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REVIEW ARTICLE

Inflammation and Immune Regulation as Potential Drug Targets in Antidepressant Treatment

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Abstract: Growing evidence supports a mutual relationship between inflammation and major depression. A variety of mechanisms are outlined, indicating how inflammation may be involved in the pathogenesis, course and treatment of major depression. In particular, this review addresses 1) inflammatory cytokines as markers of depression and potential predictors of treatment response, 2) findings that cytokines interact with antidepressants and non-pharmacological antidepressive therapies, such as electroconvulsive therapy, deep brain stimulation and physical activity, 3) the influence of cytokines on the cytochrome (CYP) p450-system and drug efflux transporters, and 4) how cascades of inflammation might serve as antidepressant drug targets. A number of clinical trials have focused on agents with immunmodulatory properties in the treatment of depression, of which this review covers nonsteroidal anti-inflammatory drugs (NSAIDs), cytokine inhibitors, ketamine, polyunsaturated fatty acids, statins and curcumin. A perspective is also provided on possible future immune targets for antidepressant therapy, such as toll-like receptor-inhibitors, glycogen synthase kinase-3 inhibitors, oleanolic acid analogs and minocycline. Concluding from the available data, markers of inflammation may become relevant factors for more personalised planning and prediction of response of antidepressant treatment strategies. Agents with anti-inflammatory properties have the potential to serve as clinically relevant antidepressants. Further studies are required to better define and identify subgroups of patients responsive to inflammatory agents as well as to define optimal time points for treatment onset and duration.

Keywords: Biomarker, cytokines, curcumin, depression, infliximab, ketamine, treatment prediction.

1. INTRODUCTION

Major depression is a severe, potentially life threatening, high prevalence disorder, which is a leading cause of medical and economic disease related burden worldwide [1-3]. Currently, no more than half of the patients treated show a response, even less achieve remission from the depressive episode [4, 5]. Hence, intensified research on the neurobiology of depressive disorders and identification of factors relevant for therapeutic advances are vital for the improvement and addition of antidepressant treatment options. As one of the most rapidly growing fields in psychiatric research, mounting evidence supports a central involvement of the inflammatory system in the etiopathogenesis of depressive disorders. Increased knowledge about the regulation of pro- and anti-inflammatory cytokines as central mediators of the inflammatory response may support the development of immunity-based antidepressant agents, as alternatives to present day more transmitter-focused pharmacological approaches. Targeting cytokine regulation as a candidate mechanism in depression may further lead to improved prediction of therapeutic outcomes and the discovery of susceptibility factors for non-response. In addition to a comprehensive summary of current knowledge of molecular mechanisms of cytokine involvement in depression, this review provides an overview of the relationship between inflammation, pharmacokinetics and pharmacodynamics of drugs as well as the connection between cytokines, mechanisms of action of antidepressants and antidepressant treatment outcome. An overview of present immunomodulators as antidepressant agents is also presented. Potential future immunological agents in antidepressant therapy for which only experimental or little clinical data exist are discussed. Emphasis is given to the molecular basis of findings (Fig. **1**).

2. PATHOMECHANISMS OF CYTOKINES IN DEPRESSION

The "inflammation hypothesis" in depression is substantiated by findings that predominantly pro-inflammatory cytokines are over-expressed in the blood of depressed subjects [6-9]. Simultaneously, prolonged high concentrations of cytokines, up-regulated by different environmental, somatic and socio-behavioural factors, may increase the risk for the development of a depressive episode

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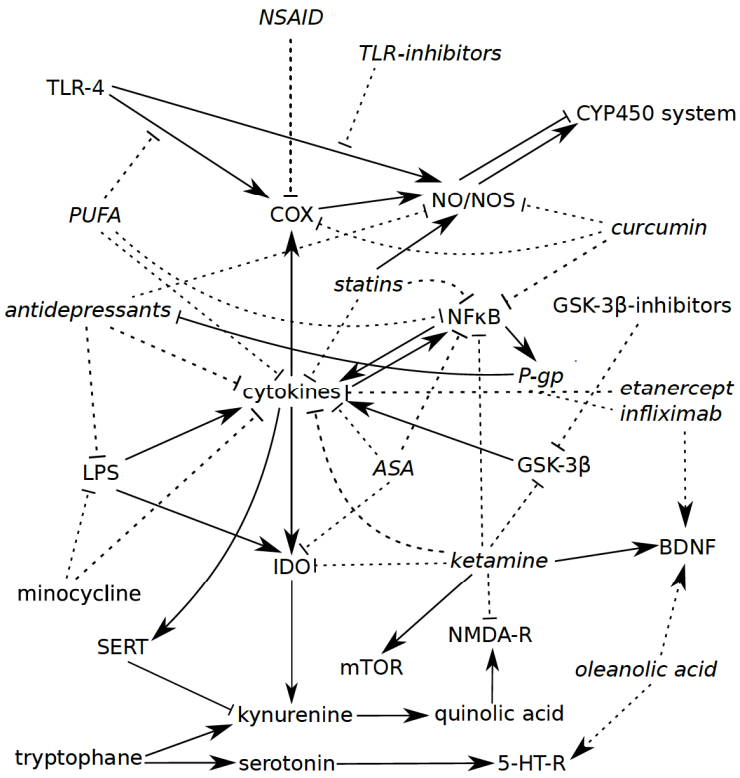

Fig. (1). Model of relevant pathomechanisms of inflammation and antidepressive drug targets in depressive disorders. Legend: ASA=acetylsalicylic acid, BDNF=brain-derived neurotrophic factor, COX=cyclooxygenase, CYP=cytochrome p-450 system, GSK-3=glycogen synthase kinase-3, 5-HT-R=serotonin receptors, IDO=indolamine-2,3-dioxygenase, LPS=lipopolysaccharide, NF-*κ*B=nuclear factor kappa-light-chain-enhancer of activated B-cells, P-gp=p-glycoprotein, NO=nitric oxide, NOS= nitric oxide synthase, NMDA-R=N-methyl-D-aspartate receptor, NSAID=nonsteroidal anti-inflammatory drugs, PUFA=polyunsaturated fatty acid, SERT=sensitive serotonin transporters, TLR=toll-like receptors. Arrows illustrate stimulation and activation, bars illustrate inhibition and blockade.

[10, 11]. Given that these relationships are not unequivocal, since not all subjects with high cytokine concentrations develop depressive symptoms and not all depressive patients exhibit elevated pro-inflammatory mediators, an inflammation and cytokine-associated subtype of depression has been recently proposed [12]. In subjects predisposed to depression, cytokines may exert pro-depressive effects in a number of ways: Cytokines induce indolamine-2,3-dioxygenase (IDO), which is involved in the metabolism of tryptophan to kynurenine and the increased transformation of kynurenine to neurotoxic quinolinic acid. A shift of tryptophan metabolism to kynurenine simultaneously reduces serotonin (5-HT) synthesis by tryptophan hydroxylase [13, 14]. Correspondingly, lipopolysaccharide (LPS)-induced inflammation results in both increase in IDO and depressive-like-behaviour whereas the blockade of IDO-activation prevents the development of depressive-like-behaviour [15]. Pro-inflammatory cytokines further negatively influence the active 5-HT fraction by up-regulating the activity and expression of antidepressant-sensitive serotonin transporters (SERT) [16, 17]. Cytokines lead to a disruption of the negative feedback loop of the HPA axis by stimulating the excessive release of corticotrophin-releasing hormone (CRH) and by facilitating glucocorticoid resistance [18, 19], with antidepressant response restoring the disturbed interaction between cytokines and the HPA-axis [20]. Cytokines also contribute to increased redox signalling of nitric oxide (NO) and NO synthase (NOS) which impairs antioxidant defence cascades relevant in depression [21, 22]. Cytokines may further be involved in decreased neuroplasticity and suppression of neurotrophic factors [23] and also related to cerebral structural alterations in depression [24].

3. THE INFLUENCE OF CYTOKINES ON PHARMACOKINETICS AND -DYNAMICS

The pharmacokinetic and -dynamic properties of an antidepressant drug are fundamental for its efficacy. Among the various responses to inflammation, cytokines have been shown to significantly affect drug metabolism as well as the transmission of drugs between cells and cell systems, especially the crossing of the blood brain barrier. In this section, we provide a selective overview of the connection between cytokines and the cytochrome p-450 (CYP) system and trans-membrane drug transport.

3.1. Inflammation and the Cytochrome p-450 System

The metabolism of the majority of antidepressants through deactivation and bioactivation relies on CYP enzymes, which are mainly located in hepatic and circulating peripheral blood mononuclear cells (PBMC) [25]. The variability of CYP-activity depends on several endogenous factors such as genetics, gender, age and morbidity as well as exogenous factors like smoking, co-medication and food

components. Moreover, the inflammation-state of an organism influences the expression and activity of CYP proteins. Since antidepressants are mainly metabolised by CYP enzymes 2D6, 1A2, 3A4 and 2C19 [26], the grade of inflammation may therefore impact on the bioavailability of a drug. Influencing PBMC could affect intracellular and systemic drug concentrations and bioavailability. *In-vitro*, the pro-inflammatory cytokines IL-2, IL-12 and IFN-γ lead to decreased expression of CYP2D6 and CYP3A4 in PBMC. Bertilsson and colleagues also showed that pro-inflammatory cytokines and macrophages decreased the mRNA expression of CYP3A4 [27]. Combined and separate application of IL-1ß, TNF-α and IFN-γ led to a marked decrease in CYP expression *via* activation of NO [28]. Further, an inverse relationship was found between the concentrations of TNF-α and IL-6 on the one side and CYP 2C19 on the other [29]. Based on the finding that these effects could be blocked by inhibitors of NOS and initiated by NO donors [30], it was concluded that NOS is one of the main contributor to the effects of the cytokines on the CYP system. Cytokines and cytokine modulators may act by alterations of transcription factor activity for CYP enzyme expression as well as changes in CYP enzyme stability [31]. As a limitation concerning the relevance of these findings in depression, the majority of studies on humans included patients with chronic inflammatory diseases or cardiovascular diseases who exhibit higher levels of pro-inflammatory cytokines than depressed subjects. Since the majority of studies revealed a cytokine-mediated blockade of CYP and since CYP mostly facilitates depletion rather than bioactivation of the majority of antidepressants, an increase in drug concentrations in depression may be expected. One exception is that the half-life of fluoxetine was significantly reduced when peginterferon-α-2b was added, indicating an accelerated depletion of fluoxetine [32]. Another recent investigation also did not detect an influence of inflammation, as defined by CRP blood levels, on serum concentrations of citalopram or venlafaxine [33]. However, overall few studies have addressed the relationship of cytokines, antidepressants and drug metabolism, limiting the transferability of the aforementioned results in the context of affective disorders and antidepressant treatment. Due to a lack of data, the assumption that altered CYP-activation may be of relevance for depressed patients with inflammatory co-morbidities, by being associated with more side effects during treatment with antidepressants [34, 35] remains hypothetical.

3.2. Impact of Inflammation on Trans-membrane Drug Transport

The blood brain barrier (BBB) is the largest obstacle to antidepressant drugs entering the central nervous system (CNS), amongst other mechanisms due to trans-membranous drug efflux transporters, which unload xenobiotics from endothelial cells back into the bloodstream. It is not well understood how cytokines influence the permeability of the BBB. In addition to involvement in the modification of tight junction structures, cytokines regulate endothelial signalling and the activity and expression of drug efflux transporters [36]. Variants of P-glycoprotein (P-gp), a product of the ATP-binding cassette (ABC) sub-family B (ABCB1)-transporter, pivotal for the transport of drugs and molecules across intra- and extra-cellular membranes, have been shown to be of relevance in antidepressant treatment outcome [37]. The expression of ABCB1-mRNA and -protein was found to be increased following cytokine stimulation, leading to reduced cellular accumulation of drugs [38, 39]. The expression of breast cancer related protein (BCRP), another important drug efflux transporter expressed on the BBB, was found reduced by IL-1ß, IL-6 and TNF-α [40]. Long-term stimulation with TNF-α increased the expression and activity of P-gp *via* nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-*κ*B), whereas short-term stimulation with a lower concentration of TNF-α led to a decrease of P-gp functioning [41]. IL-1 in contrast led to a continuous decrease in protein expression of both P-gp and BCRP [42]. The evidence that cytokines may affect drug efflux transporters, and also regulate P-gp drug-transporters in a time-and dose-dependent manner, is of potential relevance in antidepressant treatment strategies. This evidence suggests that both duration of depression and extent of inflammation influence the bioavailability of antidepressants.

4. THE RELATIONSHIP BETWEEN CYTOKINES AND DEPRESSION, ANTIDEPRESSANT TREATMENTS, AND PREDICTION OF ANTIDEPRESSANT DRUG RESPONSE

The following paragraphs summarise clinical and preclinical data indicating cytokine levels are altered in depressed subjects, relate to certain symptoms and symptom dimensions of depression, respond to drug administration, and are related to (and possibly predict) treatment outcome of antidepressant therapies.

4.1. Cytokine Levels and Depression

A large body of studies suggests both pro- and anti-inflammatory cytokines are up-regulated in depressive disorders. A number of cytokines have been investigated and found elevated, amongst them IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IFN-γ and granulocyte colony-stimulating factor (GM-CSF) [8, 43, 44]. Within the broad range of cytokines, the most extensively studied mediators are IL-1, IL-6 and TNF-α. Yet for these cytokines positive findings vary with two recent meta-analyses confirming higher levels of IL-6 and C-reactive protein (CRP) in patients with major depression and in patients at risk for depression [6, 45], whereas the association between TNF-α, IL-1β and major depression was not consistent [6]. A previous meta-analysis with medical co-morbidity as an exclusion criteria reported that blood levels of both IL-6 and TNF-α were elevated in depressed subjects [7]. Despite these reported increases in cytokines in selective populations, one may not infer that depression is associated with inflammation in all patients [46] but more probably a subtype of patients suffering from major depression [12]. There is no evidence of an across the board relationship between inflammation, depression and depressive symptoms given that the majority of patients suffering from inflammation do not exhibit a depressive syndrome and given the increased incidence for depression following treatment with cytokine-analogs [46, 47].

4.2. Antidepressants and Cytokines

Evidence is mounting that antidepressants not only exert their effect on depression by regulating neurotransmitters but also have immunosuppressive and anti-inflammatory properties. Lines of evidence suggest that pro-inflammatory cytokine production is affected by antidepressant treatment. A recent meta-analysis revealed that persistent elevations of TNF-α were associated with poorer clinical outcome of antidepressant treatment in depressed subjects [48]. It was further concluded that antidepressant therapy leads to a decrease of IL-6 independent of clinical outcome, pointing towards a general and clinically non-specific suppression of inflammatory activity during therapy [48]. At variance with these results, a previous meta-analysis found significant changes, not in TNF-α, but in IL-1 and IL-6 during therapy [49]. After 12-weeks treatment, levels of various cytokines significantly decreased, with no greater difference in those patients achieving remission from depression compared to non-depressed subjects [43]. A possible explanation was proposed based on findings that antidepressant treatment induced the up-regulation of regulatory T cells that may in turn down-regulate cytokine production, as observed by decreases in IL-1 levels [50]. Another mode of action could be the modulation of IDO during antidepressant therapy. The changes in IDO further correlated with improvement in depression severity [14]. Several preclinical studies supported the impact of a range of drugs on pro-inflammatory cytokines: In rats, imipramine and fluoxetine administration led to decreased TNF-α and IL-1ß levels as well as TNF-α and IL-1ß mRNA expression in microglia cultures [51]. Paroxetine administration reduced microglia-mediated neurotoxicity, potentially by reducing the activity of NOS and by reducing levels and mRNA of TNF-α and IL-1ß [52]. Amitryptiline further reduced NO production, TNF-α and IL-1ß-levels [53]. Chronic stress and LPS-stimulation in rats led to increased expression of TNF-α and IL-6 that could be reversed by mianserin [54]. Despite these observations of predominantly drug-induced reductions, venlafaxine administration reduced concentrations of pro-inflammatory cytokines, whereas sertraline increased the concentrations of IFN-α and IL-6. Further, irrespective of whether they led to increased or decreased concentrations of pro-inflammatory cytokines, both antidepressants induced decreased activity of NF-κB [55]. *In-vitro*-analyses of human blood samples also showed that antidepressants as a class did not unidirectionally lower cytokine concentrations but variously increased or decreased cytokine levels, depending on the antidepressant administered [56]. The mood-stabilizer lithium, alone and in combination with antidepressants, was shown to lead to an increased secretion of pro-inflammatory cytokines, which may possibly contribute to side effects of the drug and to the beneficial effects in diseases associated with immunological deficits [57]. The incubation of stimulated whole blood with different antidepressants further showed anti-inflammatory immunoregulatory effects of antidepressants through inhibition of IFN-γ and stimulation of IL-10 release [58].

4.3. Cytokines, Depressive Symptoms and Severities

There is little evidence of a relationship between cytokines and the severity of depression in humans [59], the majority of studies reporting negative findings [8, 43, 60]. IL-2-receptor and TNF-α were found positively related to decreased activity in depressed patients [61]. Only for suicidality enough data exists to draw preliminary conclusions. A meta-analysis reported that levels of IL-1β and IL-6 were significantly increased in blood and postmortem brain samples of patients with suicidality compared to non-suicidal depressive and healthy subjects [62], another review also supporting IL-2, IL-8 and TFN-α [63]. The majority of studies on this topic come from animal models of depression. Of these, one may conclude that the administration of IFN-α (and other pro-inflammatory cytokines) increased depression-like features in mice [64] and that anhedonia after chronic mild stress is followed by increases of cytokines, such as TFN-α, IL-6 and IL-10 [54]. Behavioural despair in isolated rats was further accompanied by elevated levels of TNF-α, IL-4 and IL-10 [65]. However, findings from these studies can only very limited be referenced to major depression, as much as effects of cytokine alterations on sickness behavior, a temporary, reactive syndrome with partial symptom-overlap with major depression [66].

4.4. Cytokines and Treatment Outcome

Concerning the question whether cytokines could be related to and may predict treatment outcome, data trend towards elevated levels of pro-inflammatory cytokines relating to poorer clinical response [67]. A recent investigation demonstrated that response to antidepressant treatment was differentially related to baseline CRP levels, with a better response to the serotonin reuptake inhibitor escitalopram in those patients with lower CRP levels and a better response to the norepinephrine reuptake inhibitor nortriptyline when serum levels of CRP were higher [68]. High baseline levels of TNF-α and IL-6 were associated with treatment resistance [48, 61, 69-71]. Levels of pro-and anti-inflammatory cytokines normalised after treatment only in those patients recovering from a depressive episode [43]. IL-1-polymorphisms were associated with reduced response to antidepressants [72]. Moreover, specific IL-1 genotypes were associated with treatment resistant depression [72]. In preclinical studies, mice with an astrocyte-specific deletion of TNF-α showed a lack of behavioural response to antidepressant administration [73].

5. ANTI-INFLAMMATORY AGENTS IN ANTI-DEPRESSANT TREATMENT STRATEGIES

Besides conventional antidepressants, anti-inflammatory agents have potential antidepressant properties. These include a group (NSAID, cytokine-inhibitors) with direct impact on cytokines, and active substances, primarily prescribed for non-affective disorders, but which showed antidepressant effects *via* immune-modulation (Fig. **1**).

5.1. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Treatment with NSAIDs, a group of anti-inflammatory agents inhibiting the activity of cyclooxygenase (COX)-1 and -2, has been investigated in depth in a number of trials. A recent meta-analysis provides evidence that NSAIDs, especially the COX-2-selective inhibitor celecoxib, have a

positive effect on antidepressant treatment outcome [74]. However in a recent [75] and another large study, no antidepressant effects of celecoxib or naproxen monotherapy in elderly subjects were detected [76]. Moreover, NSAIDs were reported to attenuate antidepressant effects of SSRI's in both animal models for depression as well as in STAR*D trial participants [77]. A selective review moreover inferred an aggravation of the pathophysiology of depression and an increased risk for cardiovascular diseases in depression [78]. Corresponding to the latter, a retrospective analysis showed that a combination of antidepressants with NSAIDs, except low-dose acetylsalicylic acid (ASA), in general increased the risk for later psychiatric counselling [79]. ASA may mediate its antidepressant effects by stimulating the endogenous production of anti-inflammatory mediators, by reducing oxidative stress [80] and by inhibiting the STAT6 signalling pathways that are mediated by IL-4 and IL-13 [81]. As both IL-4 and IL-13 are found associated with depression [8], regulation by ASA of cytokine-induced intracellular transcriptional cascades could explain the improvement of treatment outcome when ASA was added to treatment with antidepressants in mice [82]. In combination with antidepressants, ASA may further exert antidepressant features by inhibiting the phosphorylation of NF-κB, the expression of the indoleamine 2,3-dioxygenase (IDO) enzyme and the depletion of 5-HT [83].

5.2. Cytokine Inhibitors

Inhibiting the effects of cytokines with monoclonal antibodies is a promising therapeutic approach, though at present associated with the risk of potentially serious side-effects [84]. TNF-α blockers such as etanercept, fusing the TNF-receptor with the antibody, were demonstrated to reduce depressive symptoms in patients primarily suffering from psoriasis [85]. The administration of etanercept reduced depressive-like behaviour equivalent to imipramine in rats [86] and etanercept monotherapy in patients with treatment-resistant depression partially improved depression severity [87]. Long-term treatment with infliximab, a chimeric monoclonal antibody binding with high affinity to free and membrane-bound TNF-α, reduced overall severity of depression in those treatment-resistant patients with higher inflammatory activity, as shown by higher baseline CRP levels, but not in those patients with normal CRP-levels [88]. Also, infliximab led to improvement in sleep and arousal regulation in depressed patients [89], systems dysregulated in major depression, which were found associated with alterations in serum cytokine levels [90]. Animal studies further support an antidepressant-like effect of infliximab in rat models [91] potentially by preventing reductions in levels of hippocampal brain-derived neurotrophic factor (BDNF). For adalimumab, another monoclonal anti-TNF α-antibody, and ustekinumab, a monoclonal anti-IL-12 and anti-23-antibody, positive effects on depressive symptoms again were observed in psoriatic patients [92, 93]. Despite these initial outcomes, randomised trials in patients with major depression, other than those characterised as non-responders, are lacking.

5.3 Ketamine

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has rapid antidepressant effects, serving as a potential antidepressant in severe and chronic forms of depression [94]. Assumed modes of action range from BDNF-derived synaptogenesis in the prefrontal cortex, inhibition of glycogen synthase kinase-3 beta (GSK-3β) and activation of mammalian target of rapamycin (mTOR) [95]. Further anti-inflammatory properties are found in reducing the release of pro-inflammatory cytokines like TNF-α and IL-6 [96, 97]. Currently it is not known if ketamine's antidepressant effect may be linked to its anti-inflammatory effect, however there is some data prompting investigation of this topic. In an animal model of depression, administration of ketamine lowered levels of IL-1β, IL-6, TNF-α, IDO and the kynurenine/tryptophan ratio within the rats' hippocampus [98]. In addition to the attenuation of levels of pro-inflammatory mediators, ketamine also suppressed the depression-related nuclear translocation of NF-κB [99]. Moreover, levels of IL-6 were shown to potentially serve as a biomarker in predicting those subjects with a therapeutic benefit of ketamine [100]. Anti-suicidal effects of ketamine were suggested to be linked to interruption of the kynurenine pathway and modulating pro-inflammatory cytokines [101]. Finally, memory impairment and increases of IL-1β and TNF-α following electro-convulsive shock in rats were both positively attenuated by ketamine [102].

5.4. Polyunsaturated Fatty Acids (PUFAs)

Evidence supports specific dietary supplements having both antidepressant and anti-inflammatory properties. In depression, abnormal fatty acid profile and high co-morbidity with the metabolic syndrome are associated with increased levels of pro-inflammatory cytokines [8, 103]. Significantly reduced concentrations of PUFAs have been repeatedly demonstrated [104]. Studies demonstrated a positive effect of PUFAs on antidepressant outcome and symptom reduction [105] that was reduced for omega-3 fatty acids when controlling for the heterogeneity of the studies and publication bias [106]. Also, differing PUFA diets in heterogeneous study samples may account for the equivocal results [107, 108]. The antidepressant effect of treatment with PUFA supplements was found to depend on the proportion of eicosapentaenoic acids (EPA) to docosahexaenoic acid (DHA) in the diet [109]. EPA were shown to have a cytokine-suppressing effect [110] but also the administration of DHA reduced the expression of TNF-α and interleukin-6 [111]. The central target for the PUFA-mediated anti-inflammatory and antidepressant effects is NF-*κ*B [112], by intracellular translocation of NF-*κ*B [111], activation of the transcriptional factor peroxisome proliferator-activated receptors (PPAR)-γ [112] and the suppression of COX-2 expression by modulation of toll-like receptor 4 (TLR4) signalling pathways [113].

5.5. Statins

In contrast to studies suggesting PUFA diets to be of moderate antidepressant effect, contradictory findings emerged for statins, a family of HMG-CoA-reductase-inhibitors involved in the regulation of hyperlipidaemia. An effect as an add-on in acute depression has been found [114, 115]. However, long-term administration of statins did not lower the incidence of major depression during a five-year

period, indicating no preventive role for statins in depression [116]. Contradicting data point towards a depressogenic effect of statins in the long-term, with recommendations that this risk should be declared when prescribing a statin [117, 118]. Pathways of statins' anti-inflammatory and antidepressant properties are not resolved. On the one hand statins reduce the monocyte expression of TNF-α and IL-1β [119], levels of TNF-α and IL-6 [120] as well as chemoattractant protein-1 relevant for the activation of NF-κB [121]. On the other hand, statins stimulate the expression of NOS [122], a critical agent in inflammation in depression.

5.6. Curcumin

A further supplemental agent with anti-inflammatory and antidepressive features is curcumin, a diarylheptanoid and the principal of *curcuma longa*. Besides the potential to increase concentrations of biogenic amines within the cortex and hippocampus [123], curcuma administration led to the inhibition of COX-2, lipoxygenase (LOX), and NOS [124] and to reductions in circulating levels of TNF-α, IL-1 and NF-κB [125-127]. These mechanisms may in part account for antidepressant effects observed in preclinical investigations (for an overview see [128]). A clinical trial with curcumin monotherapy further reported an effect in antidepressant therapy when compared to placebo [129]. An add-on therapy adjunctive to a SSRI led to a slightly more favourable outcome compared to antidepressant monotherapy [130].

6. INFLAMMATION AND NON-PHARMACOLOGICAL ANTIDEPRESSANT TREATMENT

In this section, evidence for the relationships between non-pharmacological therapeutic approaches, their benefit in treatment outcome and the immune system are presented. These therapies are predominately applied as add-ons to drug administration, used in treatment-resistant depression, or are currently under investigation for their clinical efficacy.

6.1. Electroconvulsive Therapy (ECT)

ECT has consistently been reported one of the most effective treatment strategies for major depression, especially in treatment-resistant depression [131]. ECT led to a partly stimulus-dose dependent rapid increase of pro-inflammatory cytokines, suggesting neuronal depolarization as a mechanism of cytokine release [132, 133]. ECT further increased lipopolysaccharide-stimulated production of pro-inflammatory IL-6 and TNF-α, whereas cytokines with anti-inflammatory properties IL-4 and IL-10 were found unaffected [134]. After initial increase in levels, repeated ECTs led to a normalization of TNF-α in depressed patients [135]. Another study showed that ECT led to an up-regulation of IL-1β and TNF-α as well as an increase in memory impairment that were both reversed by ketamine [136]. Based on these as well as on findings of an ECT-mediated activation of microglia and an up-regulation of neurotrophins that simultaneously act as immunotrophins, the intriguing conclusion was made that ECT-induced "potentiation, rather than suppression, of inflammatory responses may be of therapeutic relevance to chronically depressed patients or a subgroup thereof" [137].

6.2. Deep Brain Stimulation (DBS)

Research on DBS as a therapy in depression has been subject to limitations of study design [138, 139]. At the same time, connections between DBS and the immune system, and relevance to antidepressant treatment, are as yet unclear. Preclinical studies suggest that DBS may lead to alterations in immunity, with findings of increased levels of pro-inflammatory IL-1, IL-6, TNF-α and IFN-γ following DBS of the ventromedial hypothalamic nucleus in rats [140]. Another study suggests that inflammation may mediate the effect of DBS, potentially related to the immediate but not long-lasting improvements after implantation in some subjects, associated with a regional inflammation that was reversed by anti-inflammatory drugs [141]. Blockade of this inflammation was hypothesised to account for poorer anti-depressive response in both DBS patients and animals treated with anti-inflammatory drugs.

6.3. Physical Activity and Sleep Deprivation

Several studies have revealed evidence for the beneficial effects of regular exercises on depressive symptoms [142-144]. Modulation of inflammation could be one of the underlying influences, since physical activity reduces the levels of circulating inflammatory mediators [145]. Less physical activity, in both depression and obesity, was associated with increased expression of cytokines, whereas moderate daily physical activity was connected to the expression of anti-inflammatory IL-10 [8]. There is evidence that cytokines, even if they do not change under exercise, could predict therapy response. Thus, higher levels of TNF-α at the beginning of an exercise-based treatment were associated with a distinct reduction of depressive symptoms, though cytokine levels did not significantly change during 12 weeks of treatment [146].

Inflammatory cytokines have effects on sleep-wake-regulation, as deduced from the impact of cytokines on sleep duration, sleep stage fractions and arousal regulation [90, 147]. Levels of wake-promoting cytokines peak during daytime [148], levels of IL-10 reduce during sleep [149], and narcoleptic and insomniac humans show higher levels of IL-4 than controls [32, 150]. Sleep deprivation (SD) is an effective treatment option in depression with rapid, but mostly not sustained, antidepressive effects. Whereas SD led to increased levels of TNF-α in healthy subjects and sleep restriction led to an increase in IL-4-to-IL-2-ratio [151, 152], SD and the recovery night differentially affected cytokine levels in depressive patients and controls [153]. Related to therapeutic outcome, high baseline levels of IL-6 were related to worse response to SD [154]. Given these two interventions where higher levels of cytokines at the beginning of treatment point towards better (physical activity) and worse (SD) therapy response, cytokines as potential markers for prediction of therapy response could thus be used for a tailored choice of the appropriate therapy.

7. IMMUNE TARGETS FOR FUTURE ANTI-DEPRESSANT THERAPY

The following section presents a selection of drug targets with antidepressant potential, supported by theoretical

considerations and preclinical findings. Except for minocycline, these substances are some distance away from examination in clinical trials but worth consideration in perspectives of antidepressant treatment (Fig. **1**).

7.1. Toll-like Receptor-inhibitors

Toll-like receptors (TLRs), especially TLR4, are a class of membrane-spanning proteins which recognize pathogen-associated molecular patterns (PAMP) and lead to the expression of cytokines. Expression of TLRs was increased in the dorsolateral prefrontal cortex in depression [155] and the expression of TLR4 was associated with the development of depressive symptoms especially in the context of a high-cholesterol-diet [156]. The TLR4-specific inhibitor TAK-242 prevented the increase of COX-2, NOS and IL-1β mRNA in the frontal cortex [157]. Modulators of TLR4, such as eritoran, have recently been generated and hypothetically may become new antidepressant agents though not enough data are yet available to support this assumption [158].

7.2. Glycogen Synthase Kinase-3-inhibitors

Glycogen synthase kinase-3 (GSK-3) is a serine/ threonine protein kinase regulating a large group of transcription factors and transcriptional modulators as well as 5-HT-receptors, whose activity was found impaired both in the cortex and in PBMC of depressed subjects [159]. *Via* stimulation of TLRs, GSK-3 leads to the up-regulation of pro-inflammatory cytokines [160], whereas blockade of GSK-3 leads to significant reductions in cytokine modulation [161]. GSK-3 can be inhibited by several antidepressants and mood stabilizers [158] and blockade of GSK-3 has been demonstrated as a central element in the antidepressant and neuroprotective effect of the more than 50 identified GSK-3-modulators [162]. The regulation of inflammation by GSK-3 may contribute to both the therapeutic actions of mood stabilizers, antidepressants and ketamine as well as to novel antidepressant drug targets that inhibit GSK3.

7.3. Oleanolic Acids

The triterpenoids or oleanolic acids, present in nutritional supplements and medicinal plants, have anti-inflammatory properties through up-regulating anti-oxidants and inhibiting pro-inflammatory signalling. Analogs are currently under investigation for the treatment of several chronic diseases and different forms of cancer. Concerning depression, no clinical trial has yet been reported. However, in animal models oleanolic acid analogs showed antidepressant effects attributed to high intrinsic activity on 5-HT-receptors [163] and by up-regulation of BDNF-related phosphorylation and activation of extracellular signal-regulated kinases [164, 165]. These preclinical data could make oleanolic acids worth considering as a part of trials searching for alternative antidepressive compounds.

7.4. Minocycline

The tetracycline derivative minocycline, an antibiotic able to cross the blood-brain barrier, may exert antidepressant properties by attenuating the expression of pro-inflammatory cytokines by LPS and by normalization of the kynurenine/tryptophan ratio as demonstrated in animals showing depressive-like behaviour [166, 167]. Minocyline may further inhibit the decreased hippocampal neurogenesis caused by up-regulated cytokines [64]. A small open-label trial with minocycline adjunctive to conventional anti-depressants showed significant improvement and no serious adverse events [168]. Randomised, double-blind studies to further elucidate the efficacy of minocycline are currently in progress [169].

8. DISCUSSION

Mounting evidence supports a central involvement of inflammation in the pathogenesis of depressive disorders. This is substantiated by high rates of comorbidities between depression and inflammatory diseases as well as an increased risk for the development of depression after sustained inflammation and treatment with pro-inflammatory agents [170]. Results of a variety of trials reporting on cytokines in depression [8, 43] allow the conclusion of increased concentrations of cytokines in patients suffering from major depression [6, 7], which supports the existence of an inflammatory cytokine-associated depressive sub-type [12]. Assumptions of an inflammatory form of depression further concur with findings showing that levels of cytokines at baseline inform prediction of antidepressant outcome. This review suggests that increased levels of cytokines could imply both beneficial and poor treatment outcome. Whereas the majority of studies report a worse outcome in those subjects with higher baseline inflammation [69, 70], an interplay between CRP levels and specific antidepressants on treatment outcome has recently been reported [68], pointing towards a relationship between the grade of inflammation, the antidepressant applied and the therapeutic outcome. In support of the latter, higher levels of IL-6 were generally associated with poor outcome when treated with conventional antidepressants but found beneficial for response when patients were treated with a NSAID [171]. In contrast to the majority of studies on pharmacotherapy, higher levels of cytokines were associated with beneficial clinical outcome of non-pharmacological ECT, DBS and physical activity [135, 141, 146]. Thus, these results suggest that the relationship between levels of cytokines and antidepressive outcome is not unequivocal but relate to the method applied. Further, the findings support the inclusion of cytokine and CRP-levels in pre-treatment investigations to guide the most appropriate and effective therapeutic strategy. Findings of associations with cytokine levels, predominantly in those patients responding to treatment [43, 149] strengthens the notion that cytokines are a mediator of effective antidepressant properties. However, in the majority of trials changes in cytokines during therapy were independent of clinical outcome (see 4.4). Hence, data point towards a cytokine-depleting effect during therapy, independent of any changes in the behavioural dimension. Relevant to this, reviewing the available data on the role of cytokines in depressive severity and separate symptoms, we did not establish a relationship between cytokines and clinical features. Nevertheless, intensified research is needed in this area, given that the majority of studies were not performed in humans or did not report on this topic.

Molecular mechanisms of the interaction between inflammation and depression include modulations of IDO, NO and NOS expression, different transmitter receptors and neurotrophic factors. Since it is of central relevance for the effectiveness of antidepressant drugs this review further addressed the impact of cytokines on CYP enzymes and transmembranous drug transporters. Pro-inflammatory cytokines were mainly shown to down-regulate the CYP-system which in consequence possibly leads to 1) minor depletion of antidepressant drugs followed by accumulation in the organism, potentially provoking side effects or exceeding the threshold for toxicity, and 2) decreased levels of active metabolites of antidepressant drugs which are incorporated as a prodrug, e.g. amitriptylinoxid, and need the CYP system to become pharmacologically active. Thus, the changes in CYP-system might result in decreased or increased bioavailability of several antidepressant drugs. Several pro-inflammatory cytokines were further found to activate transmembranous drug transporters, which decreases transport of antidepressant drugs between tissues, especially migration into the CNS through the BBB. As inflammation may reduce the drugs' bioavailability and dispersibility within the organs, inclusion of markers of inflammation in combinations with drug monitoring could help optimising antidepressant treatment.

For NSAIDs, data indicate their administration during a depressive episode to have positive effects on severity and outcome, especially when combined with conventional antidepressants [74, 77]. Efficacy of NSAIDS is not demonstrated in long-term treatment, maintenance therapy or prevention of depression. There is equivocal data on the occurrence of side-effects [78, 79]. Thus caution is required in the use of NSAIDs with constant appraisement of the benefit. Data indicate cytokine inhibitors to have antidepressive properties, however the lack of randomised trials make definite conclusions impossible at this time [85, 88]. Obstacles for their clinical use will include the potential of serious side effects, though not yet statistically quantified [74, 84], which could presumably restrict the indication to treatment-resistant depressive patients failing to respond to conventional therapies. The latter may also apply to ketamine as a future treatment option in treatment-resistant depression and suicidality. With fewer side effects than the aforementioned, supplemental PUFAs have proven efficacy in major depression, especially in those diets with positive EPA/DHA and omega 3/omega 6 fatty acids ratios [109]. For statins, benefits for short-term-use during an acute depressive episode were shown [115], however concerns for a depressogenic effect in the long-run were raised [117]. For curcumin, first results on its antidepressant effect are promising and its role will require further investigation in future trials. To summarise, on the data available, the anti-inflammatory agents in this section have all shown effects in depression and in somatic diseases highly comorbid with depression. For the prospective agents, animal studies are promising. However, not enough data are yet available to judge if antidepressive agents may be realised on the basis of these protein-inhibitors and antibiotics, given the potential of severe side-effects and the non-specificity of the anti-inflammatory modes of action.

9. CONCLUSION

Current antidepressants as well as non-pharmacological therapies exert antidepressant effects most probably in part by modulation of inflammatory cascades. Recent findings support the inclusion of cytokine- and CRP-levels into pre-treatment considerations to select the most appropriate and effective therapeutic strategy. Current immunomodulators like NSAIDs, cytokine blockers, PUFAs and curcuma are promising approaches to extend the spectrum of anti-depressant therapy, especially in the subgroup of depressive patients showing a cytokine-related depression or in those with immunity-associated comorbidities. The range of antidepressants may increase in the future if promising initial data on GSK-3, TLR-4 and oleanolic acids is verified in upcoming clinical trials.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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