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Ana Catarina Pereira, Joana Oliveira, Sónia Silva, Nuno Madeira, Cláudia MF Pereira, Maria T Cruz

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Title

Inflammation in Bipolar Disorder (BD): Identification of New Therapeutic Targets

Authors

Ana Catarina Pereira[a,b*1], Joana Oliveira[c*1], Sónia Silva[a,c], Nuno Madeira[b,d,e], Cláudia MF Pereira[a,b*2], Maria T Cruz[a,c*2]

[*1]Equally contributing first authors; [*2]Equally contributing senior authors

Affiliations

[a] University of Coimbra, Center for Innovative Biomedicine and Biotechnology (CIBB), Center for Neuroscience and Cell Biology (CNC), 3004-504 Coimbra, Portugal

[b] University of Coimbra, Faculty of Medicine, 3000-548 Coimbra, Portugal

[c] University of Coimbra, Faculty of Pharmacy, 3000-548 Coimbra, Portugal

[d] University of Coimbra, Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT), 3000-548 Coimbra, Portugal

[e] Centro Hospitalar e Universitário de Coimbra (CHUC), Department of Psychiatry, 3004-561 Coimbra, Portugal

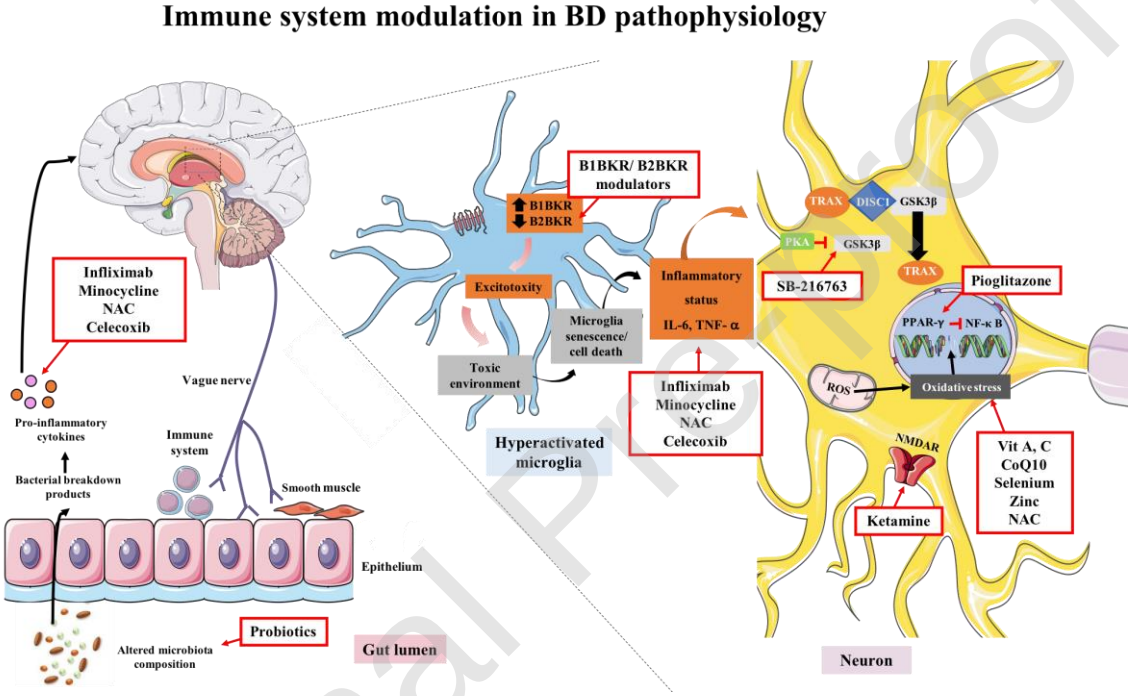
E-mail addresses

anacatarinajpp@gmail.com (Ana Catarina Pereira), joana.oliveira9@outlook.com (Joana Oliveira), sonias@ci.uc.pt (Sónia Silva), nunogmadeira@gmail.com (Nuno Madeira), cpereira@fmed.uc.pt (Cláudia MF Pereira), trosete@ff.uc.pt (Maria T Cruz)

***Corresponding author**

Sónia Silva
Faculty of Pharmacy, University of Coimbra
Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal
Phone: +351- 239 488 400
sonias@ci.uc.pt

Graphical abstract



Abstract

Bipolar disorder (BD) is a chronic and cyclic mental disorder, characterized by unusual mood swings between mania/hypomania and depression, raising concern in both scientific and medical communities due to its deleterious social and economic impact. Polypharmacy is the rule due to the partial effectiveness of available drugs. Disease course is often unremitting, resulting in frequent cognitive deficits over time.

Despite all research efforts in identifying BD-associated molecular mechanisms, current knowledge remains limited. However, the involvement of inflammation in BD pathophysiology is increasingly consensual, with the immune system and neuroinflammation playing a key role in disease course. Evidence includes altered levels of cytokines and acute-phase proteins, pathological microglial activation, deregulation of Nrf2-Keap1 system and changes in biogenic amines neurotransmitters, whose expression is regulated by TNF-α, a pro-inflammatory cytokine highly involved in BD, pointing out inflammation as a novel and attractive therapeutic target for BD. As result, new therapeutic agents including non-steroidal anti-inflammatory drugs, N-acetylcysteine and GSK3 inhibitors have been incorporated in BD treatment.

Taking into consideration the latest pre-clinical and clinical trials, in this review we discuss recent data regarding inflammation in BD, unveiling potential therapeutic approaches through direct or indirect modulation of inflammatory response.

Keywords

Bipolar disorder; Immune system; Inflammation; Cytokines; Drug therapy; Therapeutic targets.

1. Introduction

Bipolar disorder (BD) affects between 1-5% of the global population and is characterized by biphasic mood episodes of mania or hypomania and depression, expressed as recurrent episodes of changes in energy levels and behavior [1,2]. Although classic descriptions suggest a cyclic nature for BD, its natural history is frequently chronic, particularly concerning depressive states and cognitive impairment [3,4].

Residual and subthreshold symptoms frequently persist between mood episodes, making functional recovery difficult to achieve [2]. Cognitive dysfunction is also prevalent and significantly contributes to disability [2,5]. A worrying BD-related complication is undoubtedly suicide, intimately associated with depressive and mixed episodes [6].

BD is closely associated with brain morphology alterations, particularly in areas responsible for cognitive and emotional regulation, including frontal cortex, hippocampus and amygdala [7,8]. Structural neuroimaging studies have consistently reported enlargement of lateral ventricles, white matter anomalies and locoregional cortical atrophies in several brain areas, especially in the right prefrontal and temporal regions [8–10]. BD-associated cognitive deficits are proportional to the frequency and duration of episodes, leading to brain alterations and subsequent neuroprogression, resulting in more severe cognitive defects over time [11,12].

Given their significant social and economic impact, mood disorders are currently a major public health concern [13]. According to the World Health Organization, BD is the fourth leading cause of disability in individuals between 15 and 44 years old [6]. Nonetheless, until the mid-90s, when the effectiveness of valproate in manic episodes was recognized, lithium was the only available drug for BD treatment [6,14,15]. The management of patients with bipolar disorders includes, besides the acute treatment of manic or hypomanic episodes, maintenance therapy to prevent relapses and further episodes [2]. Although several new drugs have subsequently been approved for BD, including new mood stabilizers and atypical antipsychotics, these conditions are highly recurrent, even when correctly diagnosed and treated [2]. Polypharmacy is the rule, as recommended in major international guidelines [16,17].

2. Inflammation in BD pathophysiology

In the last years, several hypotheses have been proposed to achieve a better understanding of BD pathophysiology, however, the etiology, as well as the mechanisms underlying BD onset and progression are still unclear [18–20].

The immune system as a key mediator of BD progression was initially proposed based on the hypothesis that the immunologic modulation might be involved in the stabilizing mood action of lithium [21]. Indeed, both manic and depressive BD episodes are accompanied by the activation of neuroinflammation pathways, as indicated by a positive profile of acute-phase proteins, as well as by increased levels of pro-inflammatory cytokines [3,7,18]. For instance, BD-related manic stages are associated with high levels of acute-phase proteins such as haptoglobin, fibrinogen and C-reactive protein (CRP). Increased CRP levels are detected in all BD stages, however, they have been found particularly upregulated during manic episodes [12,15,22].

There are many genetic factors influencing BD susceptibility [12,23]. Although BD genetic remains a complex mosaic, there is a set of genes whose altered expression patterns are associated with phenotypes exhibited by BD patients, such as polymorphism of glycogen synthase kinase-3 (GSK3) [7]. According to its functions, GSK3 is a modulator of inflammatory responses by several mechanisms involving: 1) stimulation of pro-inflammatory cytokines production and inhibition of the anti-inflammatory cytokine IL-10; 2) inhibition of the nuclear factor erythroid 2-related factor 2 (Nrf2), a signaling pathway contributing significantly to cytoprotection against oxidative stress and concomitantly evoking an anti-inflammatory response [24–26]. Therefore, the GSK3 inhibitors may represent a useful therapeutic approach in BD treatment for modulating cytokines levels and Nrf2 activity.

As further discussed, evidences highlighting the involvement of inflammation in the course of the disease point out the innate immune system as a novel and attractive therapeutic target for BD.

2.1. Cytokines release

Cytokines are signaling molecules of the immune system and their amount in circulation is dependent on the inflammatory responses. The expression levels of cytokines oscillate according to BD phase, namely during depressive, euthymic and manic stages (**Fig.1**) [22]. Therefore, these cytokines are directly implicated in BD pathophysiology and should be considered as potential therapeutic targets. [18,24]. Tumor necrosis factor-alpha (TNF-α) is a permanent inflammatory marker of euthymic stages [22] and mania is characterized by increased levels of interleukin 6 (IL-6), as well as high levels of soluble IL-6 and IL-2 receptors (sIL-6R and sIL-2R) and of interleukin-1 receptor antagonist (IL-1RA). The inflammatory profile of depressive stages is similar, being characterized by high concentrations of pro-inflammatory cytokines namely IL-6 and TNF-α and, increased levels of sIL-6R and sIL-2R [12,22].

2.2. Oxidative stress

Oxidative stress, which is defined as an imbalance between production of reactive oxygen species (ROS) and the activity of antioxidant defenses, such as glutathione and superoxide dismutase [13], has been associated with psychiatric diseases such as BD and also linked to immune system deregulation.

Over the past years, the transcription factor Nrf2 has been pointed out as a key modulator of cellular response to oxidative stress. Furthermore, Nrf2-Keap1 system acts on the first line of inflammatory and immune modulation by regulating anti-inflammatory

gene expression and inhibiting the progression of inflammation [27,28]. Under oxidative stress conditions, free nuclear Nrf2 triggers the transcription of genes that encode antioxidant and detoxifying enzymes and related stress-responsive proteins, by binding to the antioxidant response elements located in the promoter region of these genes e.g. the anti-inflammatory gene HO-1. The increased Nrf2-dependent HO-1 expression has been associated with the inhibition of the nuclear factor kB (NF-κB), a classical signaling pathway of inflammation [27,28]. Moreover, increased HO-1 expression has a positive impact on neuroinflammation triggered by lipopolysaccharide (LPS) in mouse BV2 microglial cells and mouse hippocampal HT22 cells, as well as to the prevention of HT22 cell death [29]. In addition, Nrf2 activity has been shown to attenuate transcriptional upregulation of LPS-induced pro-inflammatory cytokines such as IL-16 and IL-1β [30]. Nrf2 activation also regulates the expression of pro-inflammatory genes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), as demonstrated by the previous study showing that Nrf2-knockout mice have increased mRNA and protein levels of inflammatory markers including COX-2 and iNOS [31]. Furthermore, several findings have demonstrated the inhibitory effect of Nrf2 on NLRP3 inflammasome activation [32–34], which is a multiprotein complex activated in response to harmful stimuli. NLRP3 inflammasome is a key mediator of the innate immune system by inducing caspase-1 activation and subsequent secretion of the proinflammatory cytokines IL-1β/IL-18 [35].

Interestingly, recent findings from Zhang and colleagues support that the Nrf2-Keap1 system is compromised in BD and is associated with the described stress resilience alterations. Indeed, postmortem brain samples revealed lower expression levels of Keap1 and Nrf2 in the parietal cortex of BD patients in comparison with controls [36]. This finding is strengthened by data demonstrating that the neuroprotective effect of lithium is

Nrf2-dependent. Accordingly, Rizak and collaborators found that chronic treatment with lithium increases nuclear levels of Nrf2 in PC12 rat cells. Moreover, the authors observed that Nrf2 knockdown suppresses lithium-induced Nrf2 expression and abolishes its protective effect on cell viability and DNA fragmentation in response to hydrogen peroxide (H_2O_2) [37]. Therefore, the pharmacological modulation of NRF2 may be a promising therapeutic approach for BD treatment.

ROS react and affect several cellular components including lipids, proteins and DNA leading to irreversible cell damage [38]. Serum levels of thiobarbituric acid reactive substances (TBARS), which are lipid peroxidation markers, and of brain-derived neurotrophic factor (BDNF),were found negatively correlated in BD patients, suggesting that oxidative status alterations may explain the BD-related BDNF depletion [39]. BDNF plays an important role in synaptic strength and plasticity, regulating differentiation and survival during neuronal maturation. Its depletion has been associated with dendritic deficits and neuronal loss [40]. The above evidence together with superoxide dismutase activation found in manic bipolar patients, which may represent a compensatory defense mechanism, highlight the impact of oxidative stress in BD pathophysiology [41]. Furthermore, comparative studies between BD type 1 and type 2 patients reported that higher levels of oxidative stress in the first case are correlated with a more severe prognosis and disease course [38].

2.3. Pathological microglia activation

During acute episodes of inflammation, microglia releases pro-inflammatory cytokines and neurotrophic factors, reducing synaptic function and preventing the subsequent harmful consequences. However, under chronic inflammation, the accumulation of pro-inflammatory cytokines prolongs microglia activation, leading to

alterations in the neuronal circuits involved in mood and cognition, especially in hippocampus, prefrontal cortex and amygdala areas [7,18].

Interestingly, Naaldijk and colleagues proposed a neuroinflammatory theory for BD progression suggesting that the pathological activation of the kinin-kallikrein system, which plays a key role in neural development, is involved in BD-related pathological microglia activation. According to this hypothesis, the remitting course of manic and depressive episodes constitutes a chronic inflammatory status, leading to microglia hyperactivation, which is characterized by the release of pro-inflammatory cytokines, namely TNF-α and IL-6. The inflammatory status induces the degradation of bradykinin and lysine-bradykinin polypeptides resulting in the constitutive induction of kinin-B1 receptor (B1BKR), as well as down-regulation and inactivation of the kinin-B2 receptor (B2BKR). B1BKR up-regulation causes excitotoxicity since its activation increases the release of glutamate, ROS levels and cytosolic Ca^{2+} concentration. B2BKR down-regulation promotes an abnormal activation of GSK-3β, increasing TNF-α levels, which in turn activates NF-κB leading to a subsequent release of pro-inflammatory cytokines. The inflammatory status together with the excitotoxic environment can ultimately lead to microglial cell death (**Fig.2**) [7]. The reduction of the microglia population may contribute to rise the frequency and intensity of BD-related episodes along disease progression affecting its physiological balance with surrounding cells, namely neurons, since microglia loss might compromise its neuroprotective phenotypes leaving neurons exposed to a pro-inflammatory environment [7,18]. Based on this hypothesis, antagonists of B1BKR and agonists of B2BKR might constitute a novel promising new therapeutic approach for BD pathology.

2.4. Changes in grey matter neurotransmitters

Abnormalities in neurotransmission, in particular the biogenic amines, have been described in bipolar subjects. Moreover, alterations in the levels of amine neurotransmitters seem to be associated with the shift between mania and depression, with high levels of urinary noradrenaline and dopamine being reported with mania and switching to mania [42,43]. Interestingly, the levels of amine neurotransmitters can be directly or indirectly modulated by pro-inflammatory cytokines. For example, IL-6 and TNF-α modulate the serotonin action through its transformation into 5-hydroxy-indolacetic acid. The reduction of serotonin levels may affect cognitive and affective functions [18,44]. In addition, inflammation can also directly interfere with the levels of both dopamine and noradrenaline. For example, some cytokines such as interferons activate the guanosine triphosphate cyclohydrolase enzyme, which in turn leads to the formation of neopterin and tetrahydrobiopterin (BH4) catabolites [6]. BH4 is an essential co-factor for the enzymes involved in the production of tyrosine, dopamine and serotonin. On the other hand, inflammation also affects the activity of 6-pyruvoyl-tetrahydropterin synthase, which promotes neopterin formation leading to a decrease of BH4 and, consequently, the levels of dopamine, norepinephrine and serotonin [18]. Furthermore, pro-inflammatory cytokines can also upregulate glutamate levels, promoting calcium influx through N-methyl D-aspartate receptors (NMDAR), resulting in pathological alterations in neuroplasticity and excitotoxicity [18,44]. Indeed, increased glutamate levels were found in BD subjects and antagonists of glutamate receptors should therefore be included in BD treatment to avoid excitotoxicity [45]. In addition to glutamatergic dysfunction, GABAergic alterations are also described in BD. Neurosteroids, which are synthesized in mitochondria from cholesterol, regulate brain neurotransmission by modulating $GABA_A$ receptors and NMDAR. Abnormal high levels of neurosteroids have been detected in the brain of BD patients [46].

During metabolism, lipid second messengers such as docosahexaenoic acid (DHA) and arachidonic acid (ArAc) are released as a result of phospholipases activation. ArAc is metabolized by cyclooxygenases/lipoxygenases (COX/LOX) generating pro-inflammatory prostaglandins, prostacyclin, thromboxane and leukotrienes. The metabolism of DHA by COX/LOX results in the production of anti-inflammatory resolvins and protectins [41]. Reduced levels of DHA in BD patients, together with findings reporting that ArAc cascade mediators, such as COX-2 and prostaglandin E1, are common targets of the therapeutic mood-stabilizers used in BD treatment, including lithium, valproic acid, and carbamazepine, suggest that alterations in lipid metabolism are implicated in BD pathophysiology [47,48]. Indeed, pathological ArAc metabolism has been associated with neurological, neurodegenerative and psychiatric disorders, including epilepsy [49]. ArAc and its end-metabolic products regulate key physiological processes in the central nervous system (CNS), including synaptic signaling and neurotransmitter release [50,51]. Thus, altered ArAc metabolism, which is also associated with ROS production, may contribute to explain the anatomical changes and reduction of neuronal density, as well as the cognitive impairments observed in BD patients [13,18].

2.5. Crosstalk between the hypothalamic-pituitary-adrenal axis, gut microbiota and inflammation

The bidirectional communication between gut and brain is regulated by 3 different pathways: 1) endocrine pathway via cortisol action; 2) immune pathway through cytokines; and 3) neural pathway through the enteric and vagal nervous system [52]. The hypothalamic-pituitary-adrenal (HPA) axis controls cortisol secretion, which regulates the permeability and barrier function of the gut [53,54]. The vagus nerve integrates the parasympathetic nervous system and modulates a set of functions namely the gut motility.

The innate and adaptive immune responses in the gut lumen aim to preserve homeostasis [55].

Recently, it was demonstrated that gut microbiota modulates the interactions within the gut-brain axis. Due to changes in microbiota composition caused by infectious agents or other harmful stimuli, bacterial breakdown products are secreted, which in turn stimulates innate immune system responses and, subsequently, the release of pro-inflammatory cytokines [54]. On the other hand, pro-inflammatory cytokines namely TNF-α, interferon and IL-6 modulate HPA axis, increasing the systemic levels of cortisol, a molecule with anti-inflammatory and immunosuppressive properties in addition to metabolic actions such as stimulation of body fat accumulation [18,56,57]. Excessive cortisol secretion is associated with a decreased regulation of glucocorticoid receptors affecting their synthesis, translocation and sensibility at the level of the pituitary gland and hippocampus [18]. The hypersecretion of cortisol has been linked to cognitive impairments, particularly in memory, and to hippocampal atrophy, as well as to high risk of developing medical co-morbidities associated with mood disorders, including obesity, diabetes and hypertension, as shown by depressed patients with high systemic levels of cortisol as a result of disturbances in HPA axis [53]. Alteration of HPA axis in BD is supported by findings suggesting that antagonists of glucocorticoid receptors have positive effects on BD-related cognitive impairments [53].

Based on the above exposure and given that gut microbiota can affect both brain neurophysiology and neurochemistry, the pharmacological manipulation of HPA axis and gut microbiota may represent novels therapeutic approaches for BD [18,54].

3. New modulators of the inflammatory response and their therapeutic potential in BD

BD pharmacological treatment is complex due to the shift between stages of disease namely mania, depression, hypomania and mixed phases. Polypharmacy is often, as a result of the combination of drugs from different pharmacological groups and with distinct mechanisms of action [6]. The traditional drugs used in BD treatment are mood stabilizers such as lithium and valproate, and second-generation antipsychotics [4,58,59]. Lithium, the first-line drug in BD therapy, has a multi-complex immunomodulatory effect. In addition to its anti-inflammatory properties expressed by the inhibition of COX-2, IL-1β and TNF-α, and by the increased synthesis of IL-10, lithium also exhibits a pro-inflammatory action by stimulating the synthesis of cytokines such as IL-6 [18,60].

Considering the fundamental role of inflammation in the pathophysiology of BD, immune system represents a novel and attractive BD therapeutic target. This review identifies potential therapeutic approaches for BD treatment through direct or indirect modulation of inflammatory response (**Table 1**).

3.1. GSK3β inhibitors

Oxidative stress triggered by various endogenous and exogenous events promotes alterations in the double DNA strands that, if not repaired, lead to cell death. Under oxidative stress conditions, the TRAX-DISC1-GSK3β complex is assembled in the cytosol of neurons to repair DNA damages. The inhibition of GSK3β dissociates the TRAX-DISC1-GSK3β complex and releases TRAX, allowing it to act in DNA repair [13]. GSK3β can be inhibited endogenously by protein kinase A or exogenously by drugs such as lithium and olanzapine, which are mood-stabilizers currently used in BD therapy with recognized GSK3β inhibitory activity [13,59,61]. Animal models whose GSK3 signaling was genetically manipulated showed antimanic and antidepressant effects [62,63]. Additionally, pre-clinical trials also support the use of GSK3 inhibitors in BD

treatment by demonstrating that the SB-216763-induced GSK3 inhibition potentiates the synaptogenic and antidepressant-like effects of low-doses of ketamine [64].

The above evidence, in particular, the well-established GSK3β inhibitor activity of lithium, together with findings indicating that the presence of polymorphisms in the promoter region of the gene encoding GSK3β affects the response to lithium, leads to the recognition of GSK3β as a potential therapeutic target for BD [62,63,65,66]. The therapeutic strategies aimed to modulate GSK3β activity are of utmost importance not only for BD treatment, as well as for other brain pathologies namely neurodegenerative diseases. Thus, the development of GSK3β inhibitors able to cross the blood-brain barrier currently represents a hot-topic in the pharmaceutical industry [62].

3.2. Non-steroidal anti-inflammatory drugs (NSAIDs)

Anti-inflammatory molecules can affect the progression of the disease because they act on the etiological processes and not only on the relief of symptoms [6,55,67]. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase-1 (COX-1) and COX-2 enzymes, thus decreasing the production of pro-inflammatory prostaglandins. NSAIDs are divided in two groups: non-selective drugs that inhibit both COX-1 and COX-2 and, selective drugs that only inhibit COX-2 enzyme [68]. Drugs from both NSAIDs groups exhibit benefic effects when used as a co-adjuvant for treating BD pathophysiology. Studies using the acetylsalicylic acid, a NSAIDs that irreversibly inhibits COX-1 and COX-2, showed a reduction of lithium doses when used as a co-adjuvant [68,69]. Celecoxib, a specific COX-2 inhibitor, is the most promising drug clinically tested for BD therapy. As described below, the results highlight its usefulness during manic phases, as a co-adjuvant for first-line antimanic drugs, such as valproate, lithium or risperidone [70,71].

3.3. N-acetylcysteine

N-acetylcysteine (NAC) was identified as a multi-target molecule [68]. At both central and peripheral systems, NAC exhibits antioxidant and anti-inflammatory properties, modulating the oxidative stress by decreasing ROS production and increasing the systemic glutathione levels, and inhibiting the cytokines production by microglial cells [18,68,72]. As a co-adjuvant drug, NAC shows promising results in all BD-phases namely antidepressant and antimanic properties, in particular when used in the acute treatment of BD [73,74].

3.4. Minocycline

Minocycline is an antibiotic from the tetracycline group with potent anti-inflammatory and neuroprotective effects. Its anti-inflammatory activity is associated with a decrease in the production of pro-inflammatory cytokines such as TNF-α, as well as with the prevention of microglial activation. The neuroprotective action is due to the reduction of oxidative stress, apoptosis and glutamate-mediated excitotoxicity [68,72]. Minocycline has been used as an off-label therapy in BD treatment since 1996, when it was firstly described in a depressive context. Indeed, adjunctive minocycline treatment is associated with a significant reduction of depressive symptoms in BD patients [18,68].

3.5. Pioglitazone

Pioglitazone, an agonist of receptors activated by gamma peroxisome proliferator (PPAR-γ), has potent anti-inflammatory properties by inhibiting the NF-κB activation. Indeed, PPAR-γ are a group of nuclear receptors that act as transcription factors, regulating gene expression. Pioglitazone is particularly efficient in the treatment of depressive states, especially when they are associated with high IL-6 levels. Thus,

pioglitazone might have therapeutic benefits in the treatment of BD patients with these characteristics, and is generally well tolerated [68].

3.6. Glutamate antagonists

Although monoamines are described as the first therapeutic target for depression, over the past few years glutamate has received rising attention. Impairment of glutamatergic transmission induces functional and structural brain alterations and, when occurring in limbic and cortical brain areas can lead to synapses reduction, as observed in BD patients [55]. Ketamine, an antagonist of NMDAR, has shown promising results in BD therapy by decreasing the deleterious excitotoxic action of glutamate. Accordingly, BD patients treated with ketamine exhibit a significant reduction of depressive symptoms [75,76]. The administration of memantine, another NDMDAR antagonist, is associated with an improvement of basic depressive symptoms including mood, quality of sleep and appetite. Curiously, memantine was suggested to improve mood more efficiently than the antidepressant mianserin [77].

3.7. TNF-α inhibitors

TNF-α is produced by various cell types including macrophages, microglia and T cells [69]. TNF-α inhibitory drugs are particularly interesting because their mechanism of action affects directly one of the core pro-inflammatory cytokines involved in BD pathophysiology [18]. Nowadays, there are four monoclonal antibodies approved by Food and Drug Administration able to inhibit TNF-α activity: adalimumab, infliximab, etanercept, and certolizumab [72]. Infliximab have shown promising antidepressant effect, especially in BD patients with high serum levels of TNF-α and CRP [78], thus

evoking the importance to prior evaluate inflammatory biomarkers in order to select BD patients who can benefit from the TNF-α inhibitors therapy [69,72].

3.8. L- methylfolate

Folic acid and its biologically active form, L-methylfolate, are key regulators of the production of neurotransmitters such as serotonin, dopamine, epinephrine and norepinephrine by increasing the bioavailability of BH4, an essential co-factor for amine neurotransmitter synthesis. Methylenetetrahydrofolate reductase enzyme is responsible for the conversion of folic acid into L-methylfolate, which is able to cross the blood-brain barrier, reaching CNS. Many psychiatric patients exhibit polymorphisms in methylenetetrahydrofolate reductase and, consequently, decreased levels of L-methylfolate in CNS [55]. Moreover, mood disorders including schizophrenia and BD have been associated with a deficit of plasma BH4 levels [79]. Thus, L-methylfolate administration represents a potential therapeutic approach for patients with decreased L-methylfolate levels, namely BD patients. The use of L-methylfolate as co-adjuvant therapy showed promising results in depressed patients with insufficient levels of L-methylfolate and high levels of inflammatory markers such as TNF-α [55].

3.9. Omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acids are found in diet and DHA is the end-product of their metabolism. The anti-inflammatory action of omega-3 polyunsaturated fatty acids is based on the competition with ArAc by COX enzymes because, as mentioned before, both ArAc and DHA are metabolized by COX enzymes. Therefore, in the presence of DHA, the ArAc metabolism is weakened leading to a decrease of prostaglandin E2 levels and, subsequently, a reduction of pro-inflammatory mediators. Recent advances

demonstrated their efficiency as a co-adjuvant for traditional BD therapy, especially in case of depressed BD patients associated with high levels of inflammatory markers [80,81].

3.10. Other options in BD treatment

The above pathophysiologic mechanisms allowed to identify novel potential therapeutic approaches for BD, whose mechanism of action consists of modulating inflammation. For instance, the signaling cascade of ArAc is a potential therapeutic target for the development of new anti-inflammatory drugs. Modulators of oxidative stress including vitamin A, selenium and zinc are also valuable therapeutic options. Molecules acting on mitochondria such as vitamin C and coenzyme Q10 are other hypothesis for BD treatment [22,59]. Coenzyme Q10 is a mitochondrial modulator with antioxidant and anti-inflammatory properties that has been indicated as a potential antidepressant drug and as a co-adjuvant for treatment of manic episodes [68]. Probiotics often used to normalize the intestinal flora are important in the bidirectional communication between the brain and gut microbiota [68,72].

Besides the pharmacological approaches, several non-pharmacological strategies contribute to physical and mental BD patients' well-being. An equilibrated diet conjugated with an active life (physical exercise) are associated with a decrease of inflammatory levels and have positive effects in BD-related medical comorbidities [55] such as obesity that promotes a pro-inflammatory status since adipocytes produce IL-6 and other pro-inflammatory cytokines [18].

4. Clinical Trials

In this section, we identify the main clinical trials developed to validate the therapeutic benefit and safety of drugs used for BD treatment (**Table 2).**

In 2008, a randomized study aiming to assess the antidepressant effect of 400 mg/day of celecoxib, a COX-2 inhibitor, in BD individuals experiencing depressive and mixed phases was conducted for 6 weeks. When compared with the placebo-treated group, the celecoxib-treated subjects showed a rapid-onset of antidepressant effects (after first week of treatment), suggesting that celecoxib might be a potential adjunctive drug to potentiate the BD treatment response [82].

A study published in 2015 investigated the potential therapeutic effect of celecoxib in valproate-treated BD patients with manic episodes not associated with psychotic feature. BD patients treated with celecoxib exhibit a significant improvement on manic-related symptoms when compared with BD patients treated with placebo. The symptoms evaluation of the clinical groups was performed considering the Young Mania Rating Scale (YMRS) [83]. A subsequent investigation carried out from the same team evaluated again the therapeutic effect of celecoxib, versus placebo, in addition to lithium and risperidone in adolescent BD patients with manic episodes [84]. According to YMRS scores, it was observed an improvement of manic symptoms in BD patients treated with celecoxib, without relevant adverse events, strengthening the previous findings that advocated the use of this drug as a therapeutic strategy for antimanic potentiation [84].

In 2019, a clinical trial designed to evaluate the therapeutic efficiency of celecoxib as a co-adjuvant for BD treatment with the antidepressant escitalopram was concluded. Depressive symptoms were evaluated based on the Hamilton Depression Scale and on the determination of inflammatory parameters such as CRP. A significant decrease of depressive symptoms was described after 4 and 8 weeks of celecoxib administration in escitalopram-treated BD patients, when compared with BD patients treated with placebo

and escitalopram. In addition, a significative decrease on CRP levels was found in BD subjects treated with celecoxib for 8 weeks, thus suggesting a reduction of inflammatory activity in these patients and highlighting CRP as a biomarker of treatment response aimed to potentiate antidepressant and anti-inflammatory effects [85].

An ongoing study aims to understand the involvement of inflammation in BD treatment response. In this clinical trial, BD patients are exposed to NAC for 6 weeks and, at the end of this period, their psychiatric condition is determined by the Montgomery Asberg Depression Assessment Scale [86].

A clinical trial, currently in phase 2, aims to determine whether probiotic supplements decrease the probability of relapses and improve the clinical course of BD patients hospitalized due to depressive episodes. After 24 weeks of treatment, intestinal inflammation of BD patients will be assessed through the determination of levels of cytokines and PRC. Primary measures, including relapse time, and secondary measures, namely score determinations from Young mania scale, Montgomery-Åsberg and Hamilton depression scales, will be also evaluated [87].

A clinical trial designed to evaluate the relationship between BD pathology, body weight, and inflammation is ongoing. The effect of minocycline exposure will be assessed in depressive BD patients by measuring the levels of inflammatory markers, namely CRP levels. Minocycline will be administered to BD patients refractory to therapy with antidepressant and mood stabilizers [88].

Other clinical trial aims to analyze the potential effect of the infliximab TNF-α inhibitor in the treatment of BD patients with high concentrations of TNF-α. In this study, BD patients treated with infliximab (5 mg/Kg) at the beginning, at second and sixth weeks are compared with BD patients treated with placebo at the same time points. The infliximab therapy is complemented by the administration of an antipsychotic or a

traditional mood stabilizer. The two clinical groups are evaluated based on the Montgomery-Äsberg Depression Assessment Scale and observed alterations in cytokines levels, cognitive function, brain volume, quality of life and suicide risk [89].

Taken together, the above studies highlight novel therapeutic strategies for BD, which are based on patient's stratification according to their inflammatory profile and on the determination of the anti-inflammatory drugs most effective for each BD subgroup [18,61]. Importantly, the results obtained in these clinical trials, currently ongoing, will provide new clues about the involvement of the innate immune system in BD and, hopefully, will open new avenues for the treatment of BD patients.

5. Discussion

BD is an object of concern for both scientific and clinical communities due to its particular characteristics including swings between depression and mania, the chronic nature and remitting course, and the limited number of available therapies as well as absence of biomarkers for diagnosis and treatment monitoring [1,2].

The development of therapeutic agents fine-tuned for each BD phase currently represents the greatest clinical challenge [4,58]. The increasing knowledge about BD pathophysiology allowed to identify the immune system and inflammation as a novel promising therapeutic target for BD [18,55,67]. As result, several drugs from different classes aiming to directly or indirectly modulate inflammation have been clinically tested in the context of BD treatment [6]. Celecoxib (COX-2 inhibitor) is the most promising drug, being described as a co-adjuvant for first-line antimanic drugs, e.g. lithium and valproate [70,71]. Clinical trials aiming to test new drugs including NAC (antioxidant), infliximab (TNF-α inhibitor), minocycline (antibiotic) and a probiotic supplement are currently ongoing [86–89]. Throughout the review, innovative modulators of

inflammation are critically discussed for BD therapy, such as Nrf2 activators, B1BKR and B1BKR modulators, GSK3 inhibitors, HPA modulators, oxidative stress modulators e.g. vitamin A, and coenzyme Q10, among others.

In conclusion, this review reinforces inflammation as a key event in the progression of BD pathophysiology, thus contributing to identify novel inflammation-related promising therapeutic approaches, namely as co-adjuvant for classic BD treatment. Nonetheless, currently available data from clinical trials of immunomodulatory drugs in BD is insufficient for recommending their use in daily practice, and such options are still absent from main pharmacological guidelines for BD (16, 17).

Abbreviations

Arachidonic acid (ArAc), Brain-derived neurotrophic factor (BDNF), Bipolar disorder (BD), Central nervous system (CNS), C-reactive protein (CRP), Cyclooxygenase-1 (COX-1), Cyclooxygenase-2 (COX-2), Cyclooxygenases/lipoxygenases (COX/LOX), Docosahexaenoic acid (DHA), Gamma peroxisome proliferator (PPAR-γ), Glycogen synthase kinase-3 (GSK3), Hypothalamic-pituitary-adrenal (HPA), Inducible nitric oxide synthase (iNOS), interleukin-1 (IL-1β) , Interleukin 6 (IL-6), Kinin-B1 receptor (B1BKR), Kinin-B2 receptor (B2BKR), Lipopolysaccharide (LPS), N-acetylcysteine (NAC), N-methyl D-aspartate (NMDAR), Non-steroidal anti-inflammatory drugs (NSAIDs), Nuclear factor erythroid 2-related factor 2 (Nrf2), Nuclear factor Kb (NF-κB), Reactive oxygen species (ROS), Soluble IL-2 receptor (sIL-2R), Soluble IL-6 receptor (sIL-6R), Tetrahydrobiopterin (BH4), Tumor necrosis factor-alpha (TNF-α), Young Mania Rating Scale (YMRS).

Author Disclosure Statement

Ana Catarina Pereira, Joana Oliveira, Sónia Silva, Cláudia MF Pereira and Maria T Cruz declare they have no competing interests. Nuno Madeira has been a consultant or advisory board member to Angelini, AstraZeneca, Ferrer and Janssen.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure legends

Figure 1. Changes in inflammatory status in BD.

Inflammatory markers were found chronically increased in BD patients and may augment during depressive and manic episodes, which contribute to BD-associated neuronal impairment. Reprinted from Bipolar Disorder and Inflammation, Joshua D. Rosenblat, Roger S. McIntyre, Psychiatr Clin North Am, 39, 125–137. Copyright (2016), with permission from Elsevier [22].

Figure 2. Pathological activation of microglia in BD.

Microglia is activated under physiological conditions, which results in the secretion of pro-inflammatory and anti-inflammatory cytokines. However, after occurrence of several acute episodes, microglia is over-activated, inducing the release of IL-6 and TNF-α. Moreover, the microglia over-activation is associated with the production of kinins and their metabolites that regulate the expression of B1 and B2 kinin receptors, contributing to propagate the inflammatory status. The toxic environment leads to neurodegeneration. Adapted from Naaldijk Y, et al. Kinins and microglial responses in Bipolar Disorder: a neuroinflammation hypothesis. Biol Chem. 2016;397:283-96 [7].

Figure 1.

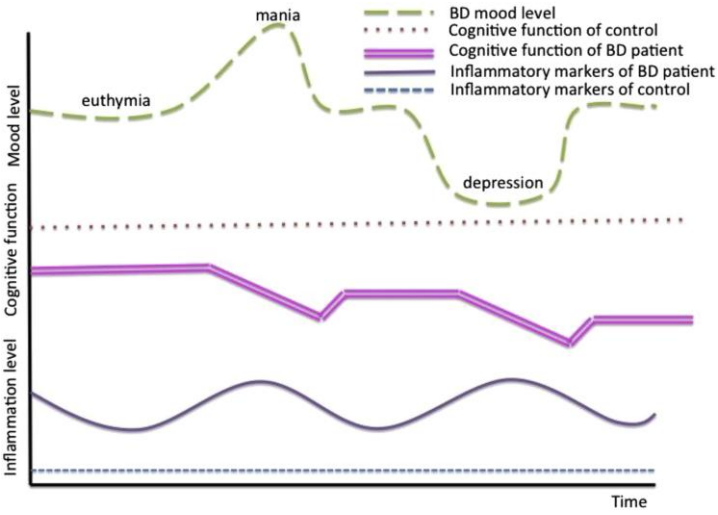

Figure 2.

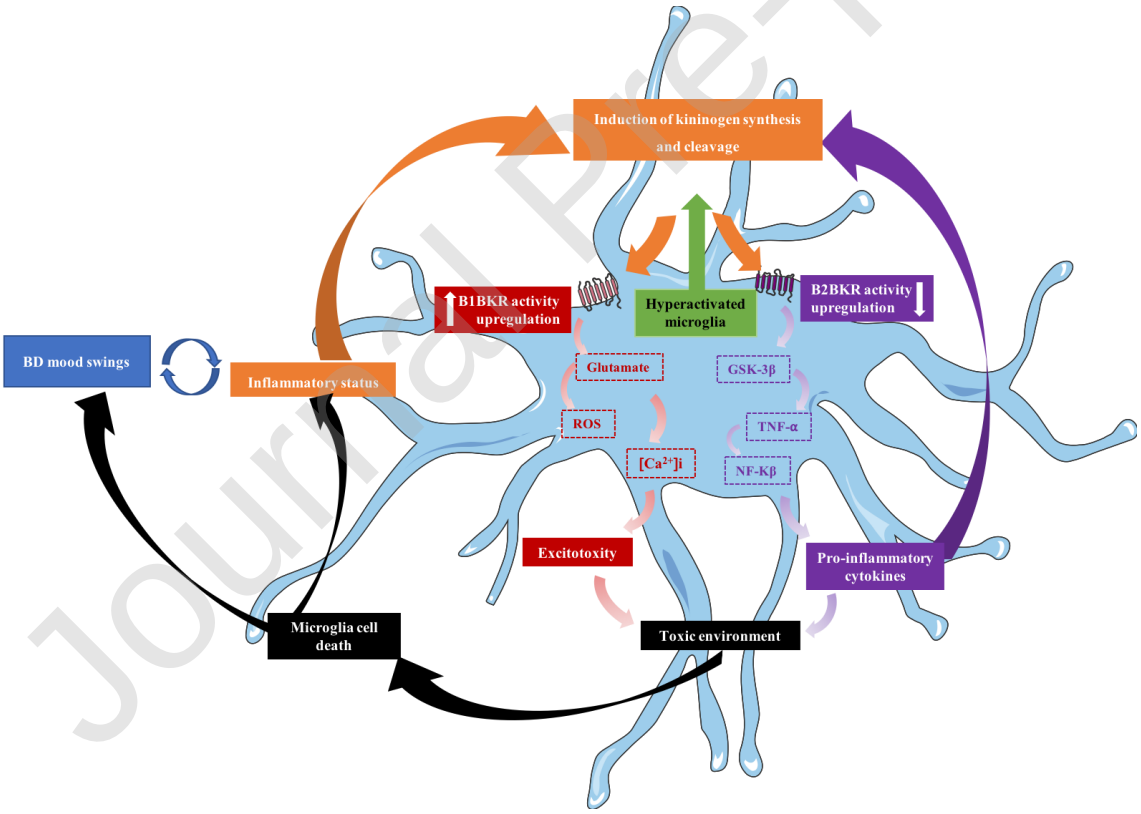

Table 1. New modulators of the inflammatory response and their therapeutic potential in BD.

References	*Drug name*	*Drug Function*	*Main conclusions*
[64]	SB-216763	Inhibits GSK3β activity	Increases of the synaptogenic and antidepressant-like effects of low-doses of ketamine
[68,69]	Acetylsalicylic acid	Inhibits COX-1 and COX-2 enzymes	Reduces medication doses when used as a co-adjuvant for lithium therapy
[70,71]	Celecoxib	Inhibits COX-2 enzyme	Improves the response of major treatments in BD patients as a co-adjuvant for first-line antimanic drugs
[73,74]	N-acetylcysteine	Decreases ROS production; Increases glutathione levels; Inhibits cytokines production	Exhibits antidepressant and antimanic effects as an adjunctive treatment for BD
[18,68]	Minocycline	Decreases pro-inflammatory cytokines production; Prevents microglial activation; Reduces oxidative stress, apoptosis and glutamate-mediated excitotoxicity	Reduces the depressive symptoms when used as an adjunctive in therapy of BD patients
[68]	Pioglitazone	PPAR-γ agonist; Inhibits NF-κB	Displays particular efficiency in the treatment of depressive states associated with high levels of IL-6
[75,76]	Ketamine	NMDAR antagonist with GSK3β inhibitory activity	Decreases the deleterious excitotoxic action of glutamate and reduces significantly depressive symptoms
[77]	Memantine	NMDAR antagonist	Improves basic depressive symptoms including mood, quality of sleep and appetite
[78]	Infliximab	Inhibits TNF-α	Exhibits antidepressant effect especially in BD patients with high serum levels of TNF-α and CRP
[55]	L-methylfolate	Increases BH4 bioavailability	Shows promising results, as a co-adjuvant therapy, in depressed patients with insufficient levels of L-methylfolate and high levels of inflammatory markers such as TNF-α

[80,81]	Omega-3 polyunsaturated fatty acids	Competes with ArAc by COX enzymes	Exhibits promising results, as a co-adjuvant therapy, in depressed patients associated with high levels of inflammatory markers

Table 2. Drugs used in clinical trials aiming to modulate inflammatory status in BD patients.

References	*Drug name/ Drug dose*	*Drug class*	*Administration route*	*Duration*	*Main conclusions*
[82]	Celecoxib (400 mg/day)	COX-2 inhibitor	Oral formulation	6 weeks	Celecoxib as a co-adjuvant drug in BD patients experiencing depressive or mixed episodes exhibits a rapid-onset antidepressant effect.
[83]	Celecoxib (400 mg/day)	COX-2 inhibitor	Oral formulation	6 weeks	Celecoxib as an adjunct in the treatment of BD patients with mania episodes shows a significantly higher remission rate.
[84]	Celecoxib 200 mg/day)	COX-2 inhibitor	Oral formulation	8 weeks	Celecoxib as a co-adjuvant displays significantly greater improvement of manic symptoms in BD patients.
[85]	Celecoxib 400 mg/day)	COX-2 inhibitor	Oral formulation	10 weeks	Celecoxib as an adjunct in BD treatment significantly decreases depressive symptoms and PCR levels.
[86]	N-acetylcysteine	Antioxidant	Oral formulation	8 weeks	Ongoing clinical trial
[87]	Lactobacillus (1 billion)	Probiotic Supplement	Oral formulation	24 weeks	Ongoing clinical trial
[88]	Minocycline (200 mg/day)	Antibiotic	Oral formulation	8 weeks	Ongoing clinical trial
[89]	Infliximab (5 mg/Kg)	TNF-α inhibitor	Intravenously	6 weeks	Ongoing clinical trial