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Progress in Neuro-Psychopharmacology & Biological Psychiatry xx (2008) xxx–xxx

Progress In
Neuro-Psychopharmacology
& Biological Psychiatry

www.elsevier.com/locate/pnpbp

Review article

TNF- α as a molecular target in bipolar disorder

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Received 8 September 2007; received in revised form 7 January 2008; accepted 8 January 2008

Abstract

The pathophysiology of bipolar disorder (BD) is poorly understood. An emerging body of evidence points to impairments in neuroplasticity, cell resilience and neuronal survival as the main neuropathological correlates of BD. It has been suggested that inflammatory cytokines, particularly TNF- α may play a critical role in this process. In the present review we examine the evidence suggesting that TNF- α regulates apoptotic cascades which may be related to neuronal and glial loss in BD. Current evidence suggests that an increase in serum levels of TNF- α takes place during manic and depressive episodes. The present article reviews the therapeutic implications of TNF- α signaling pathways involvement in the pathophysiology of BD.

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Keywords: Bipolar disorder; Cytokines; Mood disorders; NF- κ B; TNF- α

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Introduction

Traditionally, the brain has been considered as an area without contact with immune mediators, protected by the blood-brain barrier (BBB) (Schiepers et al., 2005; Gosselin and Rivest, 2007). Current information shows that brain tissue is able to engender immune processes and be influenced by them (Schiepers et al., 2005; Kronfol and Remick, 2000). The elucidation of the immunology of the central nervous system (CNS) might offer new insights regarding causes of a number of

Abbreviations: ADNF, Activity-Dependent Neurotrophic Factor; BD, Bipolar Disorder; BDNF, Brain Derived Neurotrophic Factor; CNS, Central Nervous System; CRH, Corticotrophin-releasing hormone; CSF, Cerebral Spinal Fluid; TNF- α , Tumor Necrosis Factor- α ; I- κ B, Inhibitor of κ B; MMSE, Mini Mental State Examination; NF- κ B, Nuclear Factor- κ B; NGF, Nerve Growth Factor; SOD, Superoxide dismutase.

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doi:10.1016/j.pnpbp.2008.01.006

Please cite this article as: Brietzke E, Kapczinski F, TNF- α as a molecular target in bipolar disorder, Prog Neuro-Psychopharmacol Biol Psychiatry (2008), doi:10.1016/j.pnpbp.2008.01.006

neuropsychiatric disorders, like Alzheimer's disease, schizophrenia, and mood disorders (Schiepers et al., 2005; Kronfol and Remick, 2000). In the field of mood disorders, the immune system seems to play a particularly important role. The present work will focus on the findings pertaining to the field of bipolar disorder (BD).

Epidemiological studies indicate the participation of both biological and environmental factors in the pathogenesis of BD. Recent studies have described impairments in neuroplasticity and neuronal survival among BD patients (Schloesser et al., 2007). Neuronal survival is influenced by several factors including the orchestrated action of neurotransmitters, hormones, and neurotrophins. Brain derived neurotrophic factor (BDNF) has emerged as a key mediator for synaptic plasticity, neuronal connectivity, and dendritic arborization (Post, 2007). Moreover, some studies reported decreased BDNF levels in the serum of both manic and depressive episodes of BD (Cunha et al., 2006).

In addition, it is now recognized that the long-term outcome of BD is much less favorable than previously thought, with incomplete recovery between episodes, cognitive impairment, and functioning decline (Mur et al., 2007; Martinez-Aran et al., 2007). It should be noted that morphometric studies have demonstrated that patients with BD have enlarged third and lateral ventricles (Soares et al., 2005), reduced gray matter in hippocampus and cerebellum (Moorhead et al., 2007), and reduced volumes in some areas of the prefrontal cortex (Blumberg et al., 2006; Soares et al., 2005). An increase in the size of the amygdala has also been reported (Beyer and Krishnam, 2002) and is currently considered to be one of the most consistent findings among BD patients (Phillips and Vieta, 2007). Strakowski et al. (1993) reported that even first-episode mania is associated with larger ventricles and differences in gray/white matter distribution when compared to controls, but this neuroanatomical change tends to be more pronounced with repeated episodes (Strakowski et al., 2002a). It has been argued that similar changes may occur among patients with chronic unipolar depression (for a detailed review of this topic see Campbell and McQueen, 2006). Imaging studies suggest that, in both depressive and bipolar disorder, there is a relatively low prefrontal modulation of subcortical structures; yet, limbic subcortical regions appear to differ in BD and unipolar depression (Strakowski et al., 2002b).

There is also strong evidence of the association between untreated BD and increased rates of death by cardiovascular and cerebrovascular events, giving BD a systemic dimension (Angst et al., 2002; Kupfer, 2005). One of the links between mood disorders and general medical diseases could be the increase of proinflammatory cytokines, particularly TNF- α , which is a causal factor in the development and progression of arteriosclerosis (Evans et al., 2005).

Function of inflammatory cytokines in the brain

Cytokines are proteins or glucoproteins secreted by immune cells in response to noxious stimulus. Acting together, either locally or systemically in the immune response, they function like signals among immune cells. It is now known that cyto-

kines can be secreted not only by immune cells. Cytokines are frequently regulated in cascades, where the induction of early cytokines serves to increase the production of later cytokines (Kronfol and Remick, 2000). Cytokines interact with the neuroendocrine system, e.g., the hypothalamic–pituitary–adrenocortical system, the autonomic system and the neurotransmitter system (dopamine, serotonin and glutamate) (Kim et al., 2007a).

Cytokines have high molecular weight but they may cross the BBB either through leaky areas or by active transport (Kim et al., 2007a; Pan and Kastin, 1999). In the brain, they act in specific pathways involved in mood, energy, and activity control. One example of these pathways is the glucocorticoid pathway, with some cytokines increasing corticotrophin release hormone (CRH) release in hypothalamus (Irwin and Miller, 2007; Pasic et al., 2003) or disturbing the functioning of glucocorticoids receptors (Irwin and Miller, 2007). TNF- α has also been found to significantly up-regulate the activity of the serotonin transporter, an effect that can determine reduced function of serotonergic transmission by the reduction of synaptic availability of serotonin (Irwin and Miller, 2007).

Cytokines in mood disorders

There are some studies describing a potential role of cytokines in the pathogenesis of depression. Patients with depression that are otherwise healthy seem to have activated inflammatory pathways, with increased proinflammatory cytokines, acute-phase proteins, and increased expression of chemokines and adhesion molecules (Raison et al., 2006; Yang et al., 2007, Kim et al., 2007b). In addition, specific depression symptoms could be associated with increased cytokines levels, like suicidal behavior (Kim et al., in press).

In the field of BD the findings are still limited, but there is some data affirming that mania also could be associated with a proinflammatory state. Some studies reported increased proinflammatory cytokines and hyperactivity of T helper cell 1 in bipolar disorder, with significantly higher TNF- α levels in bipolar patients during manic (Kim et al., 2007a; O'Brien et al., 2006) and depressive episodes than normal controls (O'Brien et al., 2006). Kim et al. (2007a) reported increased production of interleukin-6 and TNF- α during mania when compared with nonbipolar controls. Among such patients, interleukin-6 levels returned to the baseline after 6 weeks of treatment with mood stabilizers, but TNF- α levels continued high. Accordingly, the authors considered that interleukin-6 is a manic state marker, but TNF- α could be an enduring change (Kim et al., 2007a).

In other recent study, O'Brien et al. (2006) described that both mania and bipolar depression are associated with increased production of proinflammatory cytokines interleukin-6, interleukin-8 and TNF- α , even with the use of mood stabilizers or antipsychotic medication. No difference was observed in the concentration of anti-inflammatory cytokine interleukin-10 or in cortisol concentrations between manic subjects and controls. However interleukin-10 production was found to positively correlate with cortisol concentration in

mania. The authors considered a possible feedback axis between cortisol and proinflammatory cytokines.

TNF- α and bipolar disorder

TNF- α is a 157 amino acid cytokine and is produced in response to injury and inflammatory or infectious stimuli by macrophages, lymphocytes, neutrophils, and structural cells, including fibroblast, smooth muscle cells (Balakumar and Singh, 2006), astrocytes and microglia (Kronfol and Remick, 2000). It is considered a proinflammatory molecule, augmenting the immune response to help speed-up the elimination of pathogens and the resolution of the inflammatory challenge (Kronfol and Remick, 2000). TNF- α has several effects, including cytotoxicity, antiviral activity, transcription factor activation, and immune response regulation (Bhardwaj and Aggarwal, 2003).

TNF- α exerts its effects by binding to specific receptors named TNF-R1 and TNF-R2 (Gosselin and Rivest, 2007). TNF-R1 is more abundantly expressed, existing in most tissues and cell types and appears to be the main signaling receptor. The majority of deleterious effects produced by TNF- α seem to be mediated via this receptor. TNF-R1 mediates many actions of TNF- α , including cytokine production, activation of transcription factors like NF- κ B, and apoptosis (Bhardwaj and Aggarwal, 2003). Interestingly, TNF-R1 activation can trigger

a dual signaling cascade that in different cell types may lead to apoptosis, proliferation, differentiation, or survival (Fig. 1).

Apoptosis is the term used to describe a kind of cellular death characterized by cytoplasmic membrane blebbing, chromatin condensation, DNA rupture, and lastly by cell fragmentation. The sign for apoptosis may be triggered by intracellular or extracellular proteins, but the final effector is always the same: activation of a group of enzymes called caspases that work like a cascade by targeting and cleaving key cellular structures and promoting cell decomposition. TNF- α is a cell-surface receptor that acts like an extracellular trigger for apoptosis (Bhardwaj and Aggarwal, 2003).

In neurons and microglia, TNF- α induces apoptosis when it binds to TNF-R1. TNF-R1 contains a sequence located in the cytoplasm called death domain. This death domain sequence then binds to the death domain of a cytoplasmic adapter protein called TNF receptor associated death domain (TRADD). TRADD then recruits Fas-associated death domain (FADD). FADD activates caspase-8 and then the rest of the caspase cascade resulting in the degradation of DNA and cell death. The apical element in caspase cascade is caspase-8 activated by FADD and the last is caspase-3, which is directly responsible for cell degradation (McDonald et al., 2003). McDonald and collaborators (2003) have found increased activity of caspase-8 and caspase-3 in TNF- α incubated PC 12 cells, an understandable result taking into account the neurotoxic effect of this cytokine.

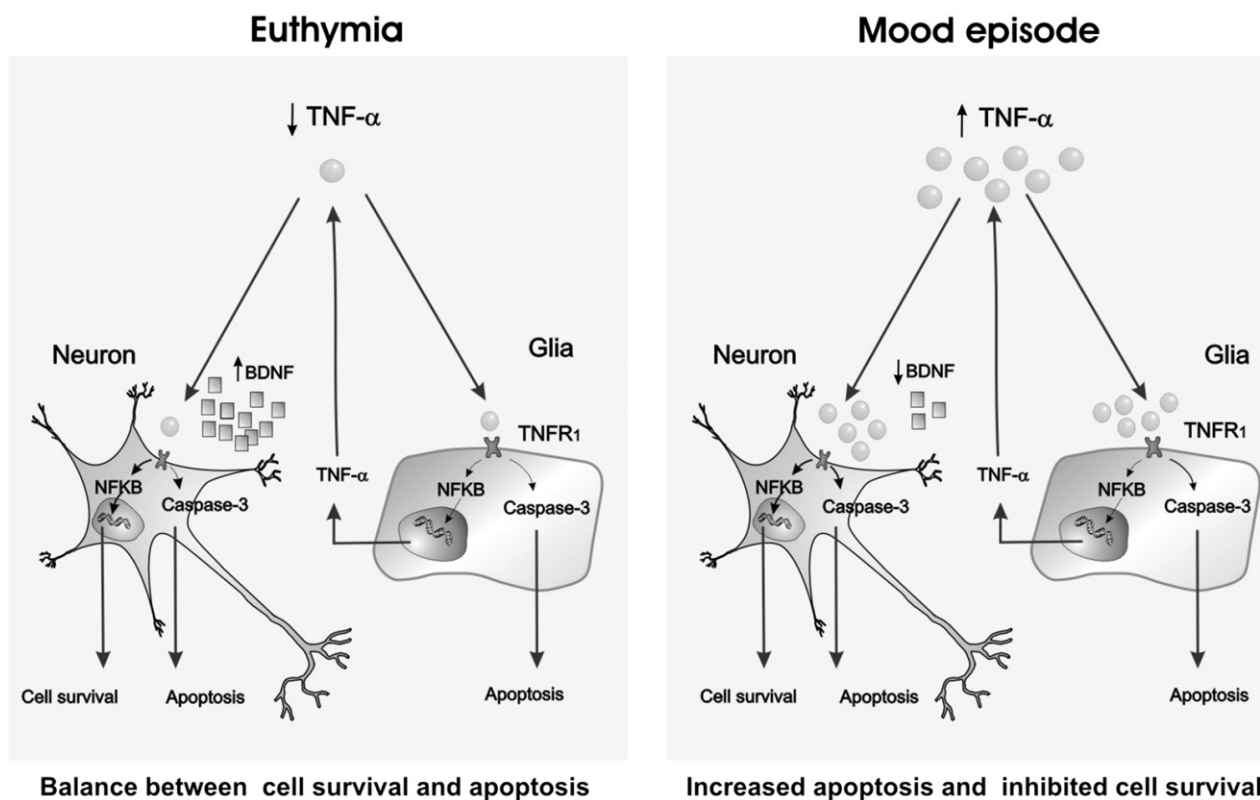


Fig. 1. During mood episodes, increased TNF- α levels enhance TNFR1 stimulation in glial cells and this activates both apoptotic routes and TNF- α production. In neurons, cell death mechanisms related to caspase activity are set into motion. In this context, neuronal translocation of NF- κ B is shut down due to lower levels BDNF (which have been described during mood episodes by Cunha et al., 2006). Therefore, we postulate that during acute mood episodes the balance between cellular life and death is shifted towards apoptosis.

Although the exact cerebral target areas of TNF- α are still being studied, animal research showed high receptor density in the hippocampus and hypothalamus (Pasic et al., 2003). TNF- α expression was documented in astrocytes, microglia, and neurons within the CNS under physiological conditions. Under inflammatory conditions the expression increases substantially (Pasic et al., 2003).

The effect of TNF- α in glial cells is especially important because the finding of marked reduction in glial cells in the prefrontal cortex of bipolar patients is associated with change in structural imaging studies. It is known that glial cells play a critical role in the regulation of the amount of synaptic glutamate concentration, in the production and release of neurotrophic factors, and are strong collaborators in the delicate balance between cellular life and death in the intimacy of the brain (Manji et al., 2003). Some studies clearly describe the reduction of glial numbers in the prefrontal cortex in both major depression and BD, (Rajkowska, 2000; Rajkowska et al., 2001). In addition, signs of necrosis and apoptosis have been observed in oligodendrocytes in the frontal cortex and caudate nucleus of bipolar patients (Uranova et al., 2004). Others have found that glial cells appear to be smaller in bipolar patients (Brauch et al., 2006) or with larger nuclei, possibly indicating that they are under strain, working harder to compensate the reduction in number of this cell type (Rajkowska, 2002). Once considered as only supportive elements, today glia seems to carry out important roles in the regulation of high order brain functions like synaptic glutamate levels, CNS energy homeostasis, liberation of trophic factors (Manji and Duman, 2001), serotonergic and noradrenergic transmission (Rajkowska, 2000). Moreover, the marked loss of glia cells observed in BD is probably related to the pathophysiology of this disorder. Interestingly, cell loss which has been described in the brain cortex of bipolar patients is significantly different from the cell loss found in classic neurodegenerative disorders, like Huntington's disease. In these cases, there is a marked loss of neurons accompanied by prominent gliosis with dramatic increases in glial cell density. Consequently, the cortex of patients with mood disorders does not exhibit neurodegeneration, but has a disturbance in neuroplasticity and cell resilience (Rajkowska, 2003). Therefore, it is possible that this cell pattern does not reflect a glial reaction to neuronal loss, which must be accompanied by gliosis but, represent a pathology that begins in glia (Rajkowska, 2002).

NF- κ B modulation of cell survival, apoptosis and TNF- α production

Under normal conditions, the brain must have a regulatory pathway of immune-induced neuronal apoptosis to limit the potential harmful effects of sustained inflammatory reactions. Although TNF- α kills cells (including neurons) by apoptosis, it may also negatively regulate its own ability to induce cell death. This appears to be mediated by the induction of NF- κ B. NF- κ B is a transcription factor present in all cell types including neuron and glial cells and could have an important function in promoting cell survival. A major insight into the function of NF- κ B

has been the observation that Rel A (a subunit of NF- κ B) knockout mice die in the embryo stage of development as a result of extensive liver apoptosis. Furthermore, cells derived from these mice demonstrate enhanced sensitivity of TNF- α -induced cell death (Sun and Anderson, 2002).

NF- κ B is present in axons, dendrites, and synaptic terminals. NF- κ B is composed of two subunits and normally retained in the cytoplasm through its association with the inhibitory I- κ B. Phosphorylation, ubiquitination, and proteolysis of I- κ B allows NF- κ B to translocate to the nucleus and induce gene transcription (Sun et al., 2001). In the nucleus, NF- κ B binds to specific sequences in the promoter/enhancer regions of a set of genes that prevents cells to undergo apoptosis (Furuno and Nakanishi, 2006). Several signals could activate NF- κ B in neurons, like TNF- α (mentioned above), the excitatory neurotransmitter glutamate, nerve growth factor (NGF), activity-dependent neurotrophic factor (ADNF), a secreted form of amyloid precursor protein, cell adhesion molecules (Mattson, 2005), glucocorticosteroids, products of virus and bacteria, and reactive oxygen species.

When activated, NF- κ B translocates to the nucleus where it binds to specific sequences of DNA and induces the transcription of genes which are important for cell survival. Among these genes are cellular inhibitors of apoptosis (cIAP), Bcl2 e Bcl-xL, TRAF1/TRAF2, superoxide dismutase (SOD) (Mattson and Meffert, 2006). Early indications that NF- κ B could promote survival in neurons came from studies of embryonic rat hippocampal cultures. When the neurons were previously incubated with TNF- α they were more resistant to death when exposed to metabolic and excitotoxic insults (Mattson and Meffert, 2006).

Moreover, Blondeau et al. (2001) developed the concept of NF- κ B as the key event in brain tolerance. When the brain is submitted to noxious stimuli applied close but below the threshold for cell death there are adaptative responses that protect it against additional stress from the same (tolerance) or other stimuli (cross-tolerance). The authors studied three models of brain injury (seizure, ischemia, and poly-unsaturated fatty acid damage) submitting hippocampal neurons of rats to them. After that, the neurons received a dose of the proconvulsive substance kainic acid or a sublethal 3-min ischemia. The pretreatment caused a rapid increase of NF- κ B DNA-binding activity and nuclear translocation of subunits of NF- κ B and led to neuronal resistance to subsequent injury. In contrast, pretreatment with a NF- κ B inhibitor diethylthiocarbamate or κ B decoy DNA eliminated the nuclear translocation of NF- κ B and the neuroprotective effects of sublethal noxious stimuli (Blondeau et al., 2001). Therefore, there is strong evidence that NF- κ B is the cell mediator of brain tolerance and the study of this process could open new avenues in the search for therapeutic strategies targeting neuronal protection.

However, the activation of NF- κ B by glial cells might indirectly promote neuronal death. Microglia and astrocytes respond to the increase of intracellular NF- κ B with the production of large amounts of reactive oxygen species, excitotoxins, and more proinflammatory cytokines (Mattson, 2005). A potential explicative model concerning the role of NF- κ B in neuronal

survival is that the activation of NF- κ B in neurons could promote their survival and the activation of this transcription factor in glial cells may induce neuronal loss (Mattson, 2005; Mattson and Meffert, 2006).

Interestingly, neurotrophic factors and cytokines could cooperate in intracellular signaling. When PC12 cells are co-stimulated with TNF- α and NGF or BDNF, the nuclear translocation of NF- κ B increases greatly whereas, neither NGF nor BDNF themselves induces NF- κ B translocation (Furuno and Nakanishi, 2006). Thus, it can be hypothesized that when neurons are exposed to inflammatory states, the presence of BDNF and NGF might limit the immune injury in the brain. In the presence of low levels of neurotrophic factors, the amplification of inflammatory damage could not be controlled.

TNF- α and NF- κ B genetics

Considering the potential role of TNF- α and NF- κ B in the pathophysiology of BD, it could be beneficial to know if a genetic variation of these proteins may confer risk for BD. There are two studies conducted with Korean participants that analyzed polymorphisms of TNF- α and investigated its relationship with BD. One of these described an association between TNFA*2 allele and BD (Kim et al., 2003) and the other found an association between the -G308A and this condition (Pae et al., 2004). Furthermore, there is a *post mortem* research investigating the brains of individuals with BD to determine the levels of RNA encoding components of the NF- κ B transcription complex. This study demonstrated increased levels of mRNA in the frontal cortex from individuals with BD compared with controls (Sun et al., 2001).

TNF- α and cognitive impairment

Cognitive decline has been well documented in bipolar patients and possibly has a negative impact on social functioning and disability. The etiology of cognitive impairment in bipolar disorder is not completely understood but it seems to be related to the number of episodes, the number of hospital admissions, and the duration of the illness. Both depressive and mania episodes related negatively to cognitive performance but mania seems to be more consistently related to a delay in verbal memory and executive functions, these deficits persist even in euthymia (Robinson and Ferrier, 2006).

There are several reports of impairments in cognitive functioning during inflammatory reactions. In animals, increases of proinflammatory cytokines impair spatial learning and disrupt hippocampus dependent memory formation (Larson and Dunn, 2001). Also, several early observations indicate that TNF- α levels increased in cerebral spinal fluid (CSF) of HIV patients and this effect is more pronounced in those with dementia rather than those without. In fact, there is some evidence that TNF- α levels are directly associated with cognitive decline in this population (Seilhean et al., 1997) and that some HIV proteins like Tat are able to reduce neuronal NF- κ B activity, which could be a possible pathway for dementia (Sui et al., 2006). TNF- α modulation could be important in others types of dementia, like

Alzheimer's disease where TNF- α level in CSF elevated 25-fold when compared to controls and TNF- α levels are correlated with clinical cognitive performance. In Alzheimer's disease, beta-amyloid stimulates TNF- α production by microglia and it could be the mechanism of neurotoxicity. In fact, a preliminary open label study with etanercept, an inhibitor of TNF- α , reported a significant improvement of the Mini Mental State Examination (MMSE) and other cognitive tests after treatment (Tobinick et al., 2006).

Despite the possibility of TNF- α functioning as a mediator of cognitive impairment in BD, until now, there are no studies evaluating this relationship.

Effects of mood stabilizers on TNF- α production and NF- κ B transactivation

Regarding the effects of mood stabilizers, one study showed that valproate suppressed TNF- α production and the inhibition of NF- κ B production *in vitro* in human glioma cells (Ichiyama et al., 2000). Thus, it can be hypothesized that valproate could interrupt the amplification of the production of TNF- α in response to the activation of TNF- α /NF- κ B in the brain and prevent the release of inflammatory cascades.

It is noteworthy that lithium has two different effects in NF- κ B, consistent with the notion that the effects of lithium are cell specific. Treatment of mouse embryonic fibroblasts with lithium decreases TNF- α -induced NF- κ B transactivation. In contrast, in neuron-like PC12 cells, lithium increases NF- κ B activity. This increase in NF- κ B activity in PC12 is associated with decreased apoptosis in these cells, suggesting that lithium-induced activation of the antiapoptotic molecule of NF- κ B contributes to the neuroprotective effects of lithium (Nemeth et al., 2002; Bournat et al., 2000). Also, lithium is a direct inhibitor of glycogen synthase kinase-3 β (GSK3 β). The activity of GSK3 β has a major influence on cell survival, with hyperactive GSK3 β increasing the susceptibility of cells to the lethal consequences of a wide variety of insults. It is possible that inhibition of GSK3 β accounts for much of lithium's neuroprotective capacity. Furthermore, GSK3 β regulates several transcription factors including NF- κ B. Bournat et al. (2000) demonstrated an inhibitory influence of GSK3 β on the transcriptional activity of NF- κ B in PC 12 cells. When the activity of GSK3 β was inhibited, the result was increased cellular survival and reduced apoptosis in a NF- κ B-dependent pathway (Jope and Bijur, 2002; Bournat et al., 2000). This effect probably is not lithium-specific and there is some evidence that lamotrigine and valproate have a similar function (Li et al., 2002).

Taking into account the studies mentioned above, it is suggested that traditional mood stabilizer medication might have some immunomodulatory actions among its therapeutic action that were not suspected before.

Conclusions

There is strong evidence that bipolar disorder involves abnormalities in multiple aspects of immunity, including TNF- α .

Probably this cytokine is not only a secondary marker of the disorder, but it might contribute to the pathophysiology of BD. The exploration of inflammatory mechanisms of BD could lead to a new wave of therapeutic options including anti-inflammatory cytokines inhibition and modification. Although its clinical benefits are still under investigation, the intriguing possibility of developing pharmacological treatments for BD which would be based on the inhibition and or the modulation of the activity of inflammatory cytokines, their receptors, and their specific signal transduction pathways is a promising approach. Such developments could bring the field closer to other areas of medicine where the main goal is the reversion of the underlying pathophysiology, instead of only treating the symptoms. Despite these exciting possibilities, it is important to remember that there are still many metabolic pathways and cytokines effects in brain that remain completely unknown.

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