Review

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Kinins and microglial responses in bipolar disorder: a neuroinflammation hypothesis

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Abstract: Bipolar disorder (BD) is a severe psychiatric disorder that affects up to 15% of the worldwide population. Characterized by switches in mood between mania and depression, its etiology is still unknown and efforts have been made to elucidate the mechanisms involved in first episode, development and progression of the disorder. Microglia activation, abnormal activity of GSK-3β and reduction in neurotrophic factor expression related to neuroinflammatory processes have been indicated to be part of the disorder's pathophysiology. Lithium, the main mood stabilizer used for the treatment and prevention of relapses, acts as an anti-inflammatory agent. Based on that, here we suggest a neuroinflammatory pathway for would be BD progression, in which microglia activation states modulated via constitutive induction of kinin-B1 receptor and reduction of kinin-B2 receptor expression and activity.

Keywords: bipolar disorder; inflammation; kallikrein-kinin system; microglia.

Introduction

Various mechanisms have been related to bipolar disorder (BD) pathology and neurodegeneration, such as oxidative stress, epigenetic modifications, dysregulation of mitochondrial functions, inflammation, and changes in neurotransmitter systems (Salvadore et al., 2010a; Berk et al., 2011; Hamdani et al., 2013). Most of them have overlapping and/or synergetic functions. For the purpose of this review we will focus on the role of bradykinin (BK) and Lys-bradykinin (or kallidin, KD) and their degradation products in microglial cells, and how this might contribute to the development and perpetuation of BD.

Bipolar disorder

BD; ICD-10-CM F31, 2015/16, formerly known as manic-depressive illness, is a severe chronic and multifaceted neuropsychiatric disorder that causes unusual shifts in mood alternating between manic euphoria and depression. This condition does not only affect the mood of patients, but also their activity levels, energy and fear-danger notions, and leads to social and biological damages causing disability of performing quotidian activities. BD is among the 10 most disabling illnesses in the world, and it is estimated that 2–15% of the worldwide population is affected by one of its types or subtypes (Dell'Aglio et al., 2013).

The bipolar spectrum recently described by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth edition* (DSM-5) (American Psychiatric Association, 2013), indicates a large scale of mood patterns, thereby allowing the possibility of diagnosing pathology (Figure 1). The diagnosis criteria for mania and hypomania are quite similar, consisting of an inflated self-esteem and grandiosity, decreased need for sleep, talkativeness, distractibility, increased goal-directed activity or psychomotor agitation, and involvement in activities that have a high potential for social, moral, ethical, physical and/or emotional painful consequences. What differentiates a manic episode from a hypomanic one, is its duration (longer for mania), the intensity of the symptoms, the presence of psychotic features and the levels of social, familiar and/or work impairments.

The bipolar major depression episode (MDE), on the other hand, is characterized as the usual depressive state (showing depressed mood and/or loss of interest/pleasure), but with higher suicidal risk than in unipolar

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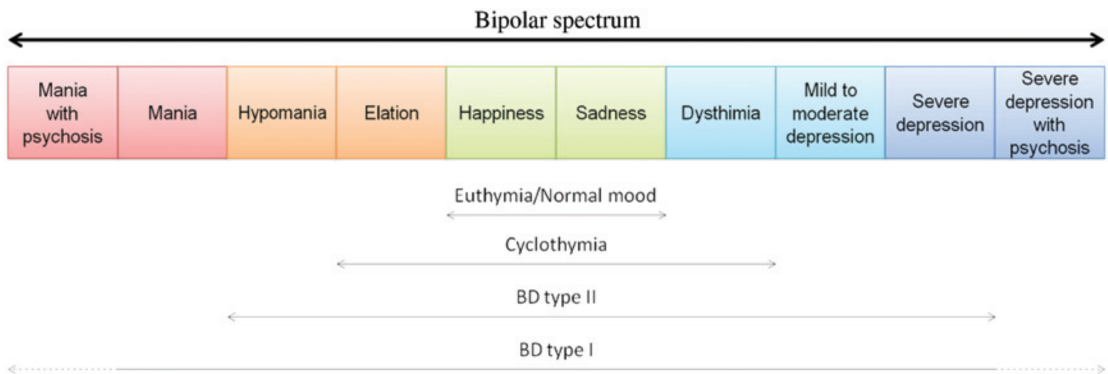

Figure 1: Bipolar disorder spectrum.
There are different subgroups of symptoms for BD. In BD type I, patients exhibit aspects of mania and depression, while in type II patients' mood switches between hypomania and depression. Patients that exhibit rapid cycling of mild symptoms – but quite more expressive than normal happiness or sadness – are classified as cyclothymia type, while euthymic behavior characterizes the state of 'normal' mood in patients and healthy subjects. Other patients exhibit mixed states; a juvenile-onset of BD has also been described. Other different kinds of mood shifting, rather than the euthymic state, can also be considered as part of bipolar spectrum.

depression (major depressive disorder, MDD). For differential diagnosis, bipolar patients are expected to show increased activity, poor concentration and increased impulsivity, accompanied by elevated mood and grandiosity. It might be episodic, occurring several days at a time. The disorder is rare in preadolescents, even being a period of life with predominant anger and irritability. Nowadays, according to the DSM-5, bipolar diagnoses include bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder.

Pathogenesis of bipolar disorder

The etiology and causes of BD are still unknown. That there is no single cause, but rather a group of factors acting together for the onset, maintenance and progression of the illness, including genetic, environmental and lifestyle factors (Belmaker, 2004; Hilty et al., 2006; Machado-Vieira et al., 2011; Fountoulakis, 2012). Furthermore, BD has an exclusive non-functional profile, i.e. the same patient will exhibit both opposite states, mania and depression, in different degrees during life. It is also known that repeated episodes enhance the risk of recurrence, causing progressive damage to the nervous system, even during the euthymic state (Tohen et al., 2003; Perlis et al., 2006; Judd et al., 2008). Together, these factors, the high rate of suicidality and multiple comorbidities commonly affecting bipolar patients result in a very severe clinical condition that reduces life expectancy by 10 years for males and 11 years for females (McIntyre et al., 2004; Chang et al., 2011). The comprehension of BD's mechanisms remains limited, despite the increasing efforts to understand its neurobiology (Jann, 2014), as well as the biological basis of its genetics, hormonal and neurotransmitter actions, intracellular signaling pathways, regulation of gene expression, oxidative stress and mitochondrial dysfunctions, among other factors (Hashimoto et al., 2007; Kim et al., 2007; Arts et al., 2008; Kunz et al., 2008; Berk et al., 2011).

From a genetic perspective, BD has an elevated inheritance pattern. Even though there is no conclusion about genes directly related to the onset and development of the disorder, a group of genes is altered in its expression patterns contributing to some of the phenotypes found in the brain of BD patients. These include serotonin transporter protein (5-HTT), catechol-O-methyltransferase (COMT), D-amino acid oxidase activator (DAOA), brain-derived growth factor (BDNF), among others (McGowan and Kato, 2008; Barnett and Smoller, 2009; Strakowski, 2012). The presence of polymorphisms of those genes has been suggested as the cause for development of BD (Collier et al., 1996; Sklar et al., 2002; Williams et al., 2006). It has also been found that polymorphisms in glycogen synthase kinase (GSK)-3 are linked to the onset of BD (Benedetti et al., 2004). Additionally, differences in the response to treatment have been found and depend on the haplotype that is present (Iwahashi et al., 2014). Recent studies on epigenetics have also shown some oxidative patterns that might be involved in the development of the disorder (Ng et al., 2008).

Treatments available for bipolar disorder

The first and most common treatment for BD for numerous decades has been the administration of lithium. However, due to its numerous side effects, the use of lithium was discontinued for a number of decades, until its reintroduction at the end of the 1940s, when it was shown that manic episodes were related to the accumulation of uric acid in patients' brains (Shorter, 2009; Salvadore et al., 2010b). Because of its neuroprotective and anti-psychotic properties, lithium has been used for acute treatment, prevention of relapse and maintenance of stable mood (Gray and McEwen, 2013; Hübers et al., 2014). Remarkably, lithium increases production of pro-inflammatory cytokines in the peripheral blood (Petersein et al., 2015).

Valproic acid (as sodium valproate salt), an anticonvulsant (AC) largely used for epilepsy, started to be used for BD at the end of the 1970s due to its anti-manic property (Lempérière, 2001). In view of that, other ACs started to be tested with success, including carbamazepine, oxcarbazepine, gabapentin, lamotrigine, among others (Post et al., 1998; Moreno et al., 2004; Muzina et al., 2005). In addition to ACs, some atypical antipsychotics (AAPs) were also introduced for the treatment of BD concomitant with the use of mood stabilizers for acute mania or its moderate/severe states (Perlis, 2007; Fountoulakis et al., 2016) as well as for depressive episodes (Fountoulakis et al., 2005). The most common AAPs are amisulpride, aripiprazol, clozapine, olanzapine and risperidone. These drugs have an inhibitory effect on inflammatory cytokine production (Prossin et al., 2013; Himmerich et al., 2014). Although antidepressants (ADs) are largely used for BD, scientists do not agree about their benefits. The roles of lithium, ACs, AAPs and ADs for the treatment of mood disorders differ depending on the nature of the compound and specially on the patient, since several biological factors are implicated in the disorder, determining treatment outcome. Despite the number of available therapies, none of them is 100% efficient (Squassina et al., 2010). The link between pharmacological mechanisms of action and the neurobiology of the disorder is still unclear and the difficulties in understanding the origin and development of BD have been long-standing obstacles in the development of new therapeutic approaches.

Molecular basis of bipolar disorder progression

Although new studies are emerging and trying to identify factors that induce or increase the likelihood for developing BD, the main initiating cause or event is still unknown. At the biological level, there is a correlation between neurogenesis and development of psychiatric disorders (Schoenfeld and Cameron, 2015). During stress conditions and inflammation, neurons located at the dentate gyrus in the hippocampus undergo a decrease in proliferation and reduced survival, meanwhile changes in behavior become imminent (Schoenfeld and Cameron, 2015). The observed loss of new neurons in adult hippocampus might be a result of microglial activation followed by the release of pro-inflammatory cytokines and a consequent toxic microenvironment (Kohman and Rhodes, 2013). Other mechanisms contribute to impairment of hippocampal neurogenesis by neuroinflammation. The inflammatory process also prevents the new neurons from incorporating into the preexisting network and affects their cellular characteristics (Kohman and Rhodes, 2013).

At the molecular level, BD is characterized by a reduction in serotonin and BDNF levels, dysfunctions in neuronal plasticity, gliosis and mainly neuroinflammation (Schneider et al., 2012; Stertz et al., 2013; Watkins et al., 2014). The reduction in serotonin and BDNF levels are due to the expression of pro-inflammatory cytokines (Koo and Duman, 2008; Miller et al., 2009; Catena-Dell'Osso et al., 2013). The analysis of blood and plasma from BD patients showed an increase, at the protein level, of the pro-inflammatory cytokines nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-kB), interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α (Maes et al., 1995; Kim et al., 2007; Ortiz-Domínguez et al., 2007; Munkholm et al., 2013) and a decrease in neurotrophic factors, such as BDNF (Kapczinski et al., 2008). The presence of pro-inflammatory cytokines plays a role in defining the mood status of patients (Table 1). Under antidepressant treatment, the concentration of pro-inflammatory cytokines normalized (Himmerich, 2011; Himmerich et al., 2013; Krügel et al., 2013). The presence of pro-inflammatory cytokines can induce MDD in patients that have not shown any prior psychiatric medical conditions, indicating a link between immune functions and psychiatric disorder (Mondelli et al., 2015). In addition, increased concentration of monocyte chemotactic protein 1 (MCP1) in cerebrospinal fluid of BD patients has been reported (Jakobsson et al., 2015), which is responsible for inducing microglia proliferation and consequently neurodegeneration. In BD, GSK-3β is found in its active form and its regulation is impaired, leading to a constant enhancement of microglia-induced neuroinflammation and reduction of regeneration by neuroprotective factors (Gould, 2006; Gould et al., 2006). Moreover, dysregulated

Table 1: Pro-inflammatory cytokines involved in mood switches of bipolar disorder patients.

Mania	Depression	Suicide	Sleep deprivation	Sadness	Remission	Euthymic
IL-1β (Söderlund et al., 2011) sIL-1R (Maes et al., 1995) IL-2 (Brietzke et al., 2009) sIL-2R (Maes et al., 1995) IL-4 (Brietzke et al., 2009) IL-6 (Maes et al., 1995; Remlinger-Molenda et al., 2012) IL-8 (O'Brien et al., 2006) INF-γ (Maes et al., 1995; Remlinger-Molenda et al., 2012) TNF-α (Ortiz-Domínguez et al., 2007) sTNF-R1 (Hope et al., 2011; Munkholm et al., 2013)	IL-1β (Remlinger-Molenda et al., 2012) IL-6 (Benedetti et al., 2002; Ortiz-Domínguez et al., 2007; Prather et al., 2009) IL-8 (O'Brien et al., 2006) INF-γ (Remlinger-Molenda et al., 2012) TNF-α (Ortiz-Domínguez et al., 2007)	IL-1β (Monfrim et al., 2014)	IL-1 (Imeri and Opp, 2009) IL-6 (Ritter et al., 2013) TNF-α (Imeri and Opp, 2009)	IL-1Rα (Hope et al., 2011) IL-6 (Hope et al., 2011) OPG (Hope et al., 2011)	IL-10 (Remlinger-Molenda et al., 2012)	IL-1β (Ritter et al., 2013) IL-4 (Brietzke et al., 2009) sTNF-R1 (Munkholm et al., 2013)

IL, Interleukin; sIL, soluble interleukin; IFN, interferon; TNF, tumor necrosis factor; sTNF, soluble tumor necrosis factor; OPG, osteoprotegerin.

GSK-3β activity in BD leads to deterioration of neural plasticity.

Post-mortem brain analysis of BD patients showed a reduction in both number of neuronal and glial cells and in the microglia size in the prefrontal cortex (Ongür et al., 1998; Rajkowska, 2000; Cotter et al., 2001; Rajkowska et al., 2001). It is still unknown why the number of glial cells is reduced even when gliosis is present in BD. It has been previously suggested that microglial cells might show reduced proliferation rates before BD onset, while cell degeneration might occur as a result of extensive inflammation due to microglia activation triggered by gliosis (Watkins et al., 2014). Additionally, histological brain analysis of frontal cortex samples showed an up-regulation of the pro-inflammatory and excitotoxicity-related proteins IL-1β, IL-1 receptor, iNOS and c-Fos suggesting that increased expression and activity rates of these might lead to cell death, brain atrophy and cognitive decline, as previously described for BD pathology (Rao et al., 2010). In the earlier stages of the disorder, interleukins and TNF-α are up-regulated while in later stages IL-6 and TNF-α levels expression are maintained (Rege and Hodgkinson, 2013). An up-regulation of all these pro-inflammatory cytokines could be related to overexpression of NF-κB; as the expression subunit of NF-κB, NF-κB2, has been found to be overexpressed in frontal cortex of BD patients (Elhaik and Zandi, 2015). The alteration in NF-κB might account for brain atrophy and apoptosis observed in BD. Moreover, enzymes involved in the arachidonic acid pathways (e.g. cytoplasmic and secretory phospholipase A2) are augmented in their expression rates in the prefrontal cortex of BD patients, contributing to an inflammatory environment (Fountoulakis et al., 2005). BD is also distinguished by an increase in pro-apoptotic proteins while reduction in antioxidant protein levels, expression is observed (Benes et al., 2006).

The role of microglial inflammatory process in bipolar disorder

The presence of dysregulated microglia is evident in the development of psychiatric disorders, such as schizophrenia, anxiety and major depression disorder (Frick et al., 2013; Réus et al., 2015), and an increase in microglial density correlates with suicide rates of different neuropsychiatric disorders (Mondelli et al., 2015). Emerging evidences point the possible role of microglial in BD pathology as inducers of neuroinflammation via kynurenine pathway.

It has been proposed that activated microglial cells release interferon (IFN)-γ enhancing the activation of the kynurenine pathway (Watkins et al., 2014). This activation would eventually result in an increase of indoleamine 2,3-dioxygenase (IDO) activity, which is responsible for tryptophan and serotonin degradation. The main consequence is the depletion of tryptophan, a serotonin precursor, compromising serotonin protein levels (Berk et al., 2011), while, at the same time, altering BDNF protein expression. Watkins and colleagues proposed that mania and depression stages seen in BD are due to a deregulated kynurenine pathway (Watkins et al., 2014).

Microglial pro-inflammatory cytokine release occurs via activation of the toll-like receptor 4, followed by the activation of NF-κB and the mitogen-activated protein kinases (MAPK) cascade (Rege and Hodgkinson, 2013). Activation of this inflammatory cascade would finally lead to oligodendrocytes cell death by apoptosis, brain blood barrier destruction, neuronal damage and mitochondrial impairment (Rege and Hodgkinson, 2013).

On the other hand, Frick and coworkers proposed different functions of microglia in psychiatric disorders (Frick et al., 2013), such as alterations in microglial function at sites where neurogenesis, neuronal function and homeostasis are affected, leading to either neuronal or synaptic dysfunctions instead of neurodegeneration. However, the exact involvement of microglial cells in psychiatric disorders remains very debatable. Stertz and colleagues have suggested a possible mechanism for microglia l involvement, known as the inflammation hypothesis in BD (Stertz et al., 2013). According to this mechanism, a first insult, probably as result of an acute episode of mania or depression, would result in neuronal damage. Microglial cells would become activated, releasing pro-inflammatory cytokines and neurotrophic factors, inducing then shortening of synaptic functions in an attempt to handle the first insult. After several insults, accumulation of pro-inflammatory cytokines released by microglial cells would lead to auto-stimulation of microglial cells transforming them into a hyperactivated state. The presence of inflammatory cytokines eventually hinders neurogenesis and neuroprection of injured neurons and contributes to a systemic toxic environment (Stertz et al., 2013).

The kallikrein-kinin system

A complex group of proteins and peptides – that includes tissue and plasma kallikreins, kininogens and kinins – consists of a system participating in nuronal differentiation and function. In the kallikrein-kinin system (KKS), the polypeptides BK and KD are vasoactive kinins generated by proteolytic cleavage of their precursors, the high molecular weight kininogen (HMWK) and the low molecular weight kininogen (LMWK), respectively. Degradation of these short-living peptides occurs by carboxypeptidases, yielding des-Arg^9-bradykinin (DBK) and Lys-des-Arg^9-bradykinin (Lys-DBK), as well as by angiotensin-converting enzymes (ACE), providing 1–5 and 1–7 BK fragments (Moreau et al., 2005). Kinins participate in many different physiological processes, such as cardiovascular homeostasis, inflammation, and neurotransmission (Appell and Barefoot, 1989; Meneton et al., 2001; Trabold et al., 2010).

BK production and release is rapidly induced in the presence of traumatic brain injury or stroke, and this peptide acts as a vasodepressor, neuroprotective and pro-inflammatory mediator (Golias et al., 2007; Martins et al., 2012) while also being an indispensable factor for intracellular Ca^{2+} mobilization (Martins et al., 2005; Martins et al., 2008; Trujillo et al., 2009). Kinins exert their functions via the activation of two transmembrane G-coupled receptors, the kinin-B1 (B1BKR) activated by DBK and Lys-DBK, and kinin-B2 (B2BKR) receptors stimulated by BK and KD. The expression of B1BKR depends on the presence of the metabolites DBK and Lys-DBK and it is activated at phase of chronic inflammation, while B2BKR are constitutively expressed and act in acute inflammatory phases and pain responses (Campbell, 2001; Couture et al., 2001). Activation of both receptors promotes intracellular calcium mobilization by inositol 1,4,5-triphosphate, production by phospholipase C-beta activity, and evoke release of nitric oxide and prostaglandins (Marceau and Regoli, 2004; Thornton et al., 2010). Both receptor subtypes are expressed by many cell types, including neurons (Couture et al., 2001), glial cells (Gimpl et al., 1992; Stephens et al., 1993; Noda et al., 2003), endothelial cells (Miyamoto et al., 1999) and vascular smooth muscle cells (Yang et al., 1999). In the human brain, components of KKS were found specifically in the thalamus, hypothalamus, cerebral cortex and spinal cord (Raidoo and Bhoola, 1997).

Bradykinin and neurogenesis

In the nervous system, components of the KKS, specially BK and other related peptides, are implicated in a wide range of physiological processes (Bhoola et al., 1992). More recently, studies have demonstrated the role of BK in neurite outgrowth, proliferation inhibition of stem cells and their differentiation into neurons (Martins et al., 2005; Trujillo et al., 2009; Trujillo et al., 2012; Nascimento et al., 2015; Pillat et al., 2015). At a molecular level, BK and B2BKR are also involved in ERK activation, acting via tyrosine kinases Pyk2 and Src (Ca^{2+}-dependent pathway), and via EGF and PKC pathway, respectively (Dikic et al., 1996; Adomeit et al., 1999). Activity and expression modulation of the B2BKR *in vitro* showed that BK can trigger neural fate determination during differentiation processes, while reducing proliferation and promoting neurogenesis under environmental mitogenic stimulus (Trujillo et al., 2012). The inhibition of B2BKR by the antagonist HOE-140 reduced the expression of the neurogenic transcription factor Ngn1, eNOS and nNOS, while upregulating the expression of the gliogenic signaling genes *Notch1* and *STAT3*. The same pattern was also observed in a B2BKR-KO mouse model, where the expression of neuronal markers was decreased in different stages of embryo development (Trujillo et al., 2012). All these data reaffirm the important role in neurogenesis and cell fate determination played by BK and B2BKR [for a recent review on the KKS in the central nervous system and brain diseases, see Negraes et al. (2015)].

Neuroprotection and inflammatory responses

Experimental studies revealed that BK can act as a central mediator of a nociceptive preconditioning, exerting cardioprotection via neurogenic activation of protein kinase C, reducing the infarct size, and ameliorating focal cerebral ischemia (Huang et al., 2015). Using hippocampal slices challenged with high concentrations of NMDA as an *in vitro* model for cerebral ischemia, protection against NMDA excitotoxicity was confirmed for B2BKR activation by BK, while the presence of the B1BKR agonist Lys-DBK abolished neuroprotective effects of BK (Martins et al., 2012).

In addition to neuroprotective roles of BK (Yasuyoshi et al., 2000; Noda et al., 2007b; Negraes et al., 2015), that kinins are able to induce neuroinflammatory responses (Passos et al., 2013). It has been shown that, in some neurodegenerative and pathological conditions, IL-1β and TNF-α secreted by infiltrating leukocytes promote up-regulation of B1BKR expression. In multiple sclerosis, it has been demonstrated that migration of T-cells is modulated by B1BKR receptor expression and function (Prat et al., 1999). Furthermore, activation of B1BKR in neutrophils promotes their migration towards the inflamed area, inducing tissue damage (Pesquero et al., 2000). Similarly, in an ischemic/reperfusion injury model, B2BKR activation has been shown to promote the production of reactive oxygen species (ROS) (Chiang et al., 2006). In airway smooth muscle cells, the presence of BK activates the expression of IL-6 via ERK/MAPK signaling pathway (Huang et al., 2003). In addition, B1BKR and B2BKR have been found to be upregulated in hippocampal neurons of patients suffering from temporal lobe epilepsy (Perosa et al., 2007) and in animal models for epilepsies (Couture et al., 2001) playing a role in the development of epilepsy.

In vitro BK treatment caused astrocytes to increase the production of ROS, matrix metalloproteinase 9 (MMP9) and heme oxygenase 1 (HO-1), resulting in neuronal cell death and brain inflammation and injury. Furthermore, B2BKR activation in glial cells induced the expression of IL-6, arachidonic acid and Ca^{2+}-dependent release of glutamate (Burch and Kniss, 1988; Parpura et al., 1994; Schwaninger et al., 1999).

In inflammatory diseases, such as diabetes, arthritis, stroke and irritable bowel syndrome, it is known that kinin receptors participate in disease onset and progression (Uhl et al., 1992; Uknis et al., 2001; Gabra and Sirois, 2002). Efforts have been made to develop therapeutic approaches targeting the function of both kinin receptors. In a mouse model for focal cerebral ischemia, B1BKR was not activated after the use of B2BKR antagonist (Gröger et al., 2005), avoiding cell death (Ding-Zhou et al., 2003) and protecting the brain against edema and cerebral infarction after stroke (Ding-Zhou et al., 2003). On the other hand, protection against cerebral ischemia was observed when B1BKR was absent (Austinat et al., 2009). These findings indicate that kinins can act as a double sword depending on the conditions, cell type and subtype of activated receptor.

Kinins in microglia cells

Microglial cells are the immune cells of the brain. They comprise approximately 10–15% of the total brain cell population (Lawson et al., 1992) and their function is to monitor changes in their surroundings. At the encounter of any physiological or biological abnormalities, microglial cells become activated by switching their morphology from ramified to amoeboid morphologies. Activated microglia can be either neuroprotective (M2 subtype) or neurotoxic (M1 subtype), depending on microenvironmental conditions (Kraft and Harry, 2011; Ekdahl, 2012; Weitz and Town, 2012). In many neurological diseases, including BD, microglial cells are found in a hyperactivated state causing neuroinflammation through release of TNF-α, IL-1β, IL-6 and NO (Weitz and Town, 2012), furthering neuronal damage and loss (Lull and Block, 2010). However, the exact underlying mechanism of microglia hyperactivation in BD is still unknown.

Kinin receptors have specific and independent functions in microglial cells. An *in vitro* study primary microglia showed that resting microglial cells did not express the B1BKR, while the B2BKR was constantly expressed. The addition of BK to the microglia culture induced B1BKR expression, while B2BKR expression was up to 50% down regulated (Noda et al., 2003, 2004). During inflammation, BK is neuroprotective by up-regulating expression rates of kinin receptor, which are responsible for reducing microglia-induced proinflammatory responses in the presence of lipopolysaccharide (LPS), leading to inhibition of TNF-α and IL-1β expression (Noda et al., 2007b). According to the author, BK prevents proinflammatory effect via B1BKR activation.

BK also induces NO release in activated microglia via inducible nitric oxidase (iNOS), and Ca^{2+} signaling pathways (Noda et al., 2007a). Acting as chemoattractant at sites of injury, B1BKR agonists promote microglial migration through B1BKR activation in a G-protein independent pathway (Ifuku et al., 2007) and mediated by Ca^{2+}-activated K^+ channel stimulation. Microglia migration was drastically reduced by the use of an antagonist of the B1BKR, but not for the B2BKR, indicating that microglia motility is B1BKR-dependent (Ifuku et al., 2007; Huisman et al., 2008). These findings were further investigated and corroborated *in vivo*. In $B1BKR^{-/-}$ KO mice, microglial motility was unaffected, but enhanced in $B2BKR^{-/-}$ knockout mice.

In addition to the role played in microglia migration, B1BKR activation does not promote either microglia membrane ruffle or expression of OX6 a marker of glial activation (Ifuku et al., 2007).

In microglia, GSK-3β regulates several processes such as migration, production of proinflammatory cytokines and subsequent inflammation-induced neurotoxicity (Yuskaitis and Jope, 2009). Inhibition of GSK-3β activity with therapeutic agents (such as lithium) prevents microglia from inducing a release of TNF-α release, demonstrating that this enzyme regulates the microglial proinflammatory response (Yuskaitis and Jope, 2009; Wang et al., 2010). Moreover, in the cardiac system, BK promotes the AKT pathway-mediated phosphorylation of GSK-3β, resulting in inhibition of this protein (Gröger et al., 2005; Yin et al., 2005). However, whether the BK-evoked inhibitory mechanism for blocking proinflammatory responses in microglial cells is the same one for inhibition of GSK-3β activity needs to be further explored.

The role of kinin in bipolar disorder via microglial cell immunomodulation

The initiating cascades of events that lead to BD are still unknown and are debatable. A MetaCore analysis of BD patients at different manifestation stages showed involvement of the KKS in BD (Song et al., 2015). One study has identified polymorphisms in the *B2BKR* gene, which are linked to BD (Gratacòs et al., 2009). Nevertheless, whether these polymorphisms are responsible for BD onset, progression or neurodegeneration has not yet been investigated. In addition, MCP-1 expression, known to act negatively in BD, is regulated by BK via the B2BKR (Marney et al., 2009).

Here we propose that BK-induced inflammatory insults via microglial hyperactivation would result in cell death and tissue damage due to an increase of excitotoxicity and inflammation markers (Figure 2).

Considering the inflammation hypothesis proposed by Stertz et al. (2013) and that microglia-induced neuroinflammation in BD alters the brain *status quo*, stimulating mood changes (Réus et al., 2015), we suggest that under any type of stress conditions, inflammation is induced resulting in microglia activation and in the release of pro-inflammatory cytokines and neurotrophic factors. The resulting inflammation would induce the production of BK and its degradation into DBK, which activates B1BKR expressed in microglial cells, promoting further increase in B1BKR expression (Noda et al., 2003). At the same time, the constitutively expressed B2BKR receptor would be down-regulated in presence of BK (Noda et al., 2007a), leading to constant activation of GSK-3β and TNF-α expression. This would, in turn, account for the abnormal expression and activity of GSK-3β, since the B2BKR is a regulator of GSK-3β activity (Yin et al., 2007). In addition, DBK, that has a longer half-life than BK (Marceau et al., 1998), can accumulate for longer periods, augmenting the activation status of B1BKR. Moreover, the B1BKR, whose desensitization and internalization rates are very slow (Mathis et al., 1996; Austin et al., 1997) compared to those of the B2BKR, can sustained longer activation status. In turn, GSK-3β induces TNF-α expression (Green and Nolan, 2012), which activates NF-kB (Schütze et al., 1995), increasing the expression of pro-inflammatory factors, such as IL-1β, IL-6, IL-8, IFN-γ, TNF-α and MMPs (Lappas et al., 2002; Lawrence, 2009; Ben-Neriah and Karin, 2011). The presence of NF-kB induces constantly the expression of B1BKR through direct binding to its promoter (Schanstra

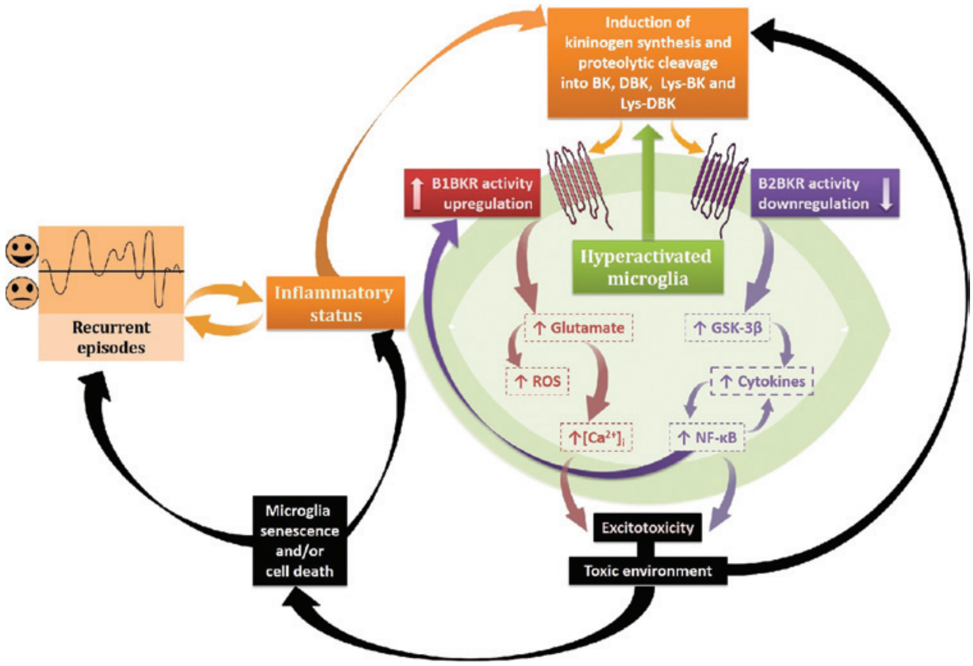

Figure 2: Kinin-induced neuroinflammatory signaling cascade in microglia in bipolar disorder brain.
Microglial cells are activated when abnormal physiological behavior in the environment is detected, releasing pro- and anti-inflammatory cytokines. An episode of mania or depression leads to an inflammatory status, activating microglia response. However, the recurrence of episodes leads to a hyperactivation of microglial cells (microgliosis), releasing only pro-inflammatory cytokines, such as TNF-α and IL-6. Together with the inflammation status, pro-inflammatory cytokines are responsible for inducing kininogen expression, up-regulating B1BKR and down-regulating B2BKR expression and activity. Upregulation of B1BKR expression and activity promotes glutamate release, eliciting an increase in ROS production and in cytosolic free calcium concentration ($[Ca^{2+}]_i$) and subsequent excitotoxicity. Down-regulation of B2BKR expression and activity results in GSK-3β activation, reducing BDNF levels and increasing TNF-α expression. TNF-α activates NF-kB, inducing the release of TNF-α (in negative feedback loop), IL-6, IL-8 and IFN-γ. The high levels of pro-inflammatory cytokines and the excitotoxicity caused by changes in kinin receptor expression generates a toxic environment that ends up with microglial cell senescence and/or death. With a reduced microglia population, new collapsing events can start to affect physiological balance, contributing to neurodegeneration and to stronger and more recurrent episodes.

et al., 1998), enhancing the induction of kinin production and further activation of the B1BKR. Its activation increases the glutamate and ROS levels as well as cytosolic Ca^{2+} concentration, promoting excitotoxicity. Microglial cells would be then hyper-activated due to the presence of constant inflammation. The combination of all these factors creates a toxic environment that can either induce microglial cells death or senescence. In addition, surrounding cells (e.g. neurons and other glial cells) would be affected as well. Therefore, the mania or depression episodes of BD patients might be a results of the inflammatory response. As inflammation increases an increment of recurrent episodes is expected.

Another clinical basis to support our hypothesis could be the correlation between KKS expression and activity levels and Alzheimer's disease (AD). It is known that kinin receptors play a role in the promotes AD etiology. Similar to BD, one of the main pathology in AD is the neuroinflammatory process. In AD, both B1BKR and B2BKR are expressed in the affected brain regions of patients with early onset of the disease (Viel and Buck, 2011). It has been suggested that the B2BKR acts as a neuroprotective receptor, while B1BKR functions as a pro-inflammatory one. Like BD, Alzheimer's disease is characterized by the high levels of IL-1β, TNF-α and NF-κB upregulating B1BKR expression levels (Passos et al., 2004; Viel and Buck, 2011). When upregulated in its expression and activity, the receptor increases in pro-inflammatory cytokine production and release. In addition, Pan et al., have demonstrated that BK induces the activation of NF-κB and the release of IL-1β in human fibroblasts (Pan et al., 1996), suggesting that BK is responsible for the initiation of inflammatory responses via B2BKR activation and cytokine production. Furthermore, Phagoo et al. postulated that BK and KD induce B2BKR expression, marking the inflammation area with the expression of pro-inflammatory cytokines and chemokines. Eventually, BK and KD are degraded into B1BKR agonists inducing its expression and prolonging the inflammatory response (Phagoo et al., 1999). In the case of major depression, which biologically resembles bipolar depression, a link has been shown between microglial cells and B1BKR expression within the onset of depression. Viana et al., have demonstrated that depression-like symptoms after LPS administration followed by a stressful behavioral test resulted in microglial activation, TNF-α production and up-regulation of B1BKR expression (Viana et al., 2010). This finding indicates the role of the B1BKR as an inducer of depressive behavior since abolishment of B1BKR activation reverses the depression phenotype.

Possible experimental design

To prove this hypothesis, an experimental design is suggested based on the molecular biology of the proposed mechanism of kinins in BD and their therapeutic potential. For that, microglial cells could be isolated from healthy brain tissue from WT animals and subjected to *in vitro* to overexpression of B1BKR. Once the overexpression is achieved, the microglia can be transplanted into the brain of a healthy WT animal, which will be later submitted to repeated stressful behavioral tests in an attempt to provoke cyclic inflammatory responses and natural cyclic recurrence. Animals that respond to the transplantation and behavioral tests could be then treated with lithium and/or other mood stabilizers to check for possible recovery.

Here we hypothesize that recurrent episodes in BD would provoke a continuous and progressive inflammatory process (via B1BKR expression and activation), leading to cell death and tissue damage. Clinical observations in bipolar patients show that repeated episodes or residual symptoms enhance the risk of future recurrences (De Dios et al., 2012), while aggravating deterioration and volumetric changes of brain tissue (Strakowski et al., 2002; Moorhead et al., 2007; Lim et al., 2013). Recent studies have even shown that neuropsychological deficits may persist during euthymic state, corroborating the idea of a continuous aggressive inflammatory environment (for a review on neurobiology of BD, see Maletic and Raison, 2014). The enhanced risk of developing comorbidities, as long as the disorder progresses, would be supported by microglia-induced cell death, as proposed in our hypothesis. This could account for the cardio- and cerebrovascular disorders often observed in bipolar patients (Bassett, 2015; Chen et al., 2015), since KKS and renin-angiotensin systems are deeply correlated (Nelveg-Kristensen et al., 2015).

Conclusion

The causes of BD are still unclear; however, the main biological outcome here presented is the involvement of neuroinflammation and its effects on neuronal and glial cells. It is already known that inflammation induces BK production reducing the expression of inflammatory markers via B2BKR activation, while DBK acts as a pro-inflammatory factor by B1BKR activation. The role of kinins and their receptors in BD have not been studied before; and we hypothesize that kininogens and the B1BKR are highly expressed in BD when compared to healthy controls. Further investigation is essential to confirm this hypothesis. If confirmed, the proposed studies could lead to the development of B1BKR antagonists as potential therapeutics for BD.

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