Journal of Psychiatric Research 70 (2015) 18–27

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Review

Dysregulation of the NF-κB pathway as a potential inducer of bipolar disorder

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ARTICLE INFO

Article history:
Received 14 April 2015
Received in revised form
7 August 2015
Accepted 10 August 2015

Keywords:
Bipolar disorder
NF-κB
Inflammation
Cytokines
Psychiatric disorders

ABSTRACT

A century of investigations enhanced our understanding of bipolar disorder although it remains a complex multifactorial disorder with a mostly unknown pathophysiology and etiology. The role of the immune system in this disorder is one of the most controversial topics in genetic psychiatry. Though inflammation has been consistently reported in bipolar patients, it remains unclear how the immunologic process influences the disorder. One of the core components of the immune system is the NF-κB pathway, which plays an essential role in the development of innate and adaptive immunity. Remarkably, the NF-κB pathway received only little attention in bipolar studies, as opposed to studies of related psychiatric disorders where immune dysregulation has been proposed to explain the neurodegeneration in patient conditions. If immune dysregulation can also explains the neurodegeneration in bipolar disorder, it will underscore the role of the immune system in the chronicity and pathophysiology of the disorder and may promote personalized therapeutic strategies. This is the first review to summarize the current knowledge of the pathophysiological functions of NF-κB in bipolar disorder.

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1. Introduction

Bipolar disorder (BD) is a major episodic chronic psychiatric illness with an accelerating course, which comprises of mood swings that range from extreme high (mania) to extreme low (depression) that appear with discrete beginnings and ends, but

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http://dx.doi.org/10.1016/j.jpsychires.2015.08.009
0022-3956/

may appear together. The changes in symptomatology over the course of the illness, sometimes termed *progression*, is characterized by increases in the frequency and severity of affective episodes over time (Zis et al., 1980; Roy-Byrne et al., 1985; Goodwin, 2002), worsening of long-term outcome (Schneider et al., 2012), reduction in the likelihood of response to appropriate treatment, both biological, such as lithium (Swann et al., 1999), and psychological, such as cognitive-behavioral therapy (Scott et al., 2006), and worsening health-related quality of life (Roshanaei-Moghaddam and Katon, 2009). The chronicity in BD and its possible contribution toward its progression alongside the growing appreciation of the profound interrelationship between the central nervous system (CNS) and immune system suggests that understanding the role of immunity in the pathophysiology of the disorder may help decipher the molecular mechanisms underlying BD.

The immune system is a neuroanatomical area of great interest in BD due to the emotional and neuronal consequences of major shifts from homeostasis. It is well established that BD is characterized by high peripheral levels of pro-inflammatory agents, such as cytokines (mainly interleukins like IL-2, IL-4, and IL-6) (Brietzke et al., 2011; Munkholm et al., 2013), tumor necrosis factors (TNF-α) (Brietzke and Kapczinski, 2008), and chemokines (e.g., CCL24 and CXCL) (Brietzke et al., 2009a). The observed increase in the peripheral pro-inflammation particularly during mood swings led a growing number of authors to propose that ongoing inflammation and related processes like neuronal death (apoptosis) may account for the observations reported in neuroimaging studies, where at least a subset of BD patients exhibit a cortical thickness reduction (Rajkowska et al., 2001; Jung et al., 2011), significant loss of gray and white matter volumes (McDonald et al., 2004; Haznedar et al., 2005; Lyoo et al., 2006), and changes in morphology and integrity of white matter tracts (López-Larson et al., 2002; Connor et al., 2011; Sprooten et al., 2013). The possibility that chronic inflammation leads to structural brain abnormalities and cognitive deficits in BD patients raised hopes that biochemical markers can be utilized to detect the illness at early stages (Jones and Thomsen, 2013) instead of carrying patient interviews and self-report questionnaires, which lack objectivity and biological validation (Frey et al., 2013). Thus far, however, efforts have met with limited success, suggesting that a more thorough understanding of the immunoregulatory mechanisms in BD is necessary.

Like all mammals, the human immune system also consists of a functionally linked group of anatomically disparate tissues and cell types, most of which are subject to rapid turnover. Orchestrating these processes that involve both cell proliferation and apoptosis requires the involvement of complex regulatory systems. One of those system is the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which has received little attention in BD studies, but its abnormal activity has been widely reported in related mental disorders, like schizophrenia (Song et al., 2009), major depression (Kim et al., 2015), and autism (Manzini et al., 2014). This review aims to bridge this knowledge gap by describing the role of NF-κB in BD and addressing key questions regarding the role of the immune system in the pathophysiology of the disorder.

2. Progression through stages predicts clinical and mental deterioration

In the course of their illness, bipolar patients may endure an increase in the frequency and severity of symptoms from early onset bipolar with "soft" spectrum conditions to later stages where the symptoms become severe (Schneider et al., 2012). Progression in BD was first documented in the pioneering work of Emil Kraepelin. Kraepelin (1921) described in detail the episodic nature of the disorder and its progression, characterized as faster recurrences (shorter intervals between episodes of high disease activity) that appeared to be dependent on the episode number. The positive feedback between the disease process and its episodes results in *episode sensitization* (Huber et al., 2003), which may be the key mechanism underlying the long-term course of recurrence in bipolar. Kraepelin also described *stress sensitization* in which early episodes of unipolar and bipolar disorders are often precipitated by psychosocial stresses, in contrast to later episodes that occur seemingly independently of psychosocial stresses after a sufficient number of recurrences (Kraepelin, 1921). The association between stress and episode sensitization is considered to be firmly established (e.g., Roy-Byrne et al., 1985; Kendler et al., 2001; Kessing and Andersen, 2004; Post, 2007; Kessing, 2008; Berk et al., 2011a; Grande et al., 2012; Post et al., 2012). Progression in bipolar has also been associated with unfavorable clinical outcomes and mental deterioration, such as escalation in frequency and duration of the episodes, shortening of inter-episodic intervals (Goodwin, 2002; Torres et al., 2007; Berk et al., 2009), lower responsiveness to treatment, particularly with lithium and cognitive behavioral therapy (Swann et al., 1999; Ketter et al., 2006; Scott et al., 2006), higher rates of comorbidity (Matza et al., 2005; Magalhaes et al., 2012), functional impairment (Roshanaei-Moghaddam and Katon, 2009; Rosa et al., 2012), increased cognitive dysfunction (Kessing and Andersen, 2004; Torres et al., 2007; Schouws et al., 2009; Post et al., 2012), and a higher risk of hospitalization and mortality due to suicide (Goldberg and Ernst, 2002; Goldstein et al., 2005; Hawton et al., 2005.

Progression in BD is characterized by the expansion of the structural abnormalities in the brain and cognitive impairment, one of the core features of BD that largely contributes to the various disabilities associated with the disorder. It encompasses phenomena like impaired response inhibition, difficulties with set shifting and sustained attention (Bora et al., 2009; Schouws et al., 2009), and slow information processing (Malhi et al., 2007; Martinez-Aran et al., 2007) that are more severe in late onset patients (Schouws et al., 2009).

The failure of the neuroprotective mechanisms to protect against the ill effects of progression was proposed to be due to dysregulated immuno-mechanisms (or immuno-mechanisms that are disrupted due to multiple mood disorders) that may be responsible to the increase in cytokine levels during acute episodes that alter neuroplasticity, cell resilience, neuronal survival (Brietzke and Kapczinski, 2008; Kunz et al., 2011), and prompt neuronal death (apoptosis) in a cycle of events that has been termed "neuroprogression" (Berk et al., 2010; Fries et al., 2012). Ongoing neuroprogressive changes were linked with tissue damage, brain structural changes, patients' increased vulnerability to future episodes of illness, relapse, neuropsychiatric illnesses and stress, and eventually cognitive impairment (Berk et al., 2010; Gama et al., 2013; Ketter et al., 2006; Waddington et al., 1998). Unfortunately, the literature on the progressive nature of cognitive impairments is scant and contradictory. For example, Torrent et al.'s (2012) repeated-measure analyses over time showed a slight improvement in attention but worsening in executive function, whereas Mora et al. (2013) showed that the cognitive functioning of euthymic bipolar patients remains, on average, steadily affected in 6 years of follow-up.

To recapitulate the pathological reorganization of the CNS along the course of the disorder, Berk et al. (2011b) opted to consider bipolar as a *neuroprogressive disorder*. It has been argued that the reactivity of the nervous system in BD is altered following repeated mood episodes, which ultimately promotes a brain rewiring that makes the patient increasingly vulnerable to follow-up episodes (Kapczinski et al., 2008; Grande et al., 2012; Vieta et al., 2013). A similar concept of *allostatic load* has also been proposed to explain

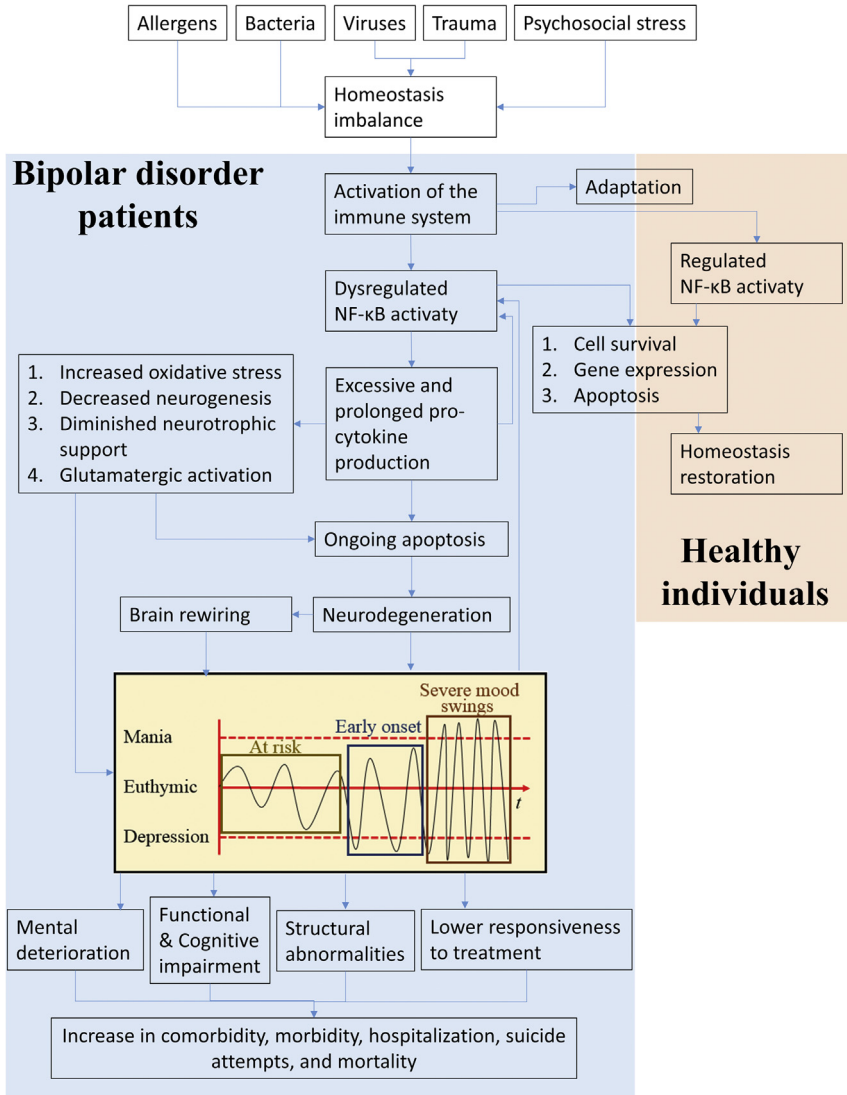

Fig. 1. A proposed schematic for the mechanism of neurodegeneration in BD patients in relation to healthy individuals.

why seemingly unrelated findings, such as cognitive impairment and higher rates of physical comorbidity and mortality observed in the course of BD, are part of the cumulative damage associated with BD (Kapczinski et al., 2008; Juster et al., 2010; Vieta et al., 2013). When encountering potentially stressful challenges, the body may respond in adaptation involving the activation of neural, neuroendocrine and neuroendocrine-immune mechanisms. This "allostasis" or "stability through change" is an essential component of maintaining homeostasis. Allostatic load thereby represents the accumulation of the bodily "wear and tear" that emerges in a state of chronic or frequent stress leading to an allostatic overload in a non-adaptive way (Kapczinski et al., 2008). It aligns with the perception of progression in that both attempt to explain why patients who undergo recurrent mood episodes are clinically perceived as less resilient (Fig. 1).

A similar hypothesis known as *kindling*, advanced by Post and associates, emphasized the role of life history in mood disorders (Post, 1992; Post and Weiss, 1997). The basic tenet of this hypothesis is that major psychosocial stressors play a greater role in the initial episodes of a mood disorder, as compared to subsequent episodes.

The frequency of the mood episodes increases over time due to the progressive decline in the threshold required to elicit these episodes, at least in a subgroup of patients. The kindling hypothesis has been well documented in animal models (Monroe and Harkness, 2005) but received mixed results in humans (Bender and Alloy, 2011).

Few limitations are common to all hypotheses. First, it is difficult to reliably identify the first onset of mood episodes, which is critical in studies that test the patient's response to potential environmental stressors. Second, no standard definition exists for stressful life events, the earliest time life events should be recorded (infancy, childhood, or adulthood), how to record life events (interview or clinical observations), and who should record life events (patient or guardians). Third, when studying the relationships between mood disorders and life events, it is often challenging to discern cause and effect. Finally, the effect of antidepressant medications may obscure the neurodevelopmental processes under study, and it is often impossible to control for their effect.

3. Inflammatory abnormalities and cognitive impairment in bipolar patients

To understand why neuroprotective mechanisms fail to account

for the progressive decline in mental health, researchers attempted to stereotype common phases over the course of the disorder. This allowed clinicians to conceptualize the disorder as a combination of episodic "stages," each with a distinct immunologic signature and clinical outcomes that converge towards clinical impairment (Kapczinski et al., 2009; Gama et al., 2013) (Fig. 1), but it remained unclear which biological mechanisms regulate them.

Several mechanisms have been proposed to account for that the clinical impairment, such as: the Dopaminergic system for which pharmacological evidence suggests that excessive dopamine neurotransmission is involved in the development of manic symptoms; the Glutamatergic system, purported to be related since mood stabilizers were shown to modulate glutamate levels which may have therapeutic value; neurotrophins like BDNF (Fernandes et al., 2011), bcl-2, neurotrophin-3 (NT-3) (Walz et al., 2007), and neurotrophin-4/5 (NT-4/5) (Walz et al., 2009), glial-derived neurotrophic factor (GDNF) (Rosa et al., 2006), and vascular endothelial growth factor that play a vital role in neuronal survival and proliferation; oxidative stress, which is linked to a fundamental abnormality in oxidative energy generation (Kato, 2007; Bauer et al., 2014); life stress and trauma that have been shown to be associated with a decrease in serum BDNF levels among BD patients (Kauer-Sant'anna et al., 2008); accelerated aging and disease trajectories (McEwen, 2003; Juster et al., 2010); and inflammation (e.g., Bauer et al., 2014). Of all the biological mechanisms purported to underlie cognitive impairment (Berk et al., 2011a; Bauer et al., 2014) inflammation was the most potent one.

At the molecular level, inflammation is a response to harmful stimuli characterized by cytokine cascades resulting in instantaneous regulatory changes of immune related genes and their transcription factors as well as cellular immune responses. At present, research regarding the relationship between inflammatory response and cognitive performance in BD is extremely limited; however, findings indicate a link between the effects of pro-inflammatory and oxidative processes, the mechanisms of neuro-inflammation and neuroprotection, and the cognitive decline observed in BD (Brietzke and Kapczinski, 2008; Stertz et al., 2013; Bauer et al., 2014). Evidence that stress elevated cytokine levels are associated with BD was provided by Dickerson and colleagues. Following the reported association between the levels of C-reactive protein (CRP), a marker of inflammation, and cognitive functioning in schizophrenia (Dickerson et al., 2012), the authors compared the levels of CRP in bipolar patients and controls. They found that elevated levels of CRP are associated with lower cognitive functioning in individuals with bipolar disorder. Although they could not explain the reasons for the association, they speculated that they are related to inflammatory processes occurring within the vasculature of the CNS, but other factors like diet and allergen exposure may also contribute to the increase in CRP levels. This group has also reported that manic episodes preceding the elevation in inflammatory markers are predictors of re-hospitalization (Dickerson et al., 2013a, 2013b). The authors speculated that cytokine activation could represent an exposure to an exogenous infectious agent, a reactivation of an endogenous agent, or the progression of an autoimmune reaction. Similarly, Lotrich et al. (2014) proposed that elevated serum levels of IL-1RA in BD patients, even during euthymic states, were associated with worse cognitive function.

Few authors went as far as to propose that the relatedness between BD and inflammation is due to autoimmunity to organ-specific antigens, implying that bipolar is, at least partially, an autoimmune disorder. This notion is not new, although empirical evidence remains scarce (Leboyer et al., 2012). Kupka et al. (2002) showed that bipolar patients tend to develop organ specific autoimmunity to thyroid peroxidase with a higher prevalence of clinically overt thyroid failure (hypothyroidism) due to autoimmune thyroiditis. A follow-up study extended these findings and reported that bipolar is associated with other organ-specific autoantibodies (Padmos et al., 2004).

Although deregulation of the immune system is not considered an autoimmune condition it may potentiate similar consequences in patients. Accumulating evidence supports the view that such deregulation represents an important vulnerability factor for psychosis, an abnormal condition expressed in BD patients that may be triggered by exogenous factors, such as allergens. For example, pollen-specific immunoglobulin E has been reported to be associated with worsening of depression scores in BD patients during high pollen season (Manalai et al., 2012). A Taiwanese nationwide study reported that adolescents with asthma are at a higher risk of developing BD in later life (Chen et al., 2014). Bergink et al. (2014) reviewed studies that discussed the relatedness between autoimmunity, inflammation, and psychosis, and proposed that psychosis may be triggered by either immune-mediated mechanisms, such as genetic predisposition, or nonimmune-mediated pathogenic mechanisms. The role of autoimmunity in modulating inflammatory pathways in psychiatric disorders remains one of the most debated topics in genetic psychiatry (Davison, 2012). In the following, we review additional mechanisms proposed to account for the changes in inflammatory pathways and their potential contribution to the etiology of BD.

4. Pro- and anti-inflammatory cytokines in bipolar

Cytokines are small signaling proteins secreted by immune cells in response to a variety of stimuli. Cytokines mediate crucial cellular functions, such as proliferation, survival, maturation, and neuroplasticity, during innate and adaptive immune responses (Brietzke and Kapczinski, 2008). Under normal physiological conditions, cytokines have beneficial roles (McAfoose and Baune, 2009); however, during excessive and prolonged activation of the immune response, cytokines can also promote several abnormalities thought to be relevant to the pathophysiology of BD. These effects include diminished neurotrophic support, decreased neurogenesis, increased glutamatergic activation and oxidative stress, induction of apoptosis in relevant cell types (e.g., astrocytes and oligodendrocytes), and deregulation of glial/neuronal interactions (reviewed in Brietzke et al., 2011).

Activation of the immune system has been repeatedly demonstrated in bipolar patients in both (Stertz et al., 2013), but direct evidence supporting progressive immune alterations in patients is limited for several reasons, including the use of assays with insufficient sensitivity and sample heterogeneity (O'Brien et al., 2006; Brietzke et al., 2009b). Because bipolar patients exhibit increased peripheral levels of inflammatory mediators mainly during acute mood episodes, studies on patients during acute episodes of depression or mania are the most informative (Brietzke et al., 2011).

The consensus among studies reviewed by Goldstein et al. (2009) is that peripheral pro-inflammatory cytokine levels increase in bipolar patients during manic and depressive episodes when compared with normal controls. For example, O'Brien et al. (2006) used high sensitivity assays to define the cytokine profile of bipolar patients in acute mania and depression compared to controls. The authors exemplified that both depression and mania states are associated with an increased production of the pro-inflammatory cytokines (TNF-α, IL-6, and IL-8). The levels of the anti-inflammatory cytokine IL-10 did not differ, but its concentration was positively correlated with cortisol concentration in mania. Focusing on different cytokines, Brietzke et al. (2009b) also reported an increase in few other pro-inflammatory cytokines (IL-2, IL-4, and IL-6) during mania compared with controls, whereas

depressed patients showed only an increase in IL-6 levels. That only IL-4 levels were increased in euthymic patients compared with healthy subjects points to the importance of studying non-euthymic patients. This may be one of the foremost reasons for inconsistent results among studies (Brietzke et al., 2009b).

Many studies have reported an increase in pro-inflammatory cytokines and hyperactivity of T helper cell type 1 in bipolar, with significantly higher TNF-α levels in patients during manic (O'Brien et al., 2006; Kim et al., 2007; Ortiz-Domínguez et al., 2007; Munkholm et al., 2013) or depressive episodes when compared with normal controls (O'Brien et al., 2006; Ortiz-Domínguez et al., 2007; Munkholm et al., 2013). On the flip side are reports of a decrease in anti-inflammatory cytokines, implying that the imbalance between pro- and anti-inflammatory cytokines plays a role in the pathophysiology of BD (Kim et al., 2007). This hypothesis is reasonable considering the neuroprotective role of some anti-inflammatory cytokines (Vitkovic et al., 2001), but it does not explain all observations. A recent meta-analysis of 30 studies reported a significant elevation of both pro- and anti-inflammatory cytokines in BD (Modabbernia et al., 2013), implying that anti-inflammatory cytokines are unable to provide the necessary neuroprotection against the harmful effects caused by pro-inflammatory cytokines elevated in both conditions.

However, until a direct causality between immune dysfunction and BD is established, the possibility of reverse causation must not be ignored. In other words, it is possible that disruptions of homeostasis caused by mood swings disrupt the activity of the immune system. There is much evidence that the CNS can influence the immune response and that psychological stress can lead to adverse immunological changes, providing a physiological pathway through which negative life events may result in an increased vulnerability to infectious and malignant disease (Hall et al., 1994). For example, it has been shown that uncontrolled anger, such as experienced during an episode, is related to a stress-induced increase in circulating pro-inflammatory cytokines like IL-6 and that a greater long-term exposure to such cytokines results in negative health consequences (Puterman et al., 2014). Mood disorders promoted by immune dysregulation and mood disorders that promotes it may be clinically similar, but are likely dissimilar at the molecular level, in which case our inability to discern these subtypes will confound case-control studies and yield erroneous results. An added complication to the study of stress-induced neurochemical changes is that events in the immune cascade, triggered by external stimuli, are changed as a consequence of the stress response itself, which also depends on prior exposures. A prior exposure to traumatic brain injury (TBI), for example, has been associated with BD. Reekum et al. (2000) reviewed five studies where BD has occurred to subjects after TBI and found a BD prevalence of 4.2% over a maximum of 7.5 years of follow-up, whereas the general community lifetime prevalence rate was 0.8%. However, conclusions should be drawn with caution since BD patients are also more prone to TBI compared to healthy controls (Malaspina et al., 2001). Identifying the molecular pathways involved in the abnormal immune activation, neuroinflammation, and alteration in neuroplasticity observed in the pathophysiology of the disorder has been the central aim of many recent analyses (e.g., Dickerson et al., 2015; Stertz et al., 2015).

5. The role of the NF-κB in innate and adaptive immunity, neuroprotection, and apoptosis

Interestingly, alongside their critical role in the process of alteration in neuroplasticity (Brietzke and Kapczinski, 2008; Potvin et al., 2008), some pro-inflammatory cytokines also stimulate receptors in neurons linked to the activation of NF-κB, a signaling pathway that modulates neuronal excitability and vulnerability to excitotoxicity (Brietzke and Kapczinski, 2008). Unfortunately, the potential molecular or environmental triggers that activate the NF-κB in brain tissue and involved in inducing bipolar are understudied. In the following, we introduce the NF-κB signaling pathway and then focus on its role in the etiology of bipolar.

The NF-κB signaling pathway plays a key role in a multitude of cellular, developmental, and organismal processes, responses, and diseases in mammals (Gilmore and Wolenski, 2012). At its simplest, this pathway represents a family of structurally related and evolutionarily conserved proteins that participate in various biological processes, including immune response, inflammation, cell growth and survival, and development (Hayden and Ghosh, 2012). From insects to mammals, there are multiple NF-κB/Rel transcription factors (2–3 in insects and 5 in humans). The vertebrate NF-κB is induced by over 150 different stimuli, including inflammatory cytokines, mitogens, growth factors and hormones (e.g., insulin), viral and bacterial pathogens, stress-inducing agents, therapeutically used drugs and chemical agents, and environmental hazards (Perkins, 2007). The toll-like receptor (TLR) pathway, for example, is one of the most highly conserved signaling pathway for activation of NF-κB. Mammalian NF-κB family is composed of five members: NF-κB1 (p105/p50) NF-κB2 (p100/p52), RelA (p65), RelB, and c-Rel. NF-κB proteins form numerous homo- and heterodimers associated with specific biological responses that stem from their ability to regulate target gene transcription differentially (Bonizzi and Karin, 2004; Perkins, 2007). In mammals, there are multiple genes at every level of the standard "core" NF-κB signaling pathway (Gilmore and Wolenski, 2012).

Due to its importance as a transcriptional regulator and because a large variety of bacteria and viruses can also activate it, the NF-κB has often been termed a "central mediator of the human immune response" (Pahl, 1999), though a more appropriate definition would be a central regulator of stress and immune responses. This reputation is well justified. NF-κB plays a critical role in the activation of immune cells by upregulating the expression of cytokines essential to the immune response. In particular, NF-κB stimulates the production of IL-1, IL-6, and TNF-α, some of which, like IL-1 and TNF-α, activate the NF-κB itself, thus initiating an autoregulatory feedback loop (Liang et al., 2004). NF-κB proteins form numerous homo- and hetero-dimers associated with specific biological responses stemming from their ability to differentially regulate target gene transcription (Bonizzi and Karin, 2004). NF-κB transcription factors, in turn, promote the expression of over 150 target genes involved in a variety of cellular processes including growth factors, cytokines, chemokines, inflammatory mediators and adhesion molecules, many of which have readily apparent relevance to plasticity (Ghosh et al., 1998; Kumar et al., 2004; Mattson and Meffert, 2006; Pahl, 1999).

NF-κB activity can also be induced by various physiological stress conditions such as ischemia/reperfusion, liver regeneration, and hemorrhagic shock. Physical stress in the form of irradiation as well as oxidative stress to cells also induce the NF-κB (Pahl, 1999). Here again, NF-κB relays the information of an imminent stress and at the same time enacts a response by promoting the transcription of genes whose products alleviate the stress condition. The diversity of NF-κB inducers originating from a wide variety of mechanisms underlie the complexity of its regulation (Kumar et al., 2004).

The generic literature distinguishes between NF-κB's two major pathways responsible for the release of NF-κB dimers from their inhibitors. **The canonical** NF-κB pathway plays a key role in the innate immunity and is triggered by many stimuli including pro-inflammatory cytokines, antigens, pathogens, receptor activator of NF-κB ligand (RANKL), and TLR ligands. Activation followed by

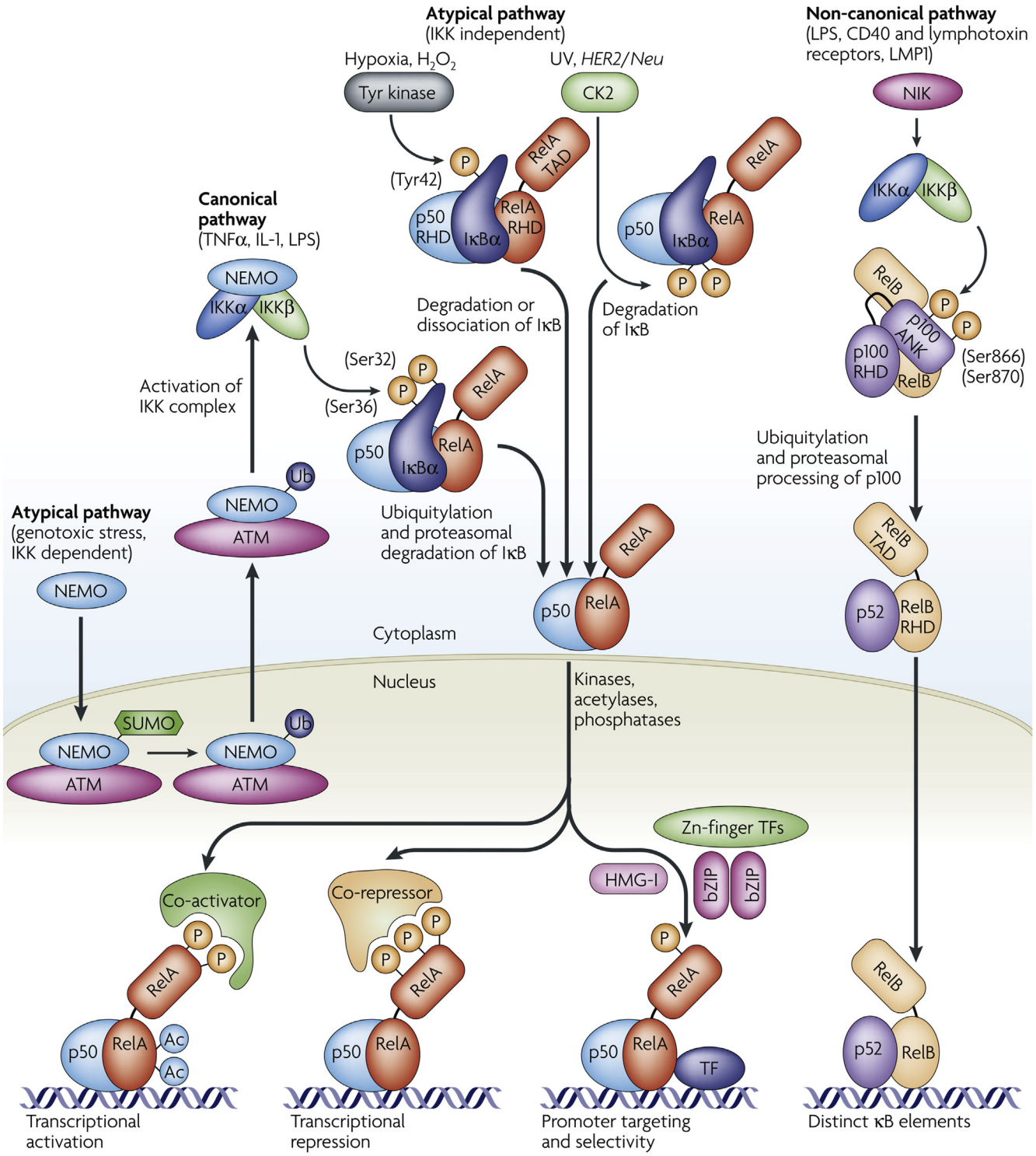

Fig. 2. An illustration of the canonical and non-canonical NF-κB pathways alongside pathways involved in their activation. **The canonical pathway** is induced by pro-inflammatory cytokines (e.g., IL-1 and TNF-α), toll like receptors (TLRs), and other stimuli like Viruses and some zinc finger proteins. It depends on the activation of IKKβ, which results in the phosphorylation (P) of IκBα at Ser32 and Ser36, leading to its ubiquitination (Ub) and subsequent degradation by the 26S proteasome. Release of the NF-κB complex allows it to relocate to the nucleus. A direct path for activation is through NF-κB's essential modifier (NEMO) in the nucleus. When NEMO is sumoylated and ubiquitinated, for example, in response to genotoxic agents, it relocates back to the cytoplasm where activation of IKKβ occurs together with ataxia telangiectasia mutated (ATM) checkpoint kinase, which helps orchestrate the cellular response to DNA damage. This complex can also be activated independently of NF-κB, which is IKK-dependent. An alternative IKK-independent route also exists. **The non-canonical pathway** is induced by various molecules involved in the immune response like chemokines and receptors (e.g., TLRs and TNFs). Under normal conditions, NIK is bound by a complex of TNF receptors that prevent non-canonical NF-κB activation, but in response to receptor stimuli, NIK is released and accumulated. NIK activates IKKα by phosphorylation of its p100 NF-κB subunit. This results in proteasome-dependent processing of p100 to p52, which can lead to the activation of p52–RelB heterodimers that target distinct κB elements. RelB contains a transcription activation domain, and it forms a stable heterodimers with p52 that can result in transcriptional activation and repression as well as promoter-specific effects. Furthermore, combined with other transcription factors, these heterologous transcription factors can target NF-κB complexes to specific promoters, resulting in the selective activation of gene expression following cellular exposure to distinct stimuli and the activation or inhibition of the two NF-κB pathways. Abbreviations: Ac, acetylation; bZIP, leucinezipper-containing transcription factor; HMG-I, high-mobility-group protein-I; IκB, inhibitor of κB; IKK, IκB kinase; LMP1, latent membrane protein-1; LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; RHD, Rel-homology domain; TAD, transcriptional activation domain; TF, transcription factor; UV, ultraviolet; Zn-finger TF, zinc-finger-containing transcription factor. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Molecular Cell Biology (Perkins, 2007), copyright 2007. Adapted by permission from Macmillan Publishers Ltd: Cell Death and Differentiation (Perkins and Gilmore, 2006), copyright 2006.

nuclear translocation of NF-κB dimers is associated with rapid increase in transcription of genes encoding chemokines, cytokines, adhesion molecules, and enzymes that produce secondary inflammatory mediators and inhibit apoptosis. These molecules are vital components of the innate immune response to invading microorganisms or in response to infection or injury. **The noncanonical** NF-κB pathway plays a central part in the adaptive immunity and can be activated by members of the TNF cytokine family, lymphotoxin β (TNFSF3), CD40 ligand (CD40L and TNFSF5), B cell activating factor (BAFF and TNFSF13B), and RANKL (Bonizzi and Karin, 2004; Lawrence, 2009; van Loo and Beyaert, 2011). A detailed illustration of the NF-κB pathway can be found in Fig. 2.

NF-κB's ubiquitous roles in inflammation and immune responses, neuroprotection, and apoptosis are most apparent in the nervous system (Mattson and Camandola, 2001). Early indications that NF-κB could promote survival in neurons came from studies of embryonic rat hippocampal cultures. Neurons incubated with TNF-α were more resistant to death once exposed to metabolic and excitotoxic insults (Mattson and Meffert, 2006; Brietzke and Kapczinski, 2008). Wang et al. (1998) reiterated that TNF-α binding to the TNF receptor (TNFR) can initiate apoptosis and added that it also activates the NF-κB transcription factors which suppress apoptosis. One of NF-κB's major anti-apoptotic role is in mature granulocytes. For example, neutrophils, which undergo daily turnover and rapid apoptosis in vitro, exhibit accelerated apoptosis as well as sensitization to pro-apoptotic stimuli following NF-κB inhibition (Hayden et al., 2006; Greten et al., 2007). A dysregulated NF-κB pathway may also result in an induction of apoptosis. One such mechanism was identified by Ikeda et al. (2011), who showed that blocking SHARPIN, a ubiquitin-binding and ubiquitin-like-domain involved in NF-κB's activation, led to rapid cell death upon TNF-α stimulation. NF-κB's protective roles sometimes have undesired results when they benefit malignant cells, making the NF-κB a target for cancer treatment (Karin, 2014). By contrast to its neuroprotective roles, NF-κB's activation by glial cells indirectly promotes neuronal death (Mattson, 2005). For example, chimeric mice lacking key component of the canonical NF-κB pathway with pronounced defect in NK cells and lymphoid lineages had experienced elevated levels of NF-kB activity in these cells, which appeared to exert a pro-apoptotic effect (Hayden and Ghosh, 2008). Consequently, it has been suggested that the NF-κB activation in glial cells may induce neuronal loss, whereas its activation in neurons could promote their survival (Mattson, 2005; Mattson and Meffert, 2006). Overall, NF-κB's activation can have contrasting roles, sometimes in the same-cell lineage, depending on the physiological context (Lawrence, 2009). Moreover, severe or loss of function mutations in NF-κB genes can be lethal, pathogenic, or steer an imbalance in the immune response (Pahl, 1999). A dysfunctional NF-κB is a major mediator of some human genetic disorders (Baldwin, 2001) and associated with many disease states such as atherosclerosis, asthma, arthritis, diabetes, inflammatory bowel disease, and viral infections. Similarly, aberrant activation occurs in the pathogenesis of a number of human diseases related to inflammation, enhanced cellular proliferation, viral infection, and genetic diseases (Kumar et al., 2004; Sun, 2011).

6. Assessing the role of NF-κB in the etiology of bipolar

The NF-κB signaling pathway has been rarely studied in bipolar patients, though investigations centered on cytokines may have indirectly assessed its role by measuring some of its products. Few studies, however, adopted more direct assessment methods. Sun et al. (2001) provided one of the first lines of evidence for the involvement of NF-κB transcription factors in the frontal cortex of bipolar patient brains. The authors carried a serial analysis of gene expression and reverse transcription-polymerase chain reaction in postmortem tissue from 19 bipolar patients and 15 controls. They found that mRNAs encoding the serotonin transporter and NF-κB2 transcription factor, a subunit of the NF-κB transcription factor complex, were both elevated in bipolar patient tissues. Since the expression of NF-κB2 is regulated by different factors, such as viruses and cytokines, the authors suggested that its over-expression is consistent with an environmental factor that contributes to the pathogenesis of the disorder. This is consistent with reports of increased BD prevalence following winter or spring birth, which suggests a possible role of infectious or inflammation factors in BD.

The crucial role of NF-κB in immune activation and dysfunction of inflammatory molecules prompted Spiliotaki et al. (2006) to test the hypothesis that NF-κB transduction cascade may be associated with the neuro-immuno-endocrine abnormalities of depression. They found that the whole cell NF-κB was significantly higher in depressed patients than controls; however, there were no significant differences in the NF-κB nuclear content and NF-κB-DNA-binding activity between the different subgroups, which may be due to the well documented effects of lithium, chronic valproate (VPA), and other antidepressants in NF-kB activation and NF-κB–DNA binding activity (Ichiyama et al., 2000; Post et al., 2000; Bartholoma et al., 2002; Rao et al., 2007). Remarkably, the findings of these studies were similar to studies showing increased levels of NF-κB activity in Parkinson and Alzheimer patients' brains (Hunot et al., 1997; Kaltschmidt et al., 1997).

To study the role of increased NF-κB activity in the brain, Rao et al. (2010) compared the protein and mRNA levels of excitotoxicity and neuroinflammatory markers in postmortem frontal cortex brains from bipolar patients and controls. The authors reported an upregulated NF-κB transcription factor in the bipolar patient's brain, which could be explained by the increased protein and mRNA levels of different inflammatory cytokines, probably due to a response to systemic and local insults. Upregulation could result in apoptosis and account for the brain atrophy and cognitive decline reported in bipolar patients. An upregulation in NF-κB activity, initiated by a stimuli and later goes out of control due to regulatory problems, can thereby be responsible for the excitotoxicity and neuroinflammation observed in the frontal cortex of bipolar patients.

Insights about the upregulation of NF-κB in psychiatric disorders prompted the search for useful approaches to deregulate it using existing mood stabilizers or newer substances. An indication to the therapeutic effects of the mood stabilizer valproate, used to treat BD, was provided by Rao et al. (2007). The authors administered valproate to rats and reported a significant reduction in NF-κB levels that may also have affected other NF-κB-regulated genes in the rats' cortex. These results insinuate that chronic valproic acid treatment can decrease the accumulation of NF-κB components in the brains of bipolar patients and mitigate the symptoms. Lithium has been reported to have two outcomes in NF-κB signaling. On one hand, treatment of mouse embryonic fibroblasts with lithium decreased TNF-α-induced NF-κB transactivation and on the other hand, lithium increased NF-κB activity in neuron-like PC12 cells, which was associated with a decreased apoptosis in these cells. These results suggest that the neuroprotective influence of lithium is due to its ability to induce the anti-apoptotic NF-κB activity (Bournat et al., 2000; Németh et al., 2002). Lithium is also a direct inhibitor of glycogen synthase kinase-3β (GSK3β), which regulates several transcription factors including NF-κB. The activity of GSK3β has a major influence on cell survival, but when it is hyperactive, GSK3β also increases the susceptibility of cells to the lethal consequences of a wide variety of insults. Inhibition of GSK3β results in an increase in cellular survival and reduced apoptosis in an NF-κB-dependent pathway (Bournat et al., 2000; Jope and Bijur, 2002;

Brietzke and Kapczinski, 2008).

Some authors have focused on curcumin ((1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-hepta-diene-3,5-dione) due to its anti-inflammatory potential which is directly related to the inhibition of NF-κB and reduction of pro-inflammatory cytokines. Gazal et al. (2014) reported that curcumin prevented the behavioral and pro-oxidant effects induced by ketamine in rats, suggesting that curcumin might be an attractive compound for preventive intervention in BD by reducing the episode relapse and the oxidative damage associated with mania. The positive outcomes of curcumin were also observed in various animal models for major depression (Kulkarni et al., 2009; Brietzke et al., 2013).

Studies of the Catechol-O-methyltransferase (COMT) provide some of the best examples for the involvement of the NF-κB in the etiology of BD. COMT regulates the homeostatic levels of neurotransmitter dopamine in the synapses and is one of the most intensively investigated genes in psychiatric illnesses (e.g., Abdolmaleky et al., 2005, 2006). COMT membrane-bound (MB-COMT) is the predominant isoform involved in the degradation of synaptic dopamine in the human brain. Abdolmaleky et al. (2006) analyzed 115 post-mortem brain samples from the frontal lobe of BD patients and showed that the MB-COMT promoter is frequently hypomethylated in patients, specifically in the left frontal lobes. The link between NF-κB and COMT expression was better understood a few years later when Tchivileva et al. (2009) reported that TNF-α downregulates COMT mRNA and protein in astrocytes. An examination of the distal COMT promoter revealed a putative binding site for NF-κB, the target of TNF-α. Similarly, Nohesara et al. (2011) reported a hypo-methylated MB-COMT promoter in DNA derived from the saliva of BD patients, suggesting that a methylation analysis of this promoter in saliva can potentially be used as an epigenetic biomarker for the disorder's state BD. Overall, these studies imply that NF-κB-mediated inhibition through COMT, contributes to the pathogenesis of inflammatory states associated with BD.

Other popular therapeutic targets of non-steroidal anti-inflammatory drugs in bipolar patients are cyclooxygenases (COX). COX received much attention due to their crucial pro-inflammatory role (Williams et al., 1999). The first of the two main COX enzymes, COX-1, is constitutively expressed in most tissues, whereas the second one, COX-2, is an inducible enzyme that responds to pro-inflammatory stimuli (Choi et al., 2009; Font-Nieves et al., 2012). These isoforms act as homodimers and were shown to form heterodimers in mice (Yu et al., 2006). Since COX-2 is regulated by NF-κB, it became the target of anti-COX therapeutics (Lee et al., 2004; Roy et al., 2011), although the use of COX-2 inhibitors in BD is currently not recommended because its potential interactions with lithium may have severe side effects. Preliminary observations of COX-1 inhibitors, however, suggest beneficial effects on the depressive symptoms of bipolar patients (Fond et al., 2013). These positive effects support the hypothesis that COX-1 inhibitors can reduce neuro-inflammatory processes with consequent beneficial improvement for bipolar patients (Choi et al., 2009).

7. Conclusions

This is the first review of the role that the NF-κB signaling pathway plays in the etiology of BD. This review also considered whether dysregulation of this signaling pathway can explain the progression of the disorder, or phrased differently, increases the allostatic load associated with worsening condition in BD patients. While evidence to the involvement of the NF-κB pathway in the etiology of BD is supported only by a handful of studies, multiple studies reported that pro-inflammatory cytokines are associated with the pathophysiology of BD and pharmacological response. These studies, though scant in quantity, appear to support the premise that dysregulation of the NF-κB signaling pathway may explain the observed progression in bipolar disorder (Fig. 1). NF-κB's activity is also known to be tightly linked with many regulators that are themselves may be NF-κB dependent and affected by life history, creating convoluted auto-regulatory feedback loops which appear to be a core feature of NF-κB. Further support to the role of NF-κB in BD can be found in studies investigating the interplay between therapeutic drugs and anti-inflammatory effects. Although not fully assessed, there is much evidence indicating that the success of drug therapy can, at least partially, be ascribed to the downregulation of the immune response either by blocking a pro-inflammatory cascade (2012) or by directly down regulating the NF-κB pathway (Ichiyama et al., 2000; Rao et al., 2007). Part of the reason for the scarcity of investigations targeting the NF-κB pathway is its high complexity. NF-κB regulates the expression of numerous genes and itself is regulated by innumerable factors such as genes products, pathogens, allergens, and stress (Kumar et al., 2004; Hayden et al., 2006).

In summary, there is evidence to support the contention that NF-κB dysregulation is an important factor in the etiology of BD and related psychiatric diseases, though whether such involvement is limited to a certain subgroup of patients or more common remains unknown. Moreover, given the broader spectrum of NF-κB's regulation, further research efforts should be directed towards identifying more specific effectors in this transcription pathway or downstream of it and highlight potential intervention strategies. Such efforts focusing on gaining a more comprehensive understanding of the role of NF-κB transcription factors in controlling immune responses and their effect of the neuroprogression in mood disorders and particularly BD may allow us one day to cross the bridge between synapse, neurology, immunology, and treatment, leading to better outcomes for BD patients.

Contributors

Eran Elhaik constructed the ideas, reviewed the literature, and wrote the manuscript.

Peter Zandi contributed manuscript editing and revisions and checks for accuracy.

Conflicts of interest

The authors declare no conflict of Interest.

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