytotoxic T cells and lymphocytes.

The common therapy of narcolepsy which is counted among the neurodegenerative diseases due to an autoimmune mediated destruction of hypocretin orexin cells in the hypothalamus are stimulating drugs such as methylphenidate or modafinil, tricyclic antidepressants or SSRIs (among conservative procedures such as sleep hygiene or coping strategies). Nevertheless, there is a promising experimental study with immunoglobulins in which four patients with hypocretin/orexin-deficient narcolepsy were treated with intravenous immunoglobulins and showed improvements regarding the frequency and severity of cataplexy controlled through polysomnographies and questionnaires [79].

Alzheimer's Disease

AD is a progressive neurodegenrative disorder which presents clinically with dementia. Its world prevalence is increasing. The number of people affected with dementia in general doubles every 20 years. Today 24 to 30 million people worldwide have dementia [80], two-thirds of those cases are likely AD.

Accumlutaion of neurofibrils, amyloid plaques and the destruction of neurons play a central role in the pathogenesis of this type of dementia which is the most common in elderly people. It seems that amyloid plaques consisting mainly of Aβ42, trigger neuroinflammatory processes that lead to a modified production of cytokines based on microglia and astrocytes activation [8].

Microglia produces IL-1 which is involved in the neurotoxic cascade. Variants of the IL- 1 gene are associated with a higher risk to develop AD [81,82]. But the role of IL-1 stays unknown: On the one hand, AD is attended by an overexpression of IL-1β which leads to an increase of phosphorylized tau protein - an important diagnostic marker of AD [83]. On the other hand, possible protective effects of IL-1β were discussed in the literature [84, 85].

AD is also associated with increased plasma levels of TNF-α [86-88]. Thereby TNF-α is presumably not only increased due to the disease, but is involved in the developement of AD itself.

Due to the theory that TNF-α is involved in the developement of AD, it could be shown that spinal treatment of 15 patients diagnosed positive for Alzeimer's with the TNF-α antagonist etanercept which is normally used in the therapy of rheumatic disorders and psoriasis, improved regarding their associated symptoms [89]. In animal experiments with transgene mice it could be shown that the genetic deletion of TNF-α receptor 1 or the pharmacological blockade of TNF-α itself lead to a decreased amyloid plaque accumulation in the brain and therefore to a reduction of learning and memory deficits [90, 91].

Further therapy strategies regarding the treatment of AD turn directly against the amyloid plaque accumulation including basically three mechanisms: the catalytic conversion of Aβ42 fibrils to less toxic forms, the opsonization of Aβ42 which leads to microglial phagozytosis and the evacuation of Aβ42 into the blood circulation.

There are epidemiologic data and clinical studies evidencing the risk reduction to develop AD during the treatment with non steroidal anti-inflammatory drugs (NSAID) [92]. Among the treatment with NSAID and cytokine antagonists experimental immunological therapies include today the application of immunglobulines and the active immunization against Aβ42 [8].

Nonetheless, in a multicenter, randomized, double-blind and placebo-controlled study by Soininen *et al*. [93] no improvement of cognitive functions could be shown for the therapy of mild to moderate AD diagnosed patients with 200 mg of celecoxib. The COX-2 selective inhibitor was not capable of slowing down the progression of AD compared to the placebo group [93].

Gilman *et al*. described 2005 the first placebo-controlled study regarding the vaccination against AD. The trial had to be interrupted because of the appearance of several cases of meningoencephalitis [94].

As mentioned before, G-CSF stimulates neuronal differentiation of adult neural stem cells in the brain. Thus, G-CSF may be a highly attractive candidate for the treatment of neurodegenerative conditions such as AD [21].

Anorexia Nervosa

AN is a common disorder among young white females characterized by abnormal eating behavior, weight regulation, and disturbances in attitudes and perceptions toward body weight and shape. Its prevalence ranges among adolescent and young women from 1 to 15%, the average prevalence rate for AN in the whole population is 0.3 % [95, 96]. The prognosis of AN remains poor, as mortality rates of 5 to 22% have been reported, mainly due to medical complications resulting from starvation and suicide [97].

Baranowska *et al.* [98] repeatedly found low plasma concentrations of neuropeptide Y (NPY) in anorectic patients, which is an orexigenic signal. This phenomenon can not be a consequence of starvation. Moreover, it may be explained by the finding that plasma concentrations TNF-α and its soluble receptor were found to be significantly higher in anorectic patients than in controls, and these remained altered even after weight restoration [99]. TNF-α is a cytokine that leads to weight loss [100]. In the general population, plasma levels of TNF-α and its receptors correlate significantly with the BMI, as they are produced from macrophages within the white fat tissue as a compensatory anorexigenic signal [101]. TNF-α additionally causes depressed mood [38]. Therefore, TNF-α may be a cause for weight loss as well as mood disturbances in anorectic patients. TNF-α, in turn, is known to inhibit the NPY orexigenic network, which is the reason why Inui *et al.* suggested these molecules as causal player in the pathophysiology of AN [102]. With this regard, we would like to mention that TNF-α gene promoter polymorphism at position -308 might be associated with a predisposition to AN and initiate the disease [103].

Considering TNF-α, one has to question why there are only a few studies available regarding AN and cytokines, although some cytokine alterations such as decreased levels of IL-2 and transforming growth factor (TGF)-β2 are described [104], and although cytokines as well as cytokine blockers are currently available drugs. Therefore, one has to question whether it would be worth trying a TNF-α blocker for the treatment of AN. But as anorectic patients are at higher risk for catching infectious diseases, one has to be very careful with drugs being additionally immunosuppressive.

IMMUNOLOGICAL EFFECTS INDUCED BY PSYCHOTROPIC DRUGS

One common side effect that can be seen in patients treated psychopharmacologically, is weight gain. This clinically important problem is seen under treatment with antidepressant as well as with antipsychotic drugs.

There have been many studies in the last few years regarding neuroendocrine and neuroimmunological mechanisms which are a part of appetite and weight regulation. Apparently, the TNF-α system seems to be involved, too: Every analyzed drug that leads to weight gain, like clozapine, olanzapine, amitryptiline or mirtazapine, activates the TNF-α system [105-108]. This activation leads to increased concentrations of sTNF-Rs and TNF-α plasma levels. The influence of mood stabilizers to the TNF-α system has been target of several studies: Carbamazepine and lithium leads to an increased in-vitro production of TNF-α of healthy persons [109] and while treated with carbamazepine, plasma levels of TNF-α, sTNF-R p55 and sTNF-R p75 rise significantly [110].

It stays ambigously wether the activation of the TNF-α system is the reason or the consequence of weight gain as a result of a psychopharmacological treatment. New data shows that adipose tissue is infiltrated of macrophages that might be the main source of inflammatory cytokines [111].

An activation of the TNF-α system seems to be specific to those drugs that induce weight gain, for drugs that hardly change body weight like haloperidole, paroxetine or venlafaxine, do not activate the TNF-α system [105, 106, 112]. Furthermore, bupropione which is used in antidepressant therapy and rather reduces body weight inhibits the TNF-α production at least in mice [113]. Studies regarding the effect of bupropione to the human TNF-α system are not published yet. Nevertheless, the increased activation level of the TNF-α system may not be an individual predictor of weight gain [114].

A second very common side effect of psychopharmacological treatment is the increase of liver enzyme plasma levels. All kinds of psychotropic drugs can be responsible and lead to liver damage [115]. In a naturalistic study with patients who were treated psychopharmacologically with a stable dose, the strongest increase of liver enzyme plasma levels could be shown for week three. The changings of the alanin-aminotranferase (ALAT) were significant positive correlated with alterations of the TNF-α plasma levels [116]. This leads to the assumption that the TNF-α system is involved in the psychopharmacologically induced increase of liver enzyme plasma levels, and therefore liver damage. Coercively, the significant correlation represented just a small part of the variance of the entire changings of the liver enzyme plasma levels which is not remarkable, for it is known that many different cytokines are involved in inflammation based changes of the liver structure [117-119].

TNF-α is one of the fundamental pyrogene molecules. Its induction does not only lead to an activation of the type 1 immune response, but also to alterations in the kynurenic acid metabolism and interference to the glutamatergic and dopaminergic systems [120]. Thus, the antipsychotic effect of certain neuroleptics like clozapine or olanzapine, might be as well accomplished by neuroimmunological changings including the activation of the TNF-α system [107, 108]. On the other hand, antidepressants reduce the type 1 immune response *in vitro* [121,122] which leads to the concept of antidepressive treatment through TNF-α blockage. As we reported several findings regarding the TNF-α system, Fig. (**1**) outlines the mentioned metabolic and neuroendocrine effects of TNF-α.

PERSPECTIVES

Immunological aspects of psychiatric and neurodegenrative disorders are evident. Therefore immunological treatment seems to be auspicious, at least as add-on therapy to established psychotropic drugs. Important studies regarding the effect of NSAID and COX-2 inhibitors to symptoms of depression and schizophrenia were introduced. In an animal model aspirin was described to show beneficial effects to the rigidity of parkinsonian rats.

Another rather new approach regarding immunological strategies against neurodegenerative disorders is the vaccination against AD with promising results, but unfortunately, the first placebo-controlled study was terminated due to the fact that 6% of the patients developed an aseptic meningoencephalitis [94, 123,124].

However, as TNF-α plays a significant role in the defense of diseases, one has to consider the side effects of blocking TNF-α signaling. An increased risk for malignancies or serious infections related to the use of TNF-α antagonists has been reported, and it has been recommended that clinicians should be aware of opportunistic infections such as tuberculosis, hystoplasmosis or Pneumocytes carinii in anti-TNF-α-treated patients [125-130]. In fact, a meta-analysis on the use of the TNF-α antagonists adalimumab and infliximab demonstrated a two-fold risk of serious infections [131], and an increased risk of developing lymphoma in patients treated with TNF-α antagonists has been observed [132, 133]. Additionally, there is evidence that patients treated with TNF-α antagonists have an increased risk of myocardial infarction [134] and cases have been reported of acute coronary syndrome after infliximab infusion therapy [135, 136]. Therefore, one has to take possible cardiovascular side effects into account while treating patients with TNF-α antagonists. Finally, three cases of progressive multifocal leucencephalopathy have been described as side effects of anti-cytokine therapy with natalizumab [137].

Besides these immunological issues, also psychiatric unintentional side effects are imaginable and described, such as the developement of a manic episode in a patient with psoriatic arthritis treated with etanercept [138].

This shows, that we are far away from using anti-cytokine therapy such as TNF-α antagonists as common drugs in psychopharmacological treatment, for there are reported severe side effects which make it necessary to prove the benefit versus the risk carefully in subject to individual risk profiles of patients.

Some pivotal elements of the immune system such as Tregs and Th17 cells have not yet been investigated in psychiatric patients. The referred studies are based on a partly obsolescent immunological concept that focuses on the Th1/Th2 balance, although the discovery of Tregs and Th17 cells have revolutionized the scientific opinion how the immune system is regulated. Therefore, the new immunological insights provide a broad spread of research perspectives in psychiatric neuroimmunology.

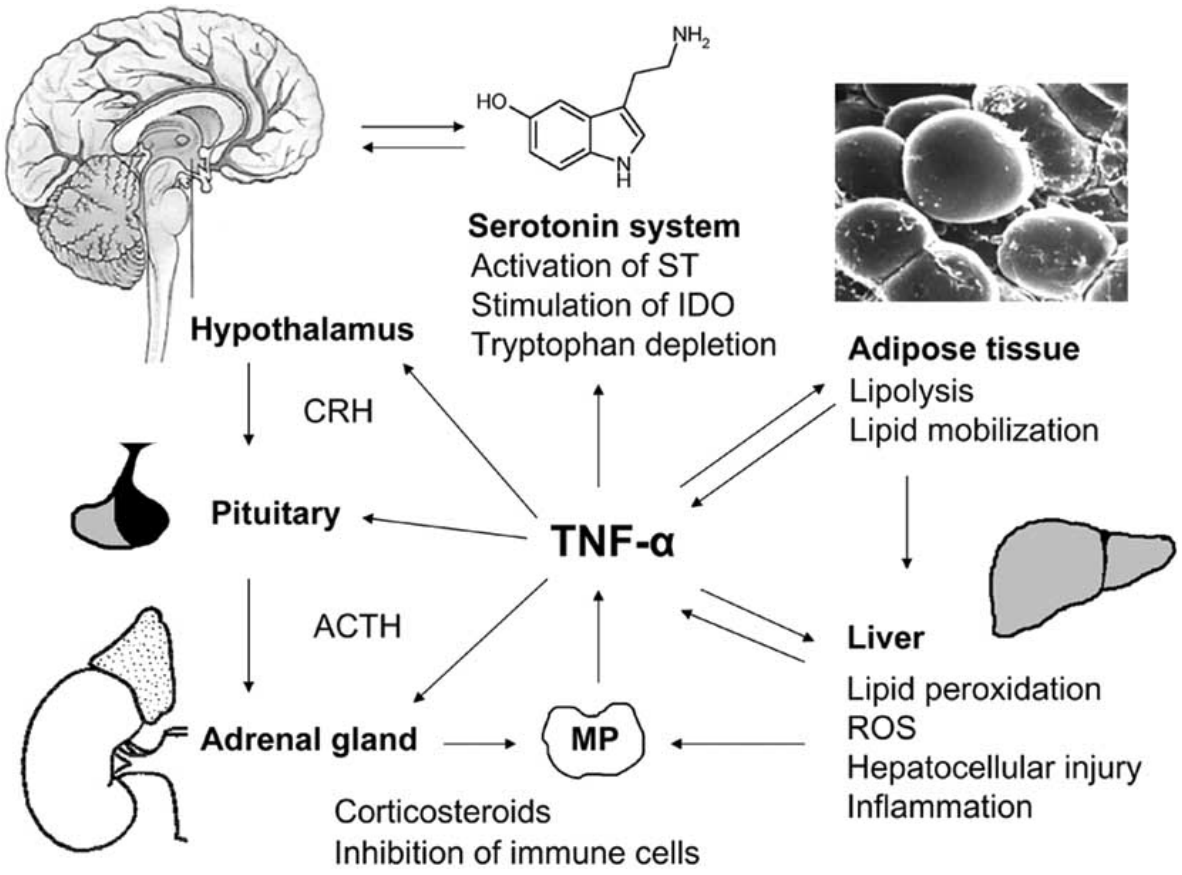

Fig. (1). Effects of TNF-α. TNF-α is secreted by macrophages during infection or inflammation. In obesity, the white adipose tissue increases production of TNF-α. TNF-α together with other cytokines activates the hypothalamo-pituitary-adrenocortical (HPA) axis resulting in the release of corticosteroids. Within the liver, TNF-α and fatty acids lead to the production of ROS and hepatocellular injury. TNF-α influences the serotonin system resulting in an enhanced serotonin reuptake and tryptophan depletion. For details see text. Abbreviations: tumor necrosis factor-alpha (TNF-α), macrophage (MP), corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), reactive oxygen species (ROS), indoleamine 2,3-dioxygenase (IDO), serotonin transporters (ST).

Table 1. Immunological Concepts of Psychiatric Disorders and their Potential Therapy

Psychiatric Disorder	Immunological Concepts	Potential Therapies
Depression	Imbalance of the type 1 and type 2 immune response with increased type 1 cytokine production such as TNF-α, IFN-α, IFN-γ and IL-1 Activation of the HPA system Activation of serotonin transporters Stimulation of the indoleamine 2,3-dioxygenase with tryptophan depletion	COX-2 inhibitors TNF-α blockers
Schizophrenia	Imbalance of the type 1 and type 2 immune response with increased type 2 cytokines (IL-4, IL-6, IL-10) and reduced type production (IL-2, IFN-γ)	COX-2 inhibitors
Narcolepsy	Autoimmune destruction of orexine neurons with participation of the TNF-α system	Immunoglobulines
Alzheimer's disease	Accumlutaion of neurofibrils, amyloid plaques (mainly Aβ42) and neuron destruction through modified cytokine production based on microglia and astrocytes activation	COX-2 inhibitors TNF-α blockers Active immunization Immunoglobulines G-CSF
Anorexia nervosa	Low plasma concentrations of NPY due to Activation of the TNF-α system	TNF-α blockers can not be recommended because of the high susceptibility for infectious diseases in anorectic patients

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