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The Involvement of TNF-α in Cognitive Dysfunction Associated with Major Depressive Disorder: An Opportunity for Domain Specific Treatments

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Abstract: Major depressive disorder is a highly prevalent, chronic and recurring disorder, associated with substantial impairment in cognitive and interpersonal functions. Accumulating evidence suggests that inflammatory processes play an important role in the etio-pathogenesis, phenomenology, comorbidity and treatment of MDD. Suboptimal remission rates and the persistence of cognitive deficits contribute to functional impairment in MDD inviting the need for the development of mechanistically novel and domain specific treatment approaches. The MEDLINE/ Pubmed database was searched from inception to February, 9th, 2014 with combinations of the following search terms: 'TNF-alpha', 'depression', 'infliximab', 'etanercept', 'adalimumab', 'golimumab' and 'certolizumab'. Preclinical and clinical evidence linking TNF-α to MDD pathophysiology were reviewed as well as the current status of TNF-α modulators as novel agents for the treatment of MDD. Experimental models and clinical studies provide encouraging preliminary evidence for the efficacy of TNF- α antagonists in mitigating depressive symptoms and improving cognitive deficits. Further studies are warranted to confirm these data in larger randomized controlled trials in primary psychiatric populations. Translational research provides a promising perspective that may aid the development and/or repurposing of mechanism-based treatments for depressive symptoms and cognitive impairment in MDD.

Keywords: Cytokines, depression, inflammation, TNF-α, TNF-α antagonists, antidepressant.

1. INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent, chronic and recurring disorder associated with elevated rates of mortality, mostly due to cardio-metabolic disturbances. The frequent persistence of cognitive deficits in MDD also in remitted phases of the disorder has been increasingly recognized as a critical determinant of poor functional outcome [1]. Extensive literature indicates that MDD is associated with elevated serum/plasma levels of immune mediators, including C-reactive protein (CRP), pro-inflammatory cytokines [including interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNF-α)] as well as chemokines [2, 3]. Major depressive disorder may be conceptualized as a neuroprogressive disorder [4] associated with the occurrence of pathophysiological abnormalities in the central nervous system (CNS), including but not limited to microglial activation [5], neuroinflammation, mitochondrial dysfunction and oxidative and nitrosative stress (O&NS) [6]. These patho-etiological mechanisms clinically translate to a more severe, recurring and treatment-resistant course of MDD, possibly associated with a greater degree of cognitive dysfunction. Notwithstanding the availability of many antidepressants, exerting their effects mainly through the inhibition of monoamine reuptake, the majority of individuals with MDD do not achieve full remission [7]. Moreover, cognitive dysfunction in MDD is frequently sub-optimally treated by conventional antidepressants, suggesting that clinical improvement may not equate to recovery [8]. As a consequence, there is a compelling need for the development of mechanistically novel neuroprotective and pro-cognitive agents for MDD [7].

The notion that anti-inflammatory agents may exert antidepressant effects is supported by several lines of evidence. In fact, cytokine network dysregulation may interfere with the mechanism of currently available antidepressants through the limitation of monoamine biosynthesis *via* the activation of indoleamine 2, 3-deoxygenase (IDO) [9]. Moreover, the effects of classical antidepressant drugs include the attenuation of pro-inflammatory responses and endocrine dysfunction [10]. Additionally, autoimmune alterations appear to be involved in MDD patho-etiology, as the presence of antibodies directed to 5-HT has been linked to somatic and cognitive symptoms higher number of previous depressive episodes [11]. As a consequence, anti-inflammatory compounds have been preliminarily evaluated as novel therapeutic treatments for MDD providing encouraging results. For instance, a

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randomized controlled trial (RCT) investigated the efficacy of celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, in 40 subjects with MDD. The foregoing study reported that response (*i.e.* reductions in depressive symptom severity) following treatment with celecoxib were associated with decreased serum IL-6 levels. [12]. Another compound showing potential for the treatment of mood disorders is the acetyl-salicylic acid (ASA). An interventional trial in MDD (N=70) reported that combined treatment with fluoxetine and ASA resulted in similar efficacy and safety to fluoxetine monotherapy [13]. Furthermore, both treatments significantly reduced oxidative stress parameters [13].

Minocycline is a second-generation tetracycline that exerts neuroprotective effects through the prevention of microglial activation and the inhibition of the release of pro-inflammatory cytokines and chemokines. In addition, it is endowed with anti-apoptotic and anti-oxidant properties [14]. The efficacy of adjunctive minocycline in mitigating depressive and psychotic symptoms has been preliminarily documented in a 6-week open-label study on individuals with MDD and psychotic features (N=25) [15].

Progress in translational research as well as neuroimaging investigations indicated that the neural circuits that support emotional dysregulation in MDD and cognitive functioning are both discrete and overlapping. As a consequence, any disruption in the fronto-subcortical circuitry can indirectly or directly contribute to a constellation of depressive and cognitive phenotypes [16]. In particular, those circuits incorporating the regions of orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC) and anterior cingulate (ACC) have been addressed as particularly relevant to the pathophysiology of MDD. The dorsal ACC, the hippocampus and the DLPFC contribute to the formation of the dorsal "cognitive" network, which has been postulated to be particularly important for executive function and plays a key role in the cognitive regulation of emotional responses. On the other hand, the perigenual ACC, the amygdala, as well as hypothalamus and the OFC are components of a ventral "'affective/emotional" network, involved in assessing the salience of emotional input as well as the generation and regulation of emotional response. Furthermore, considerable evidence support the involvement of basal ganglia, notably the striatum, in anhedonic responses and in the integration of emotional, cognitive and motor behavior [17]. Moreover, emerging evidence underscored that different components of the hippocampal structure, namely the dorsal and the ventral region, may be implicated in learning and memory processes and emotional and motivated behaviors, respectively. The ventral hippocampus is involved in the modulation of reward responses and emotional behavior through projections to nucleus accumbens, prefrontal cortex and amygdala, and stress responses by regulating the hypothalamic–pituitary–adrenal (HPA) axis. In both regions, the subgranular zone of the dentate gyrus continues to produce new neurons also in adulthood and it has been postulated that adult neurogenesis may be a pivotal mechanism sub-serving functionally dissociated cognitive and affective processes [18].

The well-established abnormalities in monoamine systems in MDD are likely to mirror aberrant cellular signaling within these circuits and are involved in the development of attentional deficits and executive dysfunction [19]. Studies of functional neuroimaging provide preliminary evidence supporting the relationship between structural/functional anomalies in the brain and the parallel increase of circulating inflammation markers (*i.e.*, TNF- α, IL-6). For instance, in patients with MDD smaller hippocampal volumes have been reported in association with increased levels of IL-6 and CRP, while immune challenge in healthy individuals has been associated with reduced connectivity of subgenual ACC to the amygdala, the medial prefrontal cortex and the nucleus accumbens [20]. These data extend the findings derived from experimental models, clinical and post-mortem studies in MDD according to which immune network dysregulation may be implicated in behavioral and cognitive changes as well as structural changes.

TNF-α is a pleiotropic cytokine that has been increasingly recognized as a central but not exclusive mediator in the CNS under physiological and pathological conditions [21] and, along with Interleukin (IL) 1 and IL-6, is among the cytokines which have been more consistently linked in literature to the pathophysiology of MDD. TNF-α administration has been conceptualized in animal models of depressive behavior [22] and TNF-α antagonists have been demonstrated to exert antidepressant and pro-cognitive effects in mice [23, 24]. In a clinical context, elevated TNF-α serum levels have been associated with non-response to treatment with SSRIs [25]. To date, only one study examined the antidepressant potential of the TNF-α antagonist Infliximab on individuals with treatment-resistant depression [26]. In a 12-week RCT sixty subjects were randomized to receive infliximab (5 mg/Kg) or placebo at baseline and at week 2, 4 and 6. As a result, while there were no differences between the two groups in the Hamilton Depression Rating Scale (HAM-D) scores, Infliximab superior to placebo in mitigating depression severity in patients exhibiting high baseline levels of inflammatory mediators (*i.e.*, high sensitivity C-reactive protein (hs-CRP) level of > 5mg/L).

In keeping with this view, the objectives of this review are: (1) to briefly review TNF-α signaling and its role in CNS function; (2) to synthesize available evidences linking TNF-α to MDD pathophysiology and (3) to review the current status of TNF-α modulators as novel drug targets MDD.

2. METHODS

The MEDLINE/Pubmed database was searched from inception to February, 9th, 2014 with combinations of the following search terms: 'TNF-alpha', 'depression', 'infliximab', 'etanercept', 'adalimumab', 'golimumab' and 'certolizumab'. Manuscripts were reviewed by two authors and original articles were included in this review after a careful analysis of overall manuscript quality. A manual search of relevant articles was also performed and the citation tracking of included papers was searched in Google Scholar for additional references. No language restrictions were applied.

3. BASIC PHYSIOLOGY AND PLEIOTROPIC FUNCTIONS OF TNF-α

TNF-α is a protein released as a soluble cytokine (sTNF-α), a homotrimer of 17-kDa monomers, after being enzymatically cleaved from its cell surface–bound precursor (tmTNF-α), a homotrimer of 26-kDa monomers by TNF-α – converting enzyme (TACE). Both sTNF-α and tmTNF-α ligands interact with either of 2 distinct receptors, namely TNF- α receptor 1 (TNF-R1, p55, CD120a) and TNF-α receptor 2 (TNF-R2, p75, CD120b). These receptors are membrane glycoproteins that specifically bind to TNF-α but differ in their cellular expression profiles, affinities for ligands and signaling mechanisms. Both sTNF-α and tmTNF-α ligands can bind to TNF-R1 and TNF-R2, but sTNF-α binds with higher affinity to TNF-R1. Receptor mediated effects of sTNF-α and tmTNF-α can lead alternatively to activation of the transcription factor nuclear factor kappa-B (NF-κB) or to apoptosis through the activation of caspase-3 and caspase-8, depending on the metabolic state of the cell [27]. Binding to TNF-Rs by ligands such as tmTNF-α or even TNF-α antagonists, can induce reverse signaling through this membrane-anchored ligand and the resulting release of intracellular calcium, cytokines production, and the expression of adhesion molecules (*e.g.*, E-selectin) is associated with caspase-dependent apoptosis [28].

TNF-α mediates a wide variety of biologic activities, modulating cell recruitment and proliferation, cell death and immune regulation [27]. Indeed, it has been recognized as an important mediator in the augmentation of host defense mechanisms against infections. Conversely, TNF-α can promote and maintain inflammation, operating in networks and cascades to regulate cellular activity in an autocrine, paracrine and endocrine manner [21]. Under pro-inflammatory conditions, the production of TNF-α can be induced by cytokines (*e.g.*, IL-1, IL-17, IL-2, interferon (IFN)-γ), granulocyte macrophage colony-stimulating factor, ischemia/hypoxia and trauma [29]. TNF-α induces the production of other cytokines, such as IL-1, IL-6, IL-8, IFN-γ and IL-2, as well as some negative-feedback regulators (*i.e.* IL-10, prostaglandins and glucocorticoids) [30]. Moreover, TNF-α can stimulate both T-cell proliferation as well as promote T-cell apoptosis and the termination of immune responses by activation-induced cell death [31]. TNF-α facilitates the activation of the adaptive immune system, up-regulates T-cell chemotaxis and induces the expression of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), C-C chemokine ligands (CCL), such as CCL19 and CCL21, as well as C-X-C chemokine ligands (CXCL) 12 and 13 [32]. Furthermore, TNF-α induces the production on reactive oxygen intermediates, nitric oxide and the rate of tissue remodeling by metalloproteinases (MMPs) [33].

4. TNF-α SIGNALING IN THE CNS

TNF-α is not only a key mediator of innate immunity, but also a physiological regulator of homeostatic cell proliferation, differentiation and programmed cell death in the CNS [34]. Accumulating evidence suggest that, under pro-inflammatory conditions, peripheral production of TNF-α, IL-1 and IL-6 by monocytes results in a subsequent production of TNF-α and other mediators in the brain *via* toll-like receptor (TLR) 4 present on circumventricular organs and choroid plexus, leading to the activation of microglia [35]. Activated microglia are in turn the main source of TNF-α within the brain, while neuronal cells and astrocytes can produce it to a minor extent [36]. Thus, the cross-talk between peripheral immune cells and immune cells within the CNS may induce a positive feedback loop that further increases the production of TNF-α and other pro-inflammatory cytokines [37]. Within the brain, the cross-talk between microglia and other glial cells, namely astrocytes and oligodendrocytes, may lead to an amplification of the inflammatory response with detrimental effects on neural, cognitive, and behavioral functions (see Fig. **1**) [38]. While astrocytes physiologically maintain the integrity of the blood brain barrier (BBB), regulate synaptic transmission and down-regulate harmful inflammation by activating the T-helper (Th) 2 response, under pro-inflammatory conditions can intensify the innate immune response by secreting complement components, chemokines and cytokines. In addition, astrocytes are strongly involved in re-uptake and metabolic conversion of glutamate. evidence indicates the presence of a reduced number of astrocytes in MDD, a diminished counterregulation of IDO activity in microglia could further contribute to alter glutamatergic neurotransmission [39]. Oligodendrocytes are actively involved in the process of myelination and are involved in the down-regulation of the inflammatory response as well by secreting anti-inflammatory cytokines. However, these cells are particularly susceptible to oxidative stress and mitochondrial injury as they contain low levels of antioxidants and express N-methyl-D-aspartate (NMDA) receptors, which expose them to glutamate excitotoxicity [40]. TNF-α has several effects on glutamate neurotransmission, including the upregulation of glutaminase in astrocytes (which converts glutamine into glutamate) and the suppression of conversion from glutamate to glutamine (glutamine synthase); increased trafficking of calcium-sensitive AMPA receptors as well as NMDA receptors and the inhibition of glutamate transport proteins [excitatory amino acid transporters (EAATs-)] (See Fig. **2**) [41]. Additionally, enhanced TNF-α signaling results in the endocytosis of gamma-aminobutyric acid (GABA) $_A$ receptors and in the consequent reduction in inhibitory synaptic transmission [42]. Moreover, TNF-α increased signaling leads to increased glutamate-mediated excitotoxicity also through dopaminergic neuronal injury [43]. Glutamate receptors on neuronal dendrites and synapses play a major role in controlling the strength of the synaptic impulse. Constitutively released TNF-α influences basal synaptic strength in the hippocampus [44] and is required for the homeostatic scaling of both excitatory and inhibitory synapses (a form of synaptic plasticity that entails uniform adjustments in the strength of all synapses on a cell in response to prolonged changes in the cell's electrical activity) [45]. However, elevated concentrations of TNF-α promote hippocampal long-term depression (LTD), thus negatively impacting the substrates which sub-serve learning and memory processes [45]. Moreover, it has been postulated that TNF-α may indirectly regulate synaptic plasticity through its inhibitory effect on mitochondrial

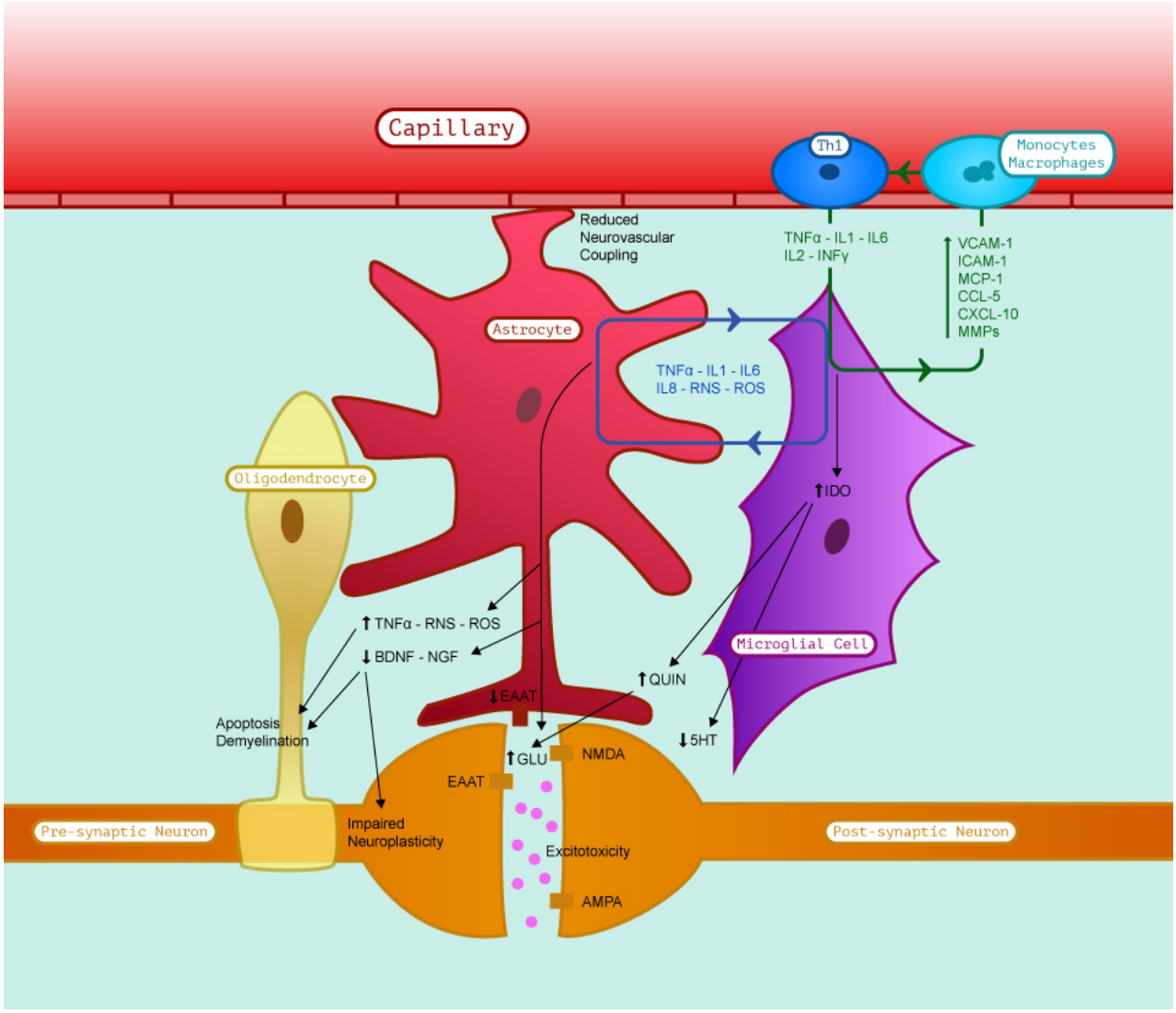

Fig. (1). Schematic representation of inflammatory pathways involved in neuroprogression. Peripheral pro-inflammatory stimuli activate microglial cells, which initiate an inflammatory cascade within the brain secreting cytokines, chemokines, adhesion molecules and reactive nitrogen and oxygen species (RNS and ROS). Astrocytes further amplify the immune response and are responsible of impaired neurovascular coupling and reduced trophic support to neurons and other glial cells. Immunoexcitotoxicity is mediated by the production of the NMDA agonist QUIN, increased TNF-mediated density and activity of AMPA and NMDA receptors and decreased Glu reuptake. The combined effect of immune mediators, nitrosative and oxidative burden and reduced production of growth factors leads foster mitochondrial dysfunction and consequent apoptotic death and impaired neuroplasticity. GLU, glutamate; IDO, indolamine 2,3 dioxygenase; 5HT, serotonin; IFN, interferon; IL, interleukin; NGF, nerve growth factor; BDNF, brain derived neurotrophic factor; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic calcium-permeable receptors; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; Th1, T Helper 1; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; CCL, C-C chemokine ligands; CXCL (C–X–C motif) ligand chemokine; MCP, monocyte chemotactic protein.

production of ATP by astrocytes, which in turn stimulates glutamate release [42].

Preclinical studies showed that perinatal and neonatal immune challenges [*e.g.*, lipopolysaccharide (LPS) injection] may cause long-lasting changes in behavioral and neurochemical parameters in adult animals, in association with increased levels of TNF-α in the hippocampus, the prefrontal cortex and nucleus accumbens [46]. Conversely, neonatal administration of high doses of TNF-α result in alterations of brain physiological development associated with anxiety- and depression-like behavior in adulthood [47]. Alterations in TNF-α concentration may affect neurogenesis in the brain in opposite ways, as low doses seem to promote the proliferation of neural precursor cells derived from the subventricular zone of neonatal mice, while the exposure to higher doses leads to apoptotic neuronal death [43] *via* TNF-R1 [48]. In fact, the activation of TNF-R1 leads to the activation of the mitogen activated protein kinase (MAP-K), notably c-Jun NH2-terminal protein kinase (JNK) and p38, which are implicated in the activation of caspases and

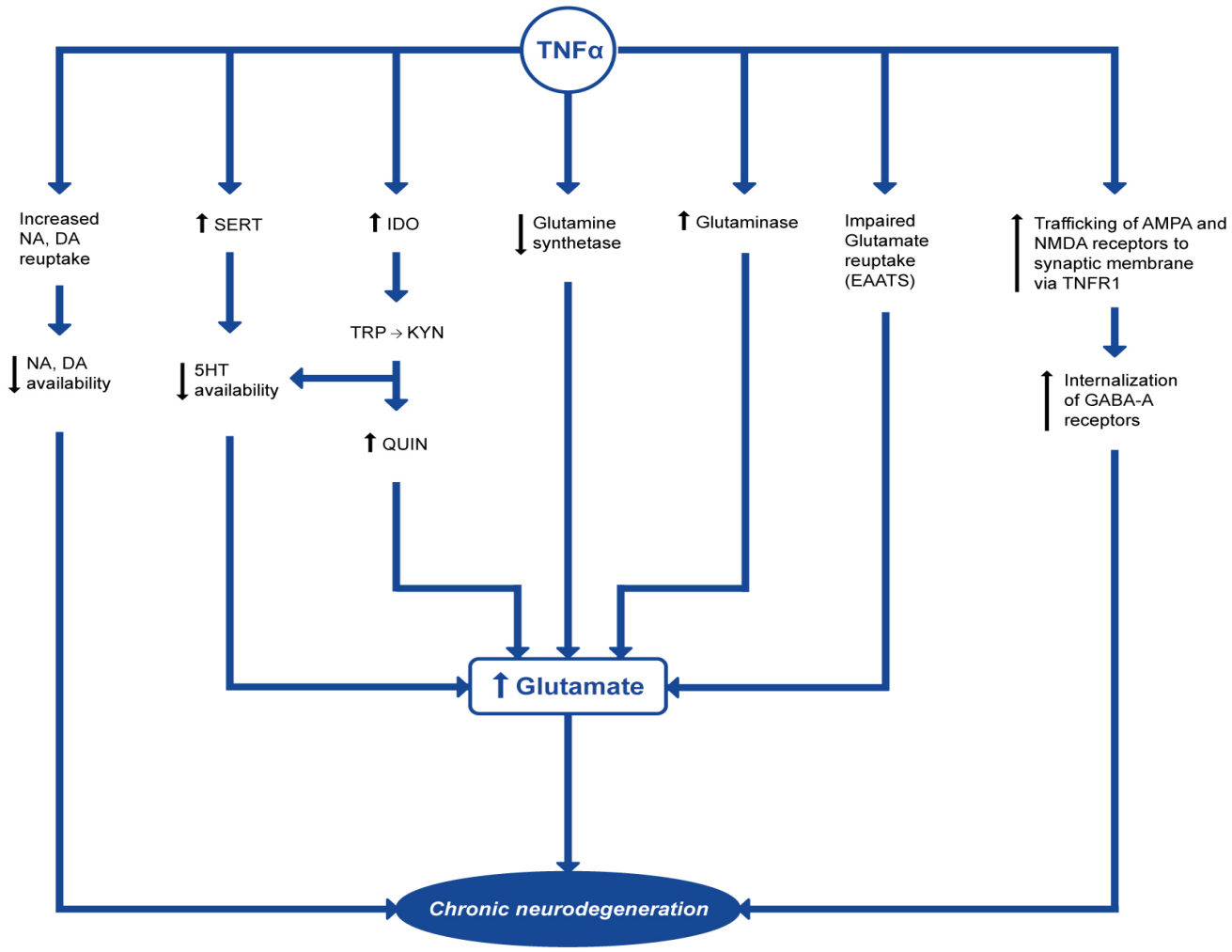

Fig. (2). TNF-α enhances excitotoxicity *via* upregulation of glutaminase, suppression of glutamine synthetase, impaired glutamate reuptake and increased trafficking of AMPA calcium- permeable receptors to the synaptic membrane and endocytosis of GABA-A receptors. These mechanisms, in association with alterations in 5-HT, DA, NA mediated neurotransmission, promote glial dysfunction and neuronal degeneration.

ultimately in apoptotic death [49]. Interestingly, TNF-α induced cell death can be blocked through the treatment with anti-TNF-α on embryonic neurons [21]. At physiological levels, neurogenesis is a continuous process required also in adulthood for normal retention of spatial and contextual memory [50]. Increased signaling through TNF-R1 while aging, as supported by evidence of increased TNF-R1/TNF-R2 ratio in the hippocampus in animal models, has been posited to be implicated in hippocampal neuronal loss and to partly account for increased risk of cognitive impairment through higher levels of excitotoxic damage [36, 51]. In fact, while TNF-R1 triggers cell-signaling pathways that promote neurodegeneration, TNF-R2 lacks the cell death domain associated with the activation of caspases and activates predominantly cascades associated with cell survival. In aged animals, the selective inhibition of TNF-R1 signaling has been associated with improved cognitive performance and reduced microglial activation, suggesting that a selective inhibition of this pathway may mitigate cognitive dysfunction [52].

5. THE ROLE OF TNF-A IN THE PATHO-PHYSIOLOGY OF MDD

5.1. Preclinical Evidence

Immune challenges (*e.g.* LPS administration or direct infusion of cytokines) are capable of inducing the so called "sickness behaviour" and concurrent deficits in learning and memory [53], along with increased levels of cytokines (*i.e.* TNF- α, IL-6, IL-1) as well as decreased expression of brain derived neurotrophic factor (BDNF) in the hippocampus [54]. The peripheral administration of TNF-α in rodents results in anhedonic behavior in conjunction with an increase in extracellular level of serotonin metabolites in the nucleus accumbens [55]. It is well documented that cytokines, including TNF-α, induce the enzyme indoleamine 2, 3- dioxygenase (IDO), which leads to serotonin deprivation by converting tryptophan in kynurenine (KYN). Microglia mainly convert KYN to the NMDA receptor agonist quinolinic acid (QUIN), which provokes lipid peroxidation and potentiates oxidative stress, thus perpetuating a vicious

circle of neurodegeneration by the induction of cytokines such as IL-1β, TNF-α and IFN- γ [9]. Moreover, TNF-α leads to the catalytic activation of the serotonin transporter (SERT), which increases the uptake of serotonin *via* p38 MAPK signaling pathway [56].

The deletion of either TNF-R1 or TNF-R2 gene has been associated with antidepressant-like effect and hedonic response in behavioral tests in comparison with wild-type mice [57]. In addition, previous evidence showed that TNF-α knocked-out mice exhibit a small, albeit significant, antidepressant-like response, in association with alterations in serotonin metabolism [58]. However, constitutive levels of TNF-α have been acknowledged to be essential in early cognitive development [59] and influence the expression of neurotrophins, such as nerve growth factor (NGF) [60] and BDNF [61]. For instance, TNF-α knocked-out young mice exhibit cognitive impairment, while TNF-R1 and TNF-R2 knocked-out adult mice manifest specific learning and memory deficits [62]. Thus, while TNF-α signaling seems to be required for physiological cognitive functioning [59], its enhanced signaling has been linked to aging related memory loss and to cognitive impairment in experimental models of neuropsychiatric and neurodegenerative diseases [24, 63].

5.2. Antidepressant Treatment and TNF-α in Preclinical Studies

Accumulating evidence from preclinical and *in vitro* studies substantiate the hypothesis that different antidepressant treatments have anti-inflammatory properties. For example, the "sickness behavior" can be attenuated or even abolished with the administration of antidepressants [64]. In a mouse model of LPS-induced inflammation bupropion significantly lowered TNF-α levels as compared to placebo [65]. The administration of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) has been reported to reduce immune activation and the levels of pro-inflammatory cytokines in the olfactory bulbectomised rat and in the stress-related paradigm [66, 67]. Additionally, pretreatment with SSRIs (fluoxetine and paroxetine) or SNRIs (venlafaxine and duloxetine), attenuated LPS-induced increases in TNF-α and increased IL-10 serum levels in mice [68].

In vitro, SSRIs potently inhibit the production by activated microglia of cytokines and free radicals [69]. In particular, fluoxetine, paroxetine and sertraline modulated the ability of murine microglia to produce TNF- α and NO [70]. Additionally, fluoxetine and citalopram significantly decreased the release of glutamate and D-serine from LPS-activated microglia in a co-culture system with ischemia-injured cortical neurons, increasing neuronal survival after an ischemic insult [71]. Moreover, TNF-α antagonism attenuated the loss in viability of injured cortical neurons, supporting the thesis that TNF-α can induce neurotoxicity by enhancing glutamate release from activated microglia in an autocrine manner [72]. Also TCAs (*e.g.* imipramine, desimipramine, clomipramine) exhibited anti-inflammatory properties *in vitro*, significantly reducing the production of TNF-α, IL-1β and IL-6 by brain cell cultures and inducing the expression of anti-apoptotic proteins (*i.e.*, Bcl-2) [64, 73]. In keeping with this view, the authors posited that the efficacy of some antidepressants could be in part associated with the decrease of TNF-α levels, maintained by chronic treatment. Complementary evidence indicates that antidepressants may influence neurotransmission also through a direct effect on serotonin receptors expressed by microglial cells, namely 5-HT2, 5-HT5 and 5-HT7 [74]. Alterations in serotonin availability in the synaptic and also in the extrasynaptic space may lead to changes in the motility and phagocytic activity of microglial cells, which constantly survey their surrounding and contact synaptic structures by random process extension and retraction, thus influencing the balance of synaptogenesis and neuronal death during physiological development and in pathologic conditions [74]. Additionally, mounting experimental evidence demonstrates that SSRIs have a profound effect on astrocytes, including the regulation of neurotransmitters and growth factors (*e.g.* BDNF, GDNF and fibroblast growth factor 2 (FGF2)), increased glucose utilization and lactate release as well as the attenuation of the release of inflammatory molecules [75]. As astrocytes are increasingly recognized to play important roles in neuronal development, neurotransmission, synaptic plasticity, these observations support a role also for astrocytes as new targets for antidepressants [76]. Taken together, these data support the notion that astrocytes and microglia represent vital members of the "quadripartite synapse" with presynaptic and postsynaptic neurons and that reciprocal interactions between these elements influence synaptic maturation or remodeling in a dynamic and highly intertwined network [77].

5.3. Clinical Evidence

A growing body of evidence links pro-inflammatory alterations to depressive symptoms, indicating a bidirectional relationship. Indeed, endotoxin administration to healthy subjects is associated with increased levels of cytokines (*i.e.* TNF-α, IL-6, IL-1) and concomitant depressed mood and cognitive impairment [78]. Immune challenge in utero has been associated with increased prevalence of psychiatric disorder in adulthood, possibly deriving from a disruption of fetal brain development [79]. Conversely, the prevalence of depression among individuals with chronic inflammatory diseases suggests that stress-associated psychiatric disorders and inflammatory diseases share in part a common pathophysiology [80]. For instance, depressive and anxiety disorders are reported as the more prevalent psychiatric comorbidities in chronic inflammatory diseases [81] and their occurrence has been correlated with higher serum levels of IL-1, IL-12, IL-18 and TNF- α [82]. Depressive symptoms in patients with chronic hepatitis C have been associated with elevated plasma levels of IL-1β and TNF-α [83]. Moreover, the persistent expression of pro-inflammatory cytokines following the initiation of therapy with interferon (INF)-α predicts the onset of depression in this population [84]. Meta-analytic evidence indicates that individuals with MDD exhibit higher concentrations of TNF-α and IL-6 as compared to controls [2]. Elevated levels of TNF-R1 and TNF-R2, which reflect TNF-α activity but maintain more stable plasmatic concentrations, thus possibly representing better markers, have also been reported in individuals with

MDD as compared to healthy controls [85, 86]. However, the findings on this topic are highly conflicting and converging evidence supports the notion that pro-inflammatory alterations are likely to be relevant only in a subset of depressed patients [87]. It is highly debated whether TNF-α levels may be differentially modulated in diverse MDD subtypes. In fact, while some reports showed no differences in TNF-α levels in patients with melancholic and atypical features [88, 89], other studies reported elevated levels of CRP, IL-6 and TNF-α in patients with atypical features, along with higher BMI, waist circumference and triglycerides, and lower high-density lipid cholesterol as compared to patients with melancholic depression, supporting the hypothesis that greater metabolic dysregulation may be related with inflammation in atypical depression [90], while HPA axis hyperactivity is a most replicated finding in melancholic depression.

Amongst genetic factors that influence the susceptibility to the development of depression [91], single nucleotide polymorphisms (SNPs) in TNF-α gene have been considered with increasing interest. However, available data have yielded inconclusive findings. For instance, while A/A genotype of the G-308A TNF-α polymorphism has been associated with increased risk of MDD [92], other studies reported that the G/G genotype of the G-308A TNF-α polymorphism significantly increase the risk for late life-MDD [93] and for suicide attempt amongst individuals with MDD [94].

Microarray mRNA expression analysis conducted on post-mortem brain tissue samples of depressed individuals, showed increased expression of tmTNF-α and decreased expression of TNF-R2 mRNA in the DLPFC [95, 96]. Similarly, protein expression levels of IL-1β, IL-6, and TNF-α were significantly increased in the prefrontal cortex of adolescent suicide victims compared with healthy control subjects [97]. Taken together, these findings suggest that a pro-inflammatory dysregulation might be particularly relevant in suicidal depressed patients [98]. Interestingly, it has been recently demonstrated that higher suicidal ideation *per se* was associated with a pro-inflammatory serum protein profile, independently of depression severity and recent suicide attempts [99]. However, both increased [100] and decreased [101] levels of circulating peripheral inflammatory markers have been reported in suicide attempters as compared to non-attempters. A potential moderational variable when interpreting these studies is that suicide attempts are accompanied by high level of psychosocial stress and previous adversities, which robustly influence systemic immune responses [100]. Childhood trauma is an environmental factor exerting a critical impact on adult inflammation and the subsequent release of cytokines [102]. Higher basal IL-6, TNF-α, and IL1- β levels have been observed in healthy adults with a history of trauma in comparisons to adults without history of trauma [103]. Additionally, persistently elevated TNF-α levels have been reported during pregnancy in women reporting history of [104]. These data entail a long-term impact of childhood trauma and stress on homeostatic systems and suggests that immune alterations may precede the development of significant stress-related psychiatric disorders.

5.4. Antidepressant Treatment and TNF-α in Clinical Trials

To date, available data on the effect of antidepressants on TNF-α levels provided results. A meta-analysis of 22 studies evaluating different antidepressants' effect on cytokines expression (*i.e.* TNF- α, IL-6 and IL-1 β) showed significant changes in serum levels of IL-1 β but not in IL-6 and TNF-α levels [105]. In a study on SSRI-resistant patients receiving treatment with bupropion, reduction in depression severity among responders was not associated with changes in TNF-α levels [25]. These data do not support the hypothesis that serum TNF-α levels decrease as a result of improvement in depressive symptoms or that a decrease in TNF-α levels is required for antidepressant efficacy, possibly suggesting that increased TNF-α levels in MDD may derive from an overall inherent dysfunction in the immune system. On the contrary, other studies indicate that the reduction of pro-inflammatory response may be associated with clinical improvement. For instance, successful response to SSRIs, amitriptyline or electroconvulsive therapy in MDD has been associated with parallel reduction of TNF-α levels in individuals with MDD [106, 107, 108]. Consistently, treatment response to venlafaxine has been coupled with a decrease in TNF-α levels during the first-episode of depression [109]. A reduction in TNF-α expression has been reported after bupropion administration, while treatment with mirtazapine increased TNF-α levels [110]. In this context, the activation of TNF-α signaling has been recognized as an early and sensitive marker of weight gain induced by psychopharmacological treatment [111]. Some evidence suggests that higher baseline levels of TNF-α may predict the response to treatment. For example, in an open-label 12-week study on individuals with MDD treated with escitalopram, higher baseline TNF-α levels predicted non-response to treatment [25]. In keeping with this view, in a previous study on individuals with SSRI-resistant depression, while depressed subjects exhibited significantly higher IL-6 and TNF-α levels as compared to healthy controls, euthymic patients who were formerly SSRI resistant had levels of pro-inflammatory cytokines similar to those of the healthy subjects, suggesting that clinical improvement may be associated with a restored immune profile [112].

6. TNF-A ANTAGONISTS: NOVEL NEURO-THERAPEUTIC AGENTS FOR MDD?

6.1. Tumor Necrosis Factors Antagonists

Currently, there are five FDA approved TNF-α antagonists: infliximab, etanercept, adalimumab, golimumab and certolizumab pegol (see Fig. **3**). TNF-α inhibitors are indicated for the treatment of Crohn's disease (CD), ulcerative colitis, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), plaque psoriasis (PP), and/or juvenile idiopathic arthritis.

Infliximab (IFX) is a chimeric protein composed of a murine variable region and human constant region. Etanercept (ETN) is a fusion protein of two TNF-R2 receptor extracellular domains and the Fc fragment of human immunoglobulin 1 (IgG1). Adalimumab (ADA) and golimumab (GLB) are fully human antibodies, while

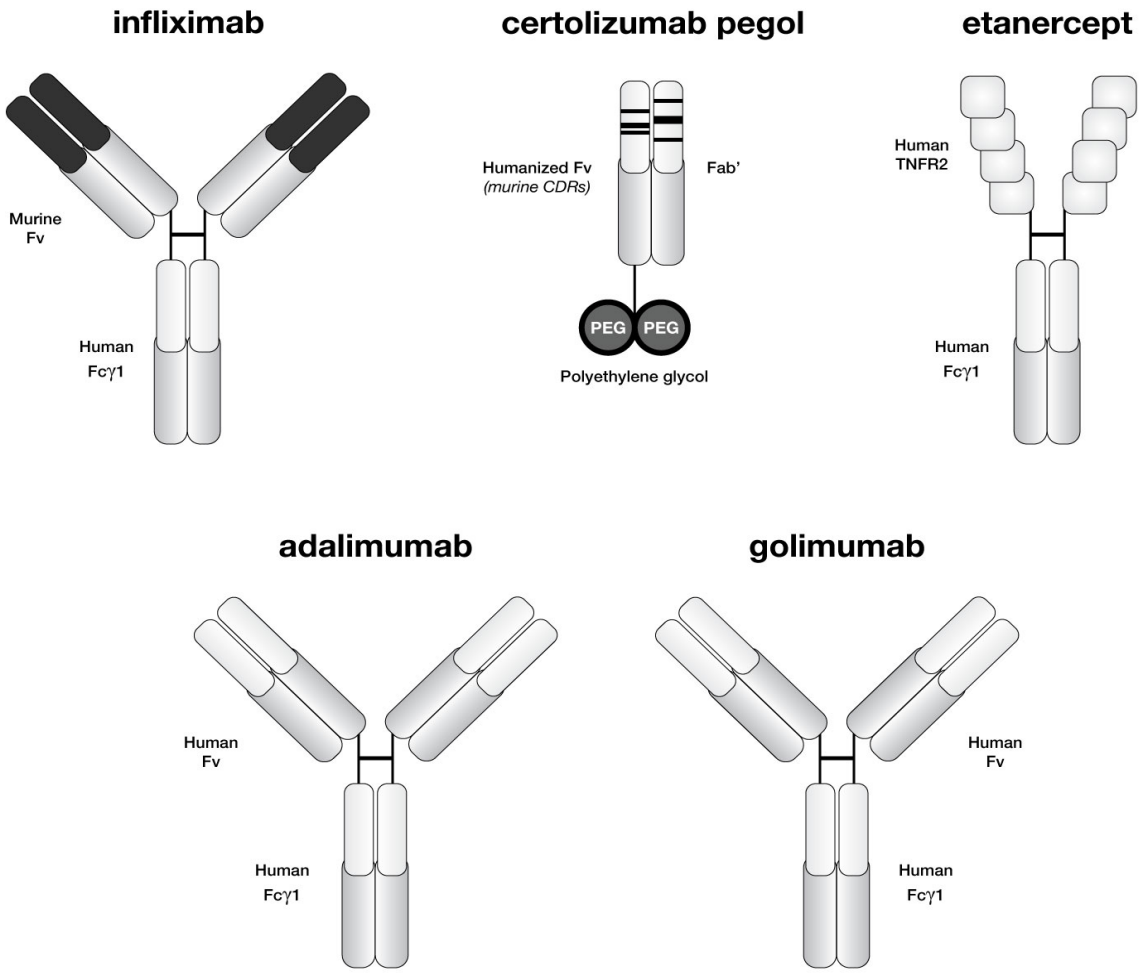

Fig. (3). Simplified diagrams of the structures of 5 TNF antagonists. Infliximab is a mouse/human chimeric monoclonal antibody of IgG1 isotype. Adalimumab and golimumab are fully human monoclonal antibodies. Certolizumab is a PEGylated Fab' fragment of a humanized IgG1 monoclonal antibody. Etanercept is a fusion protein of TNFR2 (p75) and the Fc region of human IgG1.

certolizumab (CZP) is a humanised Fab fragment conjugated to polyethylene glycol (PEG) [113].

6.2. Pre-clinical Studies

Accumulating pre-clinical evidence provides support the concept that TNF-α inhibition may alleviate depressive-like behavior [114] (Table **1**). Peripheral ETN or IFX administration exerted beneficial effects on behavioral outcome in a chronic stress model [115, 116]. ETN treatment was effective in restoring hedonic responses in an experimental model of heart failure- induced anhedonia [117]. In mice infected with bacillus Calmette-Guerin (BCG), ETN partially blunted BCG-induced IDO activation and depressive-like behavior [118]. Interestingly, in a mouse model of neuroinflammation, induced by the administration of TNF-α in the CNS, neurobehavioral changes were reversed both by treatment with centrally administrated anti-TNF-α antibodies and peripherally administrated thalidomide. Moreover, TNF-R1 gene knock-out resulted in antidepressant effects, while pretreatment with fluoxetine, imipramine or desipramine prevented TNF-α induced depressive-like behavior [22]. Furthermore, treatment with the TNF-α synthesis inhibitor 3, 6'-dithiothalidomide (DT) was able to reverse cognitive deficits induced by chronic LPS administration in rat. Improvements in hippocampus-dependent learning and memory were associated with reduced expression of genes involved in the TLR-mediated signaling pathway, typically associated with classical microglia activation [24].

6.3. Infliximab Effect on Depressive Symptoms in Chronic Inflammatory Diseases

Preliminary evidence that IFX treatment can alleviate depressive symptoms has been provided by clinical trials in patients suffering from chronic inflammatory diseases (Table **2**). A longitudinal 6-week study with patients affected by active AS (n=16) showed that the administration of IFX was associated with a decrease in depression and anxiety scores on the Beck Depression Inventory (BDI) and on the Hospital Anxiety and Depression Scale (HADS) [119]. Interestingly, the improvement in depression was not associated with improvements in physical function or pain. In a prospective study in patients with CD (n=15) treatment with IFX has been associated with a significant reduction in

Table 1. TNF-α antagonists' effect on depressive-like behaviour in experimental models. EPM, Elevated plus maze; SP, sucrose preference; FS, forced swimming; TS, Tail suspension test; CMS, chronic mild stress; KO: Knock-out.

Author	Experimental Model	Treatment	Results
[116]	Male Wistar albino rats, divided into three groups receiving: 1) saline -no stress; 2) saline-CMS; 3) IFX-CMS.	IFX 5 mg/kg, i.p. or vehicle weekly for 8 weeks	IFX reduced depression-like and anxiety-like behavior in CMS rats compared with saline-CMS group in the SP and FS test and in the EPM.
[114]	Adult male Wistar albino rats	ETN 0.8 mg/kg, s.c. or vehicle weekly for 8 weeks	ETN decreased anxiety-like behaviour in the EPM and depression-like behavior in the FS test
[22]	Male Swiss wild-type mice and TNF-R KO mice	Anti-TNF-α antibody (0.1-1 pg/site, i.c.v.), or thalidomide (30 mg/kg s.c), fluoxetine (32 mg/kg, i.p.), imipramine (15 mg/kg, i.p.), desipramine (16 mg/kg, i.p.)	Anti-TNF-α antibody or thalidomide reversed depressive-like and anhedonic behavior in the FS and SP tests. Pretreatment with Fluoxetine, imipramine or desipramine prevented TNF-α induced depressive-like behavior. TNF-R1 KO exerted an antidepressant-like effect on the FS and the TS tests
[115]	Restrained or not-restrained Male Wistar rats and Naïve non-treated non-restrained controls	ETN twice a week (0.3 mg/kg, i.p.) or imipramine (10 mg/kg, i.p.) or Ringer solution	ETN or imipramine attenuated depressive-like behavior in the FS test
[118]	Male Wild-type control mice and IFN $\gamma R^{-/-}$mice inoculated with bacille Calmette-Guerin (BCG). Primary mixed glial cultures were also established	Vehicle or ETN (2.5 mg/kg) s.c. once daily	Pretreatment with ETN partially blunted BCG-induced IDO activation and depressive-like behaviour in the FS and TS tests
[117]	Rodent model of heart failure and anhedonia	ETN	ETN restored appropriate responses to electrical brain stimulation.
[24]	Rat model of neuroinflammation induced by LPS infusion for 28 days	DT (3, 6'- dithiothalidomide) since day 29 for 14 days.	Reversion of spatial learning and memory deficits with reduction in microglia activation

depression and anxiety scores on the HAM-D, the BDI and the Symptom Checklist (SCL-90). Importantly, improvements in depression severity were only partially explained by an associated reduction in disease activity. Moreover, decrements in depressive symptom scores were correlated with decrease in levels of inflammatory markers (*i.e.* a_1 and a_2 globulin fractions) [120]. Results from another prospective study in patients with active CD (n=100) reported a beneficial effect of IFX treatment on depression scores in the Patient Health Questionnaire 9-items (PHQ-9) [121]. In a pilot, placebo-controlled trial, subjects with CD (n=14) treated with IFX reported significantly fewer depressive symptoms on the Center for Epidemiological Studies Depression scale (CES-D) [122]. A beneficial effect of IFX on comorbid psychiatric illness has been reported also in patients with psoriasis [123, 124]. Lastly, the positive effect of IFX in reducing depressive symptoms severity has been confirmed in a preliminary open-label study involving outpatients with cancer [125].

6.4. Infliximab in Major Depressive Disorder

To date, only one study evaluated the antidepressant potential of IFX in a primary psychiatric population [26]. In a double-blind randomized 12 week-trial, 60 individuals with treatment resistant depression (MDD: n=51; BD: n=9) received three peripheral intravenous IFX administrations (5 mg/kg) or placebo at week 0, 2 and 6. While treatment with IFX was not associated with overall significant decrease in HAM-D scores, patients with baseline hs-CRP concentration greater than 5 mg/L showed greater response to IFX as compared to placebo (62%vs. 33%), with an effect size of 0.41. The same significant association was observed on the Clinical Global Impression-Severity Scale (CGI). The symptoms on which IFX exerted more pronounced beneficial effects included anhedonia and psychomotor retardation as well as depressed mood and suicidal ideation. The authors postulated that these improvements may reflect functional changes in brain regions that have been reported as targets of inflammatory stimuli by previous studies, notably the basal ganglia as well as the subgenual and dorsal areas of the anterior cingulate cortex [17]. Subsequent analysis of genes expression in blood mononuclear cells from IFX responders (n = 13) versus non-responders (n = 14) revealed that response to IFX was predicted by increased expression of a network of genes regulated by the transcriptional factor hepatocyte nuclear factor (HNF) 4-alpha and associated with gluconeogenesis as well as cholesterol and lipid homeostasis. Responders also exhibited suppressed expression of pro-apoptotic genes early after the infusion, and a long-term down-regulation of transcripts related to innate immune signaling and of NF-κB, a transcriptional factor implicated in the production of pro-inflammatory cytokines [126]. Therefore, transcriptional signatures of treatment response to IFX appear to involve the regulation of existing metabolic imbalances accompanied by an increased

Table 2. Infliximab (IFX) effect on mood symptoms in chronic inflammatory diseases. PHQ-9, Patient Health Questionnaire 9-items; CES-D, Center for Epidemiological Studies Depression scale; HADS, Hospital Anxiety and Depression scale; HAM-D, Hamilton Depression Scale; SCL-90, Symptom Checklist; BDI, Beck depression Inventory; TAS-20, Toronto Alexithymia Scale, CRP, C-reactive protein; IL, interleukin; BD, bipolar disorder.

Author	Study Design	Diagnosis	Measures	Outcome
[121]	Open label, single dose, 4-week study. Patients received IFX (5-10 mg/kg i.v) and were followed-up to 9 months	Chron's disease (n=100), mean age 34 ± 11	PHQ-9 HADS TAS-20	Reduction in the proportion of depressed individuals from baseline to endpoint (24% vs. 16%)
[122]	Pilot placebo-controlled study. Patients received placebo at baseline, followed by IFX (5 mg/kg) at 2 week with follow up for 4 week	Crohn's disease (n=14 patients), mean age 32.2±8.6	CES-D every two weeks	Reduction in CES- depression scores from week 2 to endpoint
[125]	Open-label, pilot study. Patients received IFX (5 mg) at baseline and, if there was observable clinical benefit, every 4 weeks	Advanced cancer outpatients (n=17)	HADS Laboratory measures: CRP, TNF, IL 6 and leptin	Improvement in depression and anxiety subscores in 7 of 15 patients, with reductions in CRP and leptin levels
[123]	Case report (n=3). Subjects received adjunctive IFX (5 mg/kg)	1) Psoriasis and BD (male, 21 y) 2) Psoriasis and MDD with psychotic features (female, 49 y) 3) Psoriasis and BD (male, 47y)	No psychometric scales are available	1) Stabilization of BD symptoms 2) Improvement in residual depressive symptoms 3) Improvement in affective symptoms
[124]	Case report, male 66 years old, receiving IFX (4 mg/kg e very 6-8 weeks)	Chronic plaque psoriasis and MDD	No psychometric scales are available	Improvement in depression severity
[119]	Longitudinal 6-week study. IFX (5 mg/kg) was administered at weeks 0, 2 and 6.	Severe ankylosing spondylitis (AS) (n=16), mean age 36.4 ± 10.3 years	HADS BDI	Improvements in BDI scores since the first infusion and decrements in HADS scores since the second infusion.
[120]	Longitudinal, single dose of IFX (5 mg/kg), 8-week study with follow up at week 2, 4 and 8	Chron's disease (n=15), mean age 32.7± 11.4	SCL-90 BDI HAMD	Reduction in SCL-90 depression scores after correction for decrease in disease's activity.

anti-inflammatory response to TNF-α inhibition that may be beneficial in subjects that display increased inflammation and/or altered metabolic functioning. Complementary findings from studies that analyzed leukocyte expression of genes related to inflammatory cytokines in individuals with MDD before and after antidepressant treatment with escitalopram or nortriptyline showed increased baseline expression of genes including IL-1 β and TNF-α in non-responders as compared to responders [127, 128]. In this study, while higher levels of pro-inflammatory cytokines predicted lack of future response to antidepressants, antidepressant response was not related to reductions in specific cytokines levels, indicating a possible dissociation between "predictors" and " target" of response. Taken together, these results are consistent with the idea that while increased baseline inflammation predicts non-response to conventional antidepressant therapy, it may simultaneously portend a successful response to immune-targeted treatment.

6.5. Etanercept Effect on Depressive Symptoms in Chronic Inflammatory Diseases

Some preliminary data support the evidence that ETN alleviates depressive symptoms in inflammatory diseases including RA, AS and psoriasis (Table **3**). In a randomized, double-blind trial conducted on patients affected by RA, the group receiving adjunctive ETN showed greater improvement in depressive symptoms on the HADS as compared to the group treated with methotrexate (MTX) alone [129]. These findings have been replicated in a subsequent open-label study, in which patients receiving ETN plus MTX (n=281) showed lower depression and anxiety scores on the HADS, as compared to the subset receiving disease-modifying antirheumatic drugs (DMARD) + MTX (n=142) [130]. Another open-label, 24 week study on patients with moderate to severe plaque psoriasis, evaluated the effect of ETN administration in continuous versus interrupted regimen on depressive symptoms. A continuous treatment regimen resulted in sustained greater improvement in depression severity on the BDI [131]. In contrast with this finding, in another open-label, 54-week study on patients with psoriasis, receiving continuous therapy with ETN or paused treatment, both groups exhibited significant improvements in HADS-D and HADS-A scores without meaningful differences between the two arms [132]. In a randomized, double-blind, placebo-controlled trial, patients with psoriasis (n=618) were randomized to ETN or placebo for 12 weeks, followed by a 84-week open-label active-treatment period. Treatment with ETN was associated with significant improvement in

Table 3. Etanercept (ETN) effect on mood symptoms in chronic inflammatory diseases. HADS, Hospital Anxiety and Depression scale; HAM-D, Hamilton Depression Scale; SCL-90, Symptom Checklist; BDI, Beck depression Inventory; DMARD, Disease-Modifying Antirheumatic Drugs; MTX, methotrexate.

Author	Study Design	Diagnosis	Measures	Outcome
[133]	Randomized, double-blind, placebo-controlled, 12 week trial. Patients received ETN (50 mg s.c. / twice weekly)	Active psoriasis (n=620)	HAM-D BDI	Significant improvement in BDI and HAMD scores from baseline to endpoint
[134]	See [133] for results from double-blind phase. Second phase after week 12; open label ETN for 84 weeks.	Plaque psoriasis (n=591)	HAMD BDI	Increase in both groups in the percentage of HAM-D and BDI responders (>50%change) and remitters
[131]	Randomized, open-label, 24-week trial. Subjects received ETN for 12 weeks, then continued ETN for other 12 weeks or interrupted the therapy	Moderate-severe plaque psoriasis (n=2546)	BDI	Improvements in both groups in BDI scores at 12 weeks were sustained up to 24 weeks, with greater improvements in the group receiving continuous treatment
[132]	Open-label, 54-week study. A group (n = 352) received ETN 25 mg s.c. twice weekly, while the other group (n=359) received 50 mg twice weekly until adequate clinical response, with retreatment in case of psoriasis reactivation.	Moderate-severe plaque psoriasis	HADS	Improvement in HADS-D and HADS-A scores from baseline to endpoint in both groups
[129]	Randomized, double-blind, 104-weeks trial. Subjects received ETN (50 mg/weekly) plus MTX or MTX alone	Moderate-to-severe active early RA (n = 389)	HADS	Greater improvement in HADS scores in ETN-MTX group as compared to MTX group at endpoint
[135]	Randomized, double-blind, study. Subjects received ETN 50 mg twice weekly (n = 379) or weekly (n = 373) for 12 weeks and open-label ETN 50 mg twice weekly for 12 weeks	Moderate severe psoriasis (non-PsA) and psoriatic arthritis (PsA)	HADS	At baseline, 37% of patients reported symptoms of depression, which declined to 26% at week 12 and 23% at week 24.
[136]	Patient-level integrated analysis Patients received ETN 25 mg once weekly to 50 mg twice weekly or placebo for 12 –24 weeks.	Moderate severe psoriasis (non-PsA) (n = 1330) and PsA (n= 523)	HAM-D	Reduction in the percentage of depressed patients from baseline (32 % in the PsA group and 20.7 % in the non-PsA group) to endpoint (16% and 12,1% respectively)
[130]	Open-label, 24-week study. Subjects were randomized 2:1 to ETN 50 mg/weekly + MTX (n = 281) or DMARD + MTX (n = 142)	Moderate to severe active RA	HADS	Greater improvements in HADS scores in the ETN + MTX group at week 24

depressive symptoms after 12 weeks as compared to the placebo group, with greater proportions of patients exhibiting at least a 50% improvement in HAM-D or BDI scores [133]. The decrements in depressive scores were sustained in both groups up to week 96 and were not strongly correlated with the improvement in clinical psoriasis severity, thus suggesting that treatment may directly affect depression severity [134]. Moreover, in a randomized, double-blind study on subjects with psoriatic arthritis, ETN treatment was associated with a significant reduction in the percentage of patients with symptoms of depression on the HADS from baseline (37%) to weeks 12 (26%) and 24 (23%) [135]. Lastly, ETN antidepressant properties have been confirmed in a subsequent patient-level integrated analysis, including three randomized placebo-controlled trials on psoriasis. Patients with (n = 523) and without (n = 1330) psoriatic arthritis received ETN 25 mg once weekly up to 50 mg twice weekly or placebo for 12–24 weeks. The percentage of patients with significant depressive symptoms (categorized as a HAM-D score of > 7) from baseline to week 24 decreased from 32.4 to 16.1 in the arthritis-group and from 20.7 to 12.1 in the psoriasis-non arthritis group [136].

6.6. Adalimumab Effect on Depressive Symptoms in Chronic Inflammatory Diseases

The effect of ADA maintenance therapy on depressive symptoms (Table **4**) has been evaluated in patients with moderate to severe CD in a randomized, double-blind, 56-week clinical trial. Following a 4-week ADA induction therapy, patients were randomized to maintenance treatment or placebo. The group receiving ADA showed lower scores on the Zung Self-rating Depression Scale (ZDS), as compared to the placebo-group [137]. Moreover, ADA administration significantly reduced depressive symptoms in patients with moderate to severe psoriasis in a randomized, double-blind, placebo-controlled, 12-week trial, with a significant reduction in depressive symptoms on the ZDS (n = 52) [138]. A recent small longitudinal study in patients

Table 4. Adalimumab (ADA) effect on mood symptoms in chronic inflammatory diseases. ZDS, Zung Self Rating Depression Scale; PASI, Psoriasis Area and severity index; HADS, Hospital Anxiety and Depression scale; HAM-D and A, Hamilton Depression and Anxiety Scale.

Author	Study Design	Diagnosis	Measures	Outcome
[137]	Randomized, double-blind, 56 week trial. Following a 4-week ADA induction therapy subjects were randomized to receive ADA (40 mg weekly or every 2 weeks) or placebo	Moderate to severe Crohn's Disease	ZDS	Greater reduction in ZDS scores in the ADA group as compared to the placebo group at week 56
[138]	Randomized, placebo-controlled, double-blind, 12 week trial. Subjects received placebo (n=52) or ADA 40 mg weekly or other week (n=44) starting at week 1 after induction dose (80-mg) at week 0	Moderate to severe psoriasis	ZDS PASI	ADA group (n = 44) exhibited greater reduction in ZDS scores as compared to the placebo group at week 12, correlated with improvements on the PASI.
[139]	Longitudinal, 6 week study 9 patients resistant to conventional therapy with DMARD received ADA (40 mg/kg every other week) or IFX (5 mg/kg at week 0, 2 and 6).	Ankylosing spondylitis	HAM-D, HAM-A HADS	Improvements in HAM-D, HAM-A, HAD anxiety scores. No significant changes over time in HAD–D scores were observed

with AS resistant to classic anti-inflammatory therapy showed that treatment with TNF-α blockers (IFX or ADA) was associated with a significant reduction in HAM-D and HAM-A scores. A decrease in CRP levels was also reported, in correlation with changes in depression–anxiety scores [139].

7. GENETIC PREDICTORS OF RESPONSE TO TNF-A ANTAGONISTS

Several studies have sought to identify genetic markers predicting anti-TNF-α treatment outcome. Many pharmaco-genetic studies have attempted with mixed results to link TNF-α promoter polymorphisms with responsiveness to TNF-α blockers in populations affected by chronic inflammatory diseases. For example, there is meta-analytic evidence that TNF-α -308 G/G and -857 C/C genotypes predict a better response to anti-TNF-α treatment (O.R.= 2.31 and 2.17) in individuals with ankylosing spondylitis or inflammatory bowel disease as compared to A/A or A/G genotypes and C/T or T/T genotypes, respectively [140]. However, on the contrary, previous meta-analyses did not support the association between TNF-α -308 A/G polymorphism and treatment response in patients rheumatoid arthritis [141]. Other studies provided evidence that single-nucleotide polymorphisms in TNF-α -related apoptosis-inducing ligand receptor 1 (TRAIL-R1) gene and in genes involved in p38 or NFκB signalling network have been also associated with anti-TNF-α response [142]. However, genome-wide association studies provided highly heterogeneous results, frequently not consistently replicated [143]. Inconsistencies among studies could be attributed to a number of factors including sample size resulting in low statistical power, the different diseases studied, lack of consistent outcome measures and differences in the drugs investigated. Taken together, available data suggest that there may be a number of genes exerting modest effects on treatment response rather than a few genes of large effect. When considering the therapeutic potential of TNF- α antagonists for MDD, these results have to be interpreted with caution as the data were derived from populations affected by chronic inflammatory diseases, and therefore should not be extrapolated to patients with MDD. Moreover, it has to be acknowledged that the response to anti-TNF-α agents in cohorts affected by chronic inflammatory diseases is defined by improvement in disease's activity and not by measures of antidepressant efficacy. Further studies are warranted to verify and confirm these findings in primary psychiatric populations.

8. SUMMARY

Accumulating evidence from experimental models and clinical trials in chronic inflammatory diseases highlights the antidepressant properties of TNF-α antagonists. In non-primary psychiatric populations, comorbid major depression and anxiety disorders are identified less frequently in patients receiving anti-TNF-α drugs compared to patients who do not receive such medications [144]. Moreover, experimental and clinical preliminary evidence support pro-cognitive potential of TNF-α antagonists under conditions characterized by enhanced pro-inflammatory activation. A randomized, double-blind, placebo-controlled trial documented that IFX could offer therapeutic benefit to primary depressed populations who exhibit elevated baseline levels of pro-inflammatory markers.

9. CONCLUDING REMARKS

Despite important advances in neuroscience during the past several decades, less than two thirds of depressed patients achieve remission with currently available antidepressant drugs. A better understanding of neurobiology and patho-physiology of neuropsychiatric disorders is critical for the development of novel treatments with superior efficacy to conventional antidepressants and possibly disease-modifying effects in brain disorders [145]. In this context, translational research, aimed at understanding the role of the immune system in neuropsychiatric disorders, may lead to the identification of relevant targets for the development of mechanism and evidence-based psychopharmacological approaches with predictive preclinical validity. In keeping with this view, a growing body of evidence suggests that selective targeting of identified molecules may be preferred

in order to avoid the possible detrimental effect of an extensive inhibition of inflammatory processes [36]. In fact, while the cross-talk between the brain and the immune system is recognized as a relevant factor for cognition development, pro-inflammatory alterations partly account for cognitive impairment associated with psychiatric disorders and with various neurodegenerative diseases (*e.g*. Alzheimer's disease) [21]. Moreover, cognitive impairment may represents a trait marker in MDD, given that deficits present early in the illness course and persist in remitted states despite adequate psychopharmacological treatment [1].

TNF-α antagonism provided encouraging findings in improving depressive symptoms in chronic inflammatory diseases. Converging evidence from several RCTs points out a beneficial role of anti-TNF-α agents in these populations. Notwithstanding the beneficial effect exerted in these populations, data should not be extrapolated to primarily depressed patients and clear limitations of current evidence should be noted. Trials evaluating the impact on TNF-α antagonists on depressive symptoms involved highly heterogeneous populations with regard to primary diagnosis, possibly reflecting different etio-pathogenetic mechanisms in the development of depressive symptoms. The lack of placebo controls and the involvement of small sample sizes are other limitations in the design of at least some of these studies. Moreover, the use of disparate diagnostic tools in the assessment of depression severity limits between-study comparisons. Another issue affecting in the interpretation of these results is the notion that depression is a chronic illnesses is likely to be strongly influenced by ongoing disease activity activity. In this context it seems relevant that future studies aim to determine which rate of improvement in depressive symptoms' severity is explained by the reduction in disease's activity and which is primary attributable to the treatment. To date, only one study provided evidence of the potential on anti-TNF-α agents for MDD. In a randomized placebo- controlled trial on individuals with treatment resistant IFX resulted superior to placebo in mitigating symptoms severity on the HAM-D in individuals exhibiting elevated inflammation at baseline [*i.e.*, hs-CRP levels > 5mg/L]. This important finding suggests that anti-inflammatory treatment could exert beneficial effect in a subset of depressed individuals with great pretreatment immune dysfunction [26]. This study did not assess the effect of treatment on cognitive performance and further studies are warranted to confirm the antidepressant properties of TNF-α antagonists and to explore their potential on cognitive domains in primary depressed populations.

Preliminary data indicate that TNF-α antagonists may exert pro-cognitive effects in preclinical models of LPS-induced neuroinflammation and in open-label studies involving individuals with RA [146] and sarcoidosis [147]. Moreover, the administration of perispinal ETN resulted in rapid cognitive improvement in a large cohort of patients with Alzheimer's disease [148].

The encouraging data regarding safety and tolerability of these agents on populations with chronic inflammatory diseases [149] would eventually inform the repurposing of these agents for various neurodegenerative diseases [21] and neuropsychiatric disorders, including MDD, with a potential benefit on cognitive domain as well as depressive symptoms. In fact, cognitive impairment may represent a core psychopathological dimension of MDD and interventions aimed at improving cognitive functions may facilitate full functional recovery. Further research efforts are warranted also to identify through biomarkers and endophenotypes a subset of patients in which anti-inflammatory treatment may represent a novel disease-modifying therapy. Hence, the identification of biomarkers predicting the response to therapy represents a crucial goal in the personalization of treatment. Importantly, this review indicates that TNF-α antagonists may represent novel therapeutic targets that span the classical boundaries of discrete mental disorders. Therefore, TNF-α antagonists may hold promise as a domain-specific treatment and is aligned with novel approaches for drug discovery [145] as proposed by the US National Institutes for Mental Health (NIMH) [150].

CONFLICT OF INTEREST

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LIST OF ABBREVIATIONS

5-HT	=	5-hydroxytryptamine
ACC	=	anterior cingulate cortex
ADA	=	adalimumab
AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic
AS	=	ankylosing spondylitis
ATP	=	adenosine triphosphate
BD	=	Bipolar Disorder
BDI	=	Beck depression Inventory
BDNF	=	brain derived neurotrophic factor

BMI = body mass index
CCL = C-C chemokine ligands
CD = Crohn's Disease
CES-D = Center for Epidemiological Studies Depression scale
CNS = central nervous system
COX-2 = cyclooxygenase-2
CPZ = certolizumab
CRP = C-reactive protein
DLPFC = dorsolateral prefrontal cortex
DMARD = disease-modifying antrheumatic drugs
DSM IV = Diagnostic and Statistical Manual of Psychiatric Disorders IV
EPM = elevated plus maze
ETN = etanercept
FST = forced swim test
GABA = gamma-aminobutyric acid
GLB = golizumab
HADS = Hospital Anxiety and Depression scale
HAM-D = Hamilton Depression Scale
HAM-D = Hamilton rating scale for Depression
HDL = high density lipoprotein
hs-CRP = high sensitivity C-reactive protein
ICAM = intercellular adhesion molecule
IDO = indoleamine 2,3-deoxygenase
IFN = interferon
IFX = infliximab
IL = interleukin
= soluble cytokine
KYN = kynurenine
LPS = lipopolysaccharide
LTD = long-term depression
MAPK = mitogen activated protein kinase
MDD = Major Depressive Disorder
MMP = metalloproteinase
MTX = methotrexate
NGF = nerve growth factor
NMDA = N-methyl-D-aspartate
NO = nitric oxide
OFC = orbitofrontal cortex
PHQ-9 = Patient Health Questionnaire 9-items
QUIN = quinolinic acid
RA = rheumatoid arthritis
RCT = randomized controlled trial
SCL-90 = Symptom Checklist
SERT = serotonin transporter
SNRI = serotonin-noradrenaline reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
sTNF- α = soluble tumor necrosis factor
TACE = TNF- α –converting enzyme
TCA = tricyclic antidepressant
TIMP = tissue inhibitor of metalloproteinase
TLR = Toll-like receptor
tmTNF-α = transmembrane tumor necrosis factor
TNF-α R = tumor necrosis factor receptor
VCAM = vascular cell adhesion molecule

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