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Review

Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors☆

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ABSTRACT

There is now strong evidence of progressive neuropathological processes in bipolar disorder (BD). On this basis, the current understanding of the neurobiology of BD has shifted from an initial focus on monoamines, subsequently including evidence of changes in intracellular second messenger systems and more recently to, incorporating changes in inflammatory cytokines, corticosteroids, neurotrophins, mitochondrial energy generation, oxidative stress and neurogenesis into a more comprehensive model capable of explaining some of the clinical features of BD. These features include progressive shortening of the inter-episode interval with each recurrence, occurring in consort with reduced probability of treatment response as the illness progresses. To this end, emerging data shows that these biomarkers may differ between early and late stages of BD in parallel with stage-related structural and neurocognitive alterations. This understanding facilitates identification of rational therapeutic targets, and the development of novel treatment classes. Additionally, these pathways provide a cogent explanation for the efficacy of seemingly diverse therapies used in BD, that appear to share common effects on oxidative, inflammatory and neurotrophic pathways.

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Contents

1. Introduction

Despite Kraepelin (1921) first noting that manic-depressive illness has an accelerating and progressive course, the molecular foundations for this disease progression are only just beginning to be explained. By contrast, there is a wealth of clinical data supporting this pattern of an accelerating and progressive disease course which includes the observation of a progressive reduction in the inter-episode duration with recurrence (Kraepelin, 1921; Zis et al., 1980; Roy-Byrne et al., 1985; Kessing et al., 1998). Increasing episode number is linked to a reduction in the likelihood of response to appropriate treatment, both biological such as lithium (Franchini et al., 1999; Swann et al., 1999), and psychological such as CBT (Scott et al., 2006). People with more recurrent bipolar disorder (BD) tend to have higher rates of comorbidity, especially substance abuse (Brady and Goldberg, 1996), more difficulty with social adjustment (Matza et al., 2005) and increased risk of hospitalisation (Goldberg and Ernst, 2002), suicide (Hawton et al., 2005) and forensic complications (Conus and McGorry, 2002). These clinical observations suggest that BD is at least in part a neuroprogressive disorder where there is the potential for a potentially modifiable pathophysiological process to occur over the longitudinal trajectory of the illness and that part of this neuroprogressive pathophysiology is associated with inadequately compensated metabolic stress. The end point of such neuroprogressive changes would be tissue damage, structural changes and functional sequelae that are the neural substrate of mood regulation, that has the potential to increase the risk of further recurrence and reduce the potential of treatment response (Waddington et al., 1998). It is likely that this process is present or accelerates during acute exacerbations of the illness, and this paper will present data that this may be particularly true of manic relapse.

2. The structural basis and functional sequelae of neuroprogression in bipolar disorder

The observed clinical progression of BD is reflected by growing evidence of stage-related structural brain changes in affected individuals. Structural abnormalities are not consistently found at illness onset, but more commonly found in chronic and more recurrent forms of the illness. An example being, ventricular enlargement has been reported in individuals with recurrent illness that was not apparent in a cohort with during first-episode of mania (Strakowski et al., 2002). These observations that supports the notion of neuroprogressive changes over time in BD.

Progressive changes in brain structure are also supported by observations of a progressive loss of grey matter thickness associated with chronicity in people with BD (Lyoo et al., 2006). The cerebellar vermal V3 was reduced in individuals who have had multiple episodes, compared to both controls and those measured at first-episode (DelBello et al., 1999).

Bora et al. (2010) recently conducted a meta-analyses of the voxel-based morphometry (VBM) studies of gray matter in BD. Specifically, they compared gray matter volumes of 660 BD patients and 770 healthy controls and found that gray matter reduction in left rostral anterior cingulate cortex (ACC) and right frontoinsular cortex was associated with BD. Importantly, a longer duration of illness was associated with increased gray matter in a cluster that included basal ganglia, subgenual ACC and amygdala. Lithium treatment was associated with enlargement of ACC gray matter volumes, which overlapped with the region where gray matter was reduced in BD. These authors concluded that the most robust grey matter reductions in BD occur in anterior limbic regions, which may be related to the executive control and emotional processing abnormalities seen in this patient population.

Importantly, whilst there is growing evidence to suggest there are progressive changes in the CNS of individuals with BD, neuroanatomical changes are present early in the onset of the disorder. For example, males experiencing their first-episode of psychosis, displayed increased thickness in the right subcallosal limbic anterior cingulate cortex (Fornito et al., 2009). These authors interpreted this finding to suggest that relative hypertrophy in brain regions critical for regulating HPA axis activation (i.e., the anterior cingulate cortex, amygdala and pituitary) are associated with an elevated stress response around the time of psychosis onset that ultimately results in volumetric shrinkage in later illness stages. There is however novel data showing that “ultra high risk” individual who had not yet manifested a first-episode of threshold mania already show amygdala and insular volume reductions but no differences in lateral ventricular volumes (Bechdolf et al., unpublished data). This has led to the suggestion that there may be early neurodevelopmentally mediated CNS changes (Fornito et al., 2007), as well as ongoing neuroprogressive changes, that are associated with the pathophysiology of BD.

Significantly, there is now some data to suggest that some abnormalities in CNS development that underpin BD may have a

genetic basis. This comes from a study that showed that individuals with BD that had a Val66Met brain derived neurotrophic factor (BDNF) genotype had significantly lower anterior cingulate volumes than those a homozygous Val/Val genotype (Matsuo et al., 2009).

At the symptom level, cognitive impairment is also a core feature of the disorder; these deficits include impaired response inhibition, difficulties with set shifting and sustained attention (Bora et al., 2009), as well as slowed information processing (Malhi et al., 2007; Martinez-Aran et al., 2007). It is now well recognised that these cognitive impairments make a major contribution to the disability associated with the disorder (Malhi et al., 2007; Martinez-Aran et al., 2007). Unfortunately, there is very scarce cognitive data regarding longitudinal studies in BD, however, the available evidence suggests at least some of the cognitive impairment is related to the number of episodes that a person has had (El-Badri et al., 2001; Robinson and Ferrier, 2006); suggesting that like neuroanatomical changes, symptom severity shows progressive changes in individuals with BD. This notion is supported by recent findings that people with BD who have had a first or second episode displayed minimal divergence from controls in their cognitive functioning (Lopez et al., 2008). In contrast, individuals who had longstanding illness manifested significant reductions on most measures of cognition when compared to both controls and early-episode bipolar patients.

3. The biochemical foundation of neuroprogression

While Kraepelin first described the progressive nature of the disorder, Post (1992) laid the foundations of the current understanding of the progressive nature of the pathophysiology of the disorder (Post, 1992). Post based his argument on experiments using kindling in animals as a model for seizures where it was shown that if exogenous agents induced enough seizures, changes in the CNS would occur that induced spontaneous endogenous seizures in the experimental animal. Importantly, kindling can be induced by repeated long-term stimuli. Post argued that this kindling model showed that long-term multiple CNS challenges could act to permanently alter neuronal activity and this was a non-homologous paradigm for BD in which multiple episodes could permanent alter neuronal activity in people with the disorder. This slow alteration of neuronal activity would underlie the progressive changes now observed in neuroimaging studies and the changes in symptom severity. Post argues that as with kindling, changes in neuronal activity are underpinned by changes in levels of gene expression and that such changes in gene expression could underpin the higher relapse liability and deteriorating treatment response in chronic BD (Post, 1992). More recently, Post suggested that some of the detrimental outcomes in BD may be due to a failure of endogenous compensatory mechanisms that would normally minimise the impact of endogenous insults on CNS function (Post, 2007).

Kapczinski et al. (2008b) have extended this model, incorporating the allostatic load hypothesis. This describes a process whereby the combined effects of genetic load, life stressors, and aggravating factors such as substance use, combine to lead to a cumulative process of "wear and tear". These features combine with the innate neuropathology of the disorder to further disrupt those functional brain circuits responsible for mood modulation and cognition. This is thought to result in the structural changes and the associated cognitive decline observed, and the circuits that are thus further disrupted result in the decreasing responsiveness to therapy that occurs with chronicity. This neuroprogressive process additionally underlies the increasing vulnerability to future episodes of illness.

It is now becoming apparent that the biochemical foundation of neuroprogression is multifactorial and interactive, not only between pathways, but via stress sensitisation from the environment. Core components include the dopaminergic system, inflammatory cytokines, oxidative stress, mitochondrial and endoplasmic reticulum stress, and neurotrophins including BDNF (Wadee et al., 2002; Post, 2007; Berk et al., 2008c). There is also evidence for the involvement of epigenetic changes, particularly histone and DNA methylation leading to long-acting effects on gene expression (Grayson et al., 2010).

4. Mechanisms of neuroprogression

4.1. Dopaminergic system

Several lines of pharmacological evidence support the notion that excessive dopamine neurotransmission is involved in the development of manic symptoms (Berk et al., 2007c). Agents that drive dopamine, such as amphetamine, are amongst the best models of mania, whilst dopamine D_2 antagonists (Chengappa et al., 2004; Berk and Dodd, 2005; Malhi et al., 2005) are robustly anti-manic (Frey et al., 2006a,b). When considering the potential for dopamine to affect CNS function it is significant that as well as increasing dopaminergic activity, increased dopamine levels are an important source of oxidative stress in the brain, due to redox potential of dopamine (Rees et al., 2007). In addition, there is now data to suggest that antipsychotic drugs may protect against oxidative stress (Bai et al., 2002). Mechanistically, dopamine may be metabolized via monoamine oxidase with resulting production of H_2O_2 and dihydroxyphenylacetic acid (Maker et al., 1981; Berman and Hastings, 1999), or can go through non-enzymatic hydroxylation in the presence of Fe^{2+} and H_2O_2 leading to the formation of 6-hydroxydopamine (6-OHDA) (Graham et al., 1978). Both pathways have the potential to cause cellular dysfunction if oxidative status is imbalanced. 6-OHDA-mediated toxicity includes mitochondrial complex I inhibition (Rees et al., 2007) endoplasmic reticulum stress (Berman and Hastings, 1999) and activation of glycogen synthase kinase-3 (GSK-3β) (Obata, 2002). 6-hydroxydopamine is intrinsically unstable and is converted to p-quinone that in turn can activate the caspase-8 pathway ultimately resulting in apoptosis (Stokes et al., 1999). However, the enzyme glutathione S-transferase confers neuroprotection as it promotes the conjugation of glutathione and p-quinone to form a stable end product that does not enhance overall toxicity. As glutathione is the primary antioxidant defense in the brain, the reaction with p-quinone results in a depletion this antioxidant and in turn leaves the cell more vulnerable to oxidation (Grima et al., 2003).

4.2. Glutamatergic system

Similar to dopamine, the glutamatergic system has also been implicated in the pathophyisology of bipolar disorder. Mood stabilizers, such as lamotrigine, have been shown to modulate glutamate levels and this may be involved in their therapeutic value (Krystal et al., 2002). A review of MRS studies has shown increases in glutamate levels, most commonly in the anterior cingulate cortex and prefrontal cortex, that appear to be related to illness state (Yuksel and Ongur, 2010). There are reductions in glutamine/glutamate levels following treatment, which correlate with symptom severity, further implicating a role of glutamatergic dysfunction in the underlying pathology of bipolar disorder (Frye et al., 2007; Yoon et al., 2009). Furthermore, while in its infancy, there is support for genetic mutations, centred around the glutamate pathway, that may be implicated in bipolar disorder (Cherlyn et al., 2010).

Glutamate plays an important role in the mediation of oxidative balance. Increased glutamate levels may result in excitotoxicity, mediated by reactive species production, following calcium influx. Elevated intracellular calcium is a persistent finding in bipolar

disorder, both basal levels, as well as increases stimulated by dopaminergic (Berk et al., 1994), serotonergic (Berk et al., 1995; Plein and Berk, 2000) and glutamatergic transmission (Berk et al., 2000; Plein and Berk, 2001). Modulation of glutamatergic pathways may indeed regulate calcium influx thus preventing cellular damage. Intravenous ketamine has been studied as a model of NMDA receptor antagonist, with rapid antidepressant effects in preliminary studies (Diazgranados et al., 2010). Its psychomimetic side effects, however, limit its widespread clinical use, and it will probably remain an interesting research tool (Machado-Vieira et al., 2009). Nevertheless, it should be probably noted as a cautionary tale that hypofunction of glutamatergic transmission might also contribute to oxidative stress, and NMDA-R antagonists cause a significant additional increase in reactive oxygen species (Zuo et al., 2007).

Glutamate is also one of the three amino acids responsible for the production of the most ubiquitous antioxidant in the brain, glutathione, and disruptions in the glutamate pathway may impact on glutathione levels. The role of the glutamatergic system in inflammation is discussed in the next section.

4.3. Inflammation

Inflammation is a condition characterized by cytokine cascades, cellular immune responses, increased levels of acute phase proteins and complement factors. Interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) are the primary inflammatory mediators that activate nuclear factor κB (NFκB), which in turn activates the production of cytokines, such as IL-6 and IL-8, and T-cell derived cytokines, such as interferon-γ (IFNγ) (Gordon and Martinez, 2010). IL-1β, IL-6 and TNFα, in turn, induce the production of acute phase proteins, such as haptoglobin and C-reactive protein (CRP) (Maes, 1993). Inflammation is accompanied by counter inflammatory responses, which dampen the primary inflammatory response, e.g., increased levels of the IL-1 receptor antagonist (IL-1RA). There is increasing evidence suggesting that chronic, mild inflammatory processes in the periphery and the brain (neuroinflammation) are involved in the pathophysiology of BD. BD is accompanied by moderately increased plasma levels of pro-inflammatory cytokines, such as interleukin-IL-6 and tumor necrosis factor-α; and increased IL-1β, NKκB and IL-1RA protein and mRNA levels in post-mortem frontal cortex of bipolar patients (Maes et al., 1995; Ortiz-Dominguez et al., 2007; Drexhage et al., 2010; Rao et al., 2010). Also, increased acute phase protein levels, including haptoglobin and CRP (Maes et al., 1997; Dickerson et al., 2007); and complement factors, such as higher plasma C3C or C4 concentrations are associated with BD (Maes et al., 1997; Wadee et al., 2002).

Depression commonly occurs in illnesses associated with inflammation, such as coronary artery disease, lupus and rheumatoid arthritis (Goldstein et al., 2009). Interestingly, the infusion of pro-inflammatory cytokines is perhaps the best experimental human model of depression, and elevated levels of cytokines are known to be associated with both depression and mania (Wadee et al., 2002). Recently Goldstein et al. (2009) reviewed the literature and found 27 articles concerning inflammation and BD that suggested BD and inflammation are linked through shared genetic polymorphisms and gene expression. This link is further evidenced by altered cytokine levels during symptomatic (i.e., mania and depression) and asymptomatic intervals of the illness (Goldstein et al., 2009). This corroborates the previous hypothesis that inflammatory mediators could be related to the episode-related cognitive decline in BD (Brietzke and Kapczinski, 2008). Levels of tryptophan and kynuerine-dependent tryptophan index have been shown to be decreased in bipolar mania (Myint et al., 2007). Furthermore, increased kynurenine was found in post-mortem investigation of the anterior cingulate cortex in BD, which corresponded with increased density, and intensity of tryptophan 2,3-dioxygenase positive glial cells (Miller et al., 2006). While it has been proposed that kynurenic acid may be neuroprotective (Foster et al., 1984), metabolites of the tryptophan/kynurenic pathway have been shown to have neurotoxic properties (Smith et al., 2007) and increases in the kynurenine pathway may be linked to inflammation in BD.

Certain components of the inflammatory process may be state dependant. In mania, elevation of IL-6 resolves with clinical remission, while TNF-α does not appear to change with remission (Kim et al., 2007b). In depression, the baseline production of TNF-α is significantly increased, whereas TNF levels are reduced during treatment in the responder subgroup only (Lanquillon et al., 2000). Reynolds et al. (2004) also showed that recombinant TNF infusions in rats obliterate the improved performance caused by desipramine in forced swim tests (Reynolds et al., 2004). These data take on increased significance given recent finding show increased levels of transmembrane TNF-α (tm-TNF) in the cortex of individuals with depression (Dean et al., 2009). Taken together, these data provide evidence that changes in levels of TNF-α in the CNS are associated with mood symptoms in humans. Importantly, tmTNF-α is the target molecule for drugs developed to have peripheral anti-inflammatory activity action, and there is early data that suggest that these drugs may act as antidepressants (Tyring et al., 2006). Conversely, it has been shown that the antidepressant venlafaxine decreases pro-inflammatory markers in blood of depressed individuals (Piletz et al., 2008). Together, these finding suggest that tmTNF-α may offer a potential therapeutic target to moderate CNS inflammatory process and the symptoms of mood disorders.

There is further data implicating inflammatory pathways in the pathophysiology of BD. For example, an association of the -511C/T polymorphism of IL-1β with grey matter deficits in bipolar patients has been reported (Papiol et al., 2008). This is supported by evidence showing increased IL-1β (and MyD88 which modulates IL-1 binding) levels in both protein and mRNA from post-mortem frontal cortex samples (Rao et al., 2010). There is also evidence for HPA axis activation associated with increased IL-1β levels in the disease and by intracerebroventricular infusion (Connor and Leonard, 1998). It has been hypothesized that some mediators of inflammation are related to neuroprogression in BD (Brietzke and Kapczinski, 2008; Brietzke et al., 2009a,b). This posit is based on the findings that inflammatory cytokines and chemokines are activated during depression and even more prominently in acute mania. Moreover, these changes are not present during euthymia and therefore, it has been hypothesized that inflammatory mediators could be related to the episode-related cognitive decline in BD. In this regard there is preliminary evidence of a stage-related impact on cytokines (Berk et al., 2007a) because the pro-inflammatory cytokines IL-6 and TNF-α were elevated in both early and late stage disorder, whereas, the anti-inflammatory cytokine IL-10 was increased only in the early stage of the disorder (Kauer-Sant'Anna et al., 2009). Notably, TNF-α, while elevated throughout the course, was higher later in the disorder suggesting the inflammatory state is more perturbed later in the course of the disorder. This might be a result of either progression of the primary underlying process, or a consequence of failure of adaptive homeostatic mechanisms occurring as part of neuroprogression.

When considering the possible role for oxidative stress and inflammatory process in BD it is important to note that some mood stabilizers, like lithium, valproate (VPA), carbamazepine, and lamotrigine, have been shown to suppress (brain) cyclooxygenase-2 and prostaglandin PGE_2 (Bosetti et al., 2002; Bazinet et al., 2006; Lee et al., 2008; Goldstein et al., 2009). Lithium and VPA may also decrease the activation or production of nuclear factor kappaB (Ichiyama et al., 2000; Rao et al., 2007). All these outcomes would be viewed as protecting against oxidative stress/inflammatory pro-

cesses. The selective COX-2 blocker, celecoxib, displays potential efficacy in the treatment of BD (Nery et al., 2008). Statins, which have intrinsic anti-inflammatory properties, appear to be associated with lowered risks of mood disorders in community studies (Pasco et al., 2010) and in cohorts of individuals with cardiac disorders (Stafford and Berk, in press).

At present there are limited suggestions as to the mechanism by which changes in inflammatory pathways could induce the symptoms of BD. However, it is of interest that in peripheral tissue inflammation has been shown to reduce levels of muscarinic M_2 receptor (Fryer and Jacoby, 1993). Moreover, it has also been shown that increasing levels of TNF-α reduces the expression of that receptor (Haddad et al., 1996). This leads to the intriguing possibility that the increased levels of TNF-α in the cortex, as has been shown in subjects with major depressive disorder (Dean et al., 2009), could be implicated in the decrease in levels of muscarinic M_2 receptors that have been reported in the cortex of subjects with major depressive disorders and BD (Gibbons et al., 2009). Given the recently established link between the muscarinic M_2 receptor and human cognition (Jones et al., 2004) the ability of inflammatory mechanisms to regulate the expression of this receptor and the decreased levels of this receptor in the cortex of subjects with mood disorders provides a mechansim by which changes in inflammatory pathways could cause the cognitive deficits associated with such disorders.

Inflammation also impacts other transmitter systems. The presence of a proinflammatory state activates the tryptophan- and serotonin-degrading enzyme indoleamine 2,3-dioxygenase (IDO), leading to increased consumption of tryptophan. Stimulation of IDO and kynurenine monooxygenase by pro-inflammatory states further results in the production of tryptophan catabolites. This may cause lowered mitochondrial energy metabolism, the generation of free radicals and lipid peroxidation, and an increase in neuroexcitatory and neurotoxic effects that may lead to neurodegenerative effects. The increased consumption of serotonin and its precursor tryptophan via activation of IDO might also explain the reduced availability of serotonergic neurotransmission in MD (Muller and Schwarz, 2007). Tryptophan catabolites, such as quinolinic acid potently agonize the N-methyl-D-aspartate (NMDA)-receptor causing neurotoxic effects through receptor over-activation (Stone and Perkins, 1981; Schwarcz et al., 1983). Moreover, quinolinic acid inhibits glutamate uptake that causes elevated glutamate concentrations (Tavares et al., 2002). In depression, activation of IDO not only causes production of detrimental tryptophan catabolites, but also depletes plasma tryptophan, thus decreasing brain serotonin turnover (Maes et al., 1999). This pathway may also play a role in acute mania (Myint et al., 2007).

This relationship between monoamines and cytokines may be bi-directional; the release of monoamine neurotransmitters, particularly noradrenaline, provides tonic sympathetic control on cytokine production and hence on the balance of pro-inflammatory/anti-inflammatory cytokines. In an animal model of depression, lipopolysaccharide induced TNF-alpha response was significantly higher in reserpine-treated mice and this response was reduced by desipramine disruption of noradrenaline reuptake (Szelenyi and Vizi, 2007). The cholinergic system, implicated in mood regulation similarly interacts with the immune system. Cholinergic receptors such as the alpha7 nicotinic acetylcholine receptors modulate pro-inflammatory cytokine synthesis (Wang et al., 2009a), and the cholinergic anti-inflammatory pathway inhibits cytokine releases in models of acute inflammatory disease (Li et al., 2010). The glutamatergic system has been implicated with neuronal excitotoxicity. Raised levels of glutamate have been observed with neuronal death in neurodegenerative diseases (Zou et al., 2010). Glutamate is cleared by astrocytes, where glutamate is converted to glutamine (Choi et al., 1987). Glutamate clearance may be reduced by an interaction between inflammatory cytokines and astrocytes (Zou et al., 2010).

A further biomarker of interest is leptin, which has a critical primary role in obesity. Obesity itself is a risk factor for depression (Solin et al., 1997). Elevated levels of leptin have been shown to be a risk factor for depression in prospective studies (Pasco et al., 2008a), and leptin has significant effects in modulation of immune processes (Fernandez-Riejos et al., 2010).

While these direct effects of inflammation on intracellular and extracellular signalling are essential to our understanding of how the immunological system interacts with behaviour, there is another general effect of inflammation that must be considered, that of dysregulated energy generation and its accompanying effect upon the accumulation of oxidative stress.

4.4. Oxidative stress and mitochondrial dysfunction

Many lines of evidence link BD to a fundamental abnormality in oxidative energy generation (Kato, 2007). Brain energy generation is increased in mania, and decreased in depression, a critical finding with high clinical face validity (Baxter et al., 1985), and there is corresponding evidence of an increased basal metabolic rate in mania and a higher VO_2 max, independent of calorific intake (Caliyurt and Altiay, 2009). Mitochondria are intracellular organelles that play a crucial role in adenosine triphophatase (ATP) production and also serve as calcium buffers and regulators of apoptosis (Fattal et al., 2007; Stuchebrukhov, 2009). During the "hopping" of electrons along the mitochondrial electron transport chain (ETC), single electrons sometimes escape and result in a single electron reduction of molecular oxygen to form a superoxide anion ($O_2^{\bullet -}$), especially in complex I (NADH: ubiquinone oxidoreductase) (Green et al., 2004).

Mitochondrial dysfunction in BD is further suggested by impaired brain energy metabolism, high rates of comorbidity of BD with mitochondrial diseases, the effects of mood stabilizers on mitochondria, increased mitochondrial DNA deletion in the neural tissue of BD patients and the association of mitochondrial DNA mutations/polymorphisms with BD (Kim et al., 2007a; Shao et al., 2008; Berger et al., 2010). Moreover, in a study of the human transcriptome in the cortex of subjects with BD and schizophrenia it is significant that up-regulation of the expression of a number of mitochondrial genes differentiated medication-free BD from control subjects and subjects with schizophrenia (Iwamoto et al., 2005). Somewhat contrasting to these findings is the finding that down-regulation of mitochondrial gene expression in the hippocampus differentiates BD from schizophrenia (Konradi et al., 2004). However, both studies agree that changes in mitochondrial gene expression appear to be a critical component of the pathophysiology of BD.

Whilst it is still not totally clear how changes in mitochondrial gene expression could cause BD, it has been proposed that mitochondrial DNA mutations or polymorphisms result in altered mitochondrial Ca^{2+} regulation (Kato, 2007). Elevated basal intracellular calcium is documented in individuals with BD (Berk et al., 1994). Increased glutamate receptor-mediated increases in calcium are also present, that ultimately alters neuroplasticity and may contribute to the excitotoxic processes reported in BD (Berk et al., 2000; Kato, 2007).

More focussed studies have recently reported a reduction in the activity of complex I of the mitochondrial ETC in prefrontal post-mortem brain tissue in BD, but not schizophrenia or major depression (Andreazza, 2009). In terms of mitochondrial dysfunction, there is evidence in BD of altered expression of subunits from mitochondrial ETC complex I (Konradi et al., 2004; Sun et al., 2006). Furthering these findings, Cheng et al. (2006), using genome-wide linkage scans, suggested linkage of chromosome 19p13 in BD where the majority of complex I subunits genes are located (Cheng et al.,

2006). Given the mitochondrial hypothesis of BD, it is of considerable interest that lithium increases the activity of mitochondrial complexes I/II and II/III in human brain tissue (Maurer et al., 2009).

The reactive oxygen species (ROS) generated along the ETC are detoxified by antioxidant enzymes. When mitochondrial and cytoplasmic antioxidant systems are overwhelmed by elevated levels of ROS damage can occur to DNA, lipids (cell and organelle membranes) and proteins (receptors, transcription factors and enzymes) (Lenaz et al., 2000).

Alterations in antioxidant enzymes have been reported in BD. For example, Andreazza et al. (2007) found that superoxide dismutase activity is increased during the manic and depressed phases of BD, but not in euthymia (Andreazza et al., 2007). This is corroborated in part by Machado-Vieira et al. (2007) who reported increased activity of SOD in unmedicated manic BD patients (Machado-Vieira et al., 2007a). Catalase activity was decreased in euthymic patients (Andreazza et al., 2007) and increased in unmedicated manic patients (Machado-Vieira et al., 2007a). Interestingly, treating BD using the glutathione precursor and free radical scavenger, N-acetyl cysteine (NAC) reduces depressive symptoms and improves functioning and quality of life (Berk et al., 2007b). There is additionally data that there are stage-dependent changes in oxidative parameters. The activity glutathione reductase, and GST are increased in late stage patients compared to early stage patients and controls (Andreazza et al., 2009). This stage-related change in oxidative biology may form part of the progressive failure of compensatory mechanisms over time, and may in part underlie the phenomenology of the staging process.

In contrast, studies have shown increased lipid peroxidation occurring as a result of uncompensated oxidative stress that is present independent of the phase of the illness (Andreazza et al., 2007; Machado-Vieira et al., 2007a). In addition, increased levels of lipid peroxidation were found in the cingulate cortex of patients with BD (Wang et al., 2009b). It is important to emphasize that oxidative damage to membrane phospholipids leading to alteration in fluidity, may induce cell death (Mahadik et al., 2001). Accumulation of oxidative damage is thought to lead to neuronal cell death by apoptosis or as a consequence of aggregation of oxidized proteins, which may result in impairment of mood stabilizing mechanisms (Fig. 1).

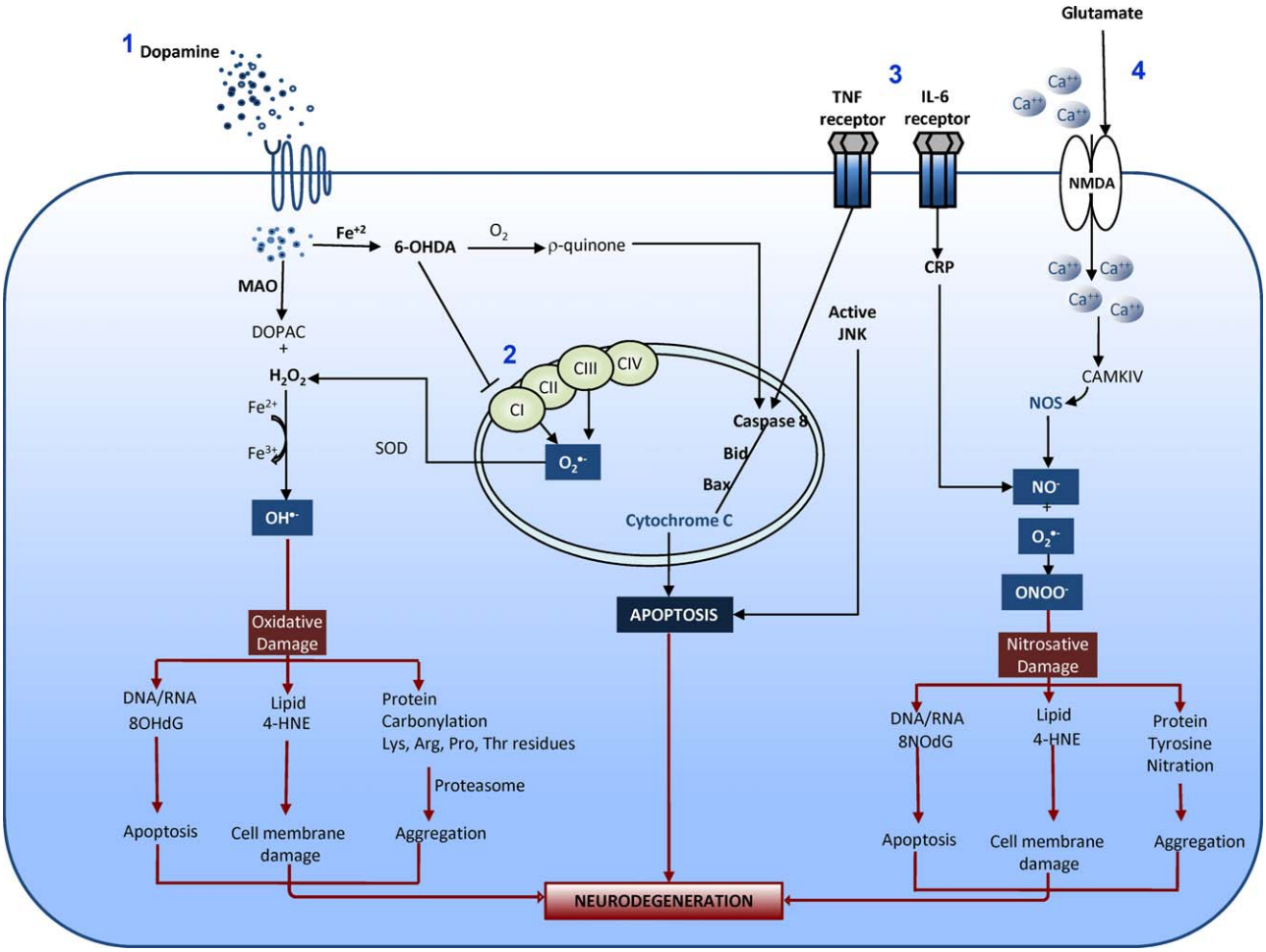


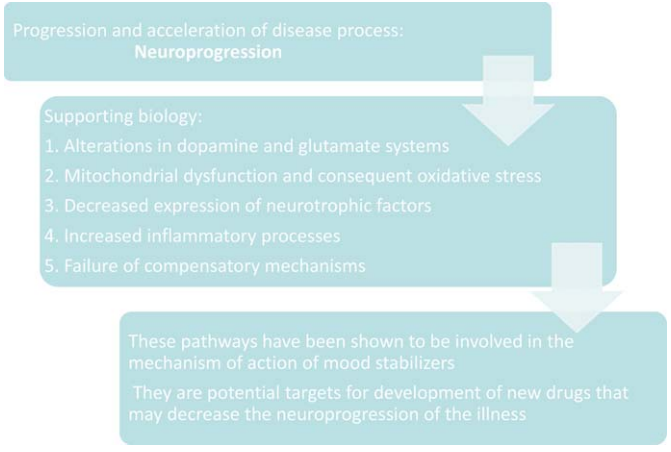
Fig. 1. Potential contributing pathways involved in bipolar disorder. To date a multitude of potential contributing factors implicated in bipolar disorder have been identified. These include alterations in dopamine, glutamate metabolism and inflammation potentially leading to mitochondrial dysfunction and consequent increasing in apoptosis, cell membrane damage and protein aggregation. (1) Increased dopamine release leads to augment the metabolization process. Dopamine can be metabolized via monoamine oxidase (MAO) or suffer auto-oxidation by reacting with iron (Fe^{2+}). Dopamine reaction with MAO leads to produce reactive oxygen species (ROS), peroxide hydrogen (H_2O_2). It may react with Fe^{2+} generating one of the most reactive free radical, the hydroxyl (OH^-), which can induce oxidation of DNA, protein and lipids. The autoxidation by Fe^{2+} of the dopamine produces 6-hidrydopamine and p-quinone that, respectively, might inhibit mitochondrial electron transport chain or activate caspase-8. (2) Mitochondrial electron transport chain dysfunction will in turn produce more ROS and consequent oxidation of biomolecules. (3) Activation of pro-inflammatory receptor, such as TNF-alpha and IL-6 might induce activation of apoptosis process trough caspase activation or augment the nitric oxide (NO) production. (4) Other possible pathway that increases the oxidative stress in BD is the activation of NMDA receptor trough glutamate. Its activation will increase the calcium influx and consequent NO production, which leads to nitrosative damage to DNA, proteins and lipids. Oxidative and nitrosative damage can possible induce to membrane damage, protein aggregation and apoptosis initiation, in a situation where oxidative defences are already vulnerable.

4.5. Neurotrophins

Neurotrophins such as BDNF, bcl-2, and vascular endothelial growth factor (VEGF) play a key role in neuronal survival and proliferation. Alterations in neurotrophins are well documented in BD (Kim et al., 2009) and treatments can alter neurotrophin levels, for example lithium induces bcl-2 expression in neurons (Sassi et al., 2002) and increases VEGF expression by astrocytes by a GSK-3 dependent pathway (Guo et al., 2009). There are reported associations between BDNF gene polymorphisms and BD (Lohoff et al., 2005; Vincze et al., 2008; Matsuo et al., 2009; Xu et al., 2010).

Decreased BDNF is reported in acute episodes of mania and depression and these changes have been shown to correlate to the severity of episodes (Cunha et al., 2006; Machado-Vieira et al., 2007b; Fernandes et al., 2009). Acute mood episodes have been shown be associated with decreased BDNF levels both in medicated (Cunha et al., 2006) and unmedicated patients (de Oliveira et al., 2009). This seems to support the notion that the main factor related to lower BDNF levels in depression and mania is the presence of symptoms, not medication status. Further, in a recent study Tramontina et al. (2009) showed that manic patients who responded to treatment are likely to experience a sharp increase in their serum BDNF after the resolution of the acute episode (Tramontina et al., 2009). This data supports the notion that BDNF serum levels are a reliable marker of the activity of BD, although there may be more proximal correlates of disease activity and the relationship between inflammation and BDNF levels complicates the picture. Of note, other neurotrophins have shown similar patterns in acute mood episodes (Rosa et al., 2006; Walz et al., 2007, 2009).

Reduced serum BDNF levels may be related to decreased levels of this neurotrophin in the brain, supporting the notion that part of the neuroprogression in BD may be related to a decrease in BDNF levels in acute episodes (Kapczinski et al., 2008a) with a cumulative effect as the disorder progresses (Kapczinski et al., 2008b). Supporting a stage-dependant change in neurochemistry in BD, Kauer-Sant'Anna et al. (2009) has shown that levels of BDNF appear to be normal in the early stages of the disorder in euthymic subjects, and decrease only in the latter stages (Kauer-Sant'Anna et al., 2009). As such, one possibility is that serum BDNF displays both state changes during acute illness and slower changes that accompany neuroprogression. This finding is again concordant with Post's theory that there is a failure of compensatory mechanisms with neuroprogression in BD (Post, 2007) (Scheme 1).



Scheme 1.

4.6. Epigenetic mechanisms

Tsankova et al. (2006) found that repeated stress in mice could increase histone H3K27 methylation in the hippocampus with suppressive effects upon the BDNF gene promoter region. Interestingly, this effect was reversed by imipramine (Tsankova et al., 2006). The study of epigenetic mechanisms in BD is in its early stages; however it provides a strong candidate mechanism for how kindling effects and treatment resistance may occur. Kato et al. (2005) have suggested that epigenetic mechanism may underlie some of the discordance between monozygotic twins with BD (Kato et al., 2005). There is some evidence that treatment may have effects on epigenetics. Valproate has been shown to inhibit the activity of histone deacetylases, ultimately resulting in decreased DNA methylation of the reelin promoter (Chen et al., 2002). There is similar evidence suggesting that like VPA, there may be epigenetic changes potentially relevant to BD following lithium treatment. Lithium and VPA both inhibit glycogen synthase kinase-3 (GSK-3) and histone deacetylase, which may further activate the promoter IV of BDNF (Yasuda et al., 2009).

5. Neuroprotection

Neuroprotection may be a viable and realistic goal in treating BD. There are two types of pathological processes amenable to intervention. Firstly, normal physiological processes that happen in excess, for example excitotoxicity, pruning or excessive apoptotic activity. Secondly, the failure of trophic processes, such as reduced neurogenesis, senescence of progenitor cell generation and differentiation can also be targeted. Such an approach would involve regulating the processes of growth, regeneration and the rescue of brain cells that may be at risk of damage or even death (Berger et al., 2007). Hence, there are a number of targets for neuroprotection, and understanding the different pathways involved may open a range of potential therapeutic targets (Table 1).

Table 1
Potential therapeutic agents useful as neuroprotective factors and the targeted pathways.

Pathway	Potential therapeutic agent
Blocking of excitotoxicity	NMDA receptor antagonists
Induction of anti-apoptotic factors such as bcl-2 or BDNF, GDNF, NT-3 and VEGF	Lithium or atypical antipsychotics
Inhibition of key enzymes such as the 'apoptosis executioners' caspases 3, 6, 7	Lithium, eicosapentaenoic acid
Stabilization of mitochondrial cell membranes	Valproate
Direct inhibition of cell death signalling pathways by blocking direct death pathways and preventing the activation of caspase 8 mediated cell death pathways	TNF-inhibitors
Augmentation of major radical scavengers such as glutathione	N-acetyl cysteine
Scavenging ROS produced in the mitochondria during beta-oxidation	Coenzyme Q10 and lipoic acid
Inhibition of NFKB	Curcuma, fluoxetine, and mood stabilizers
Blocking GSK-3	Mood stabilizers
Blocking COX-2	NSAIDS
Inflammatory and oxidative pathways	Statins
Epigenetic modification	Valproate, Lithium
Synaptogenesis	Erythropoetin

6. Neuroprotective effects of known bipolar agents

One of the conundrums in BD is that many of the agents that are useful in managing the disorder at first glance appear to share few properties. However, it is now known that established mood stabilizers impact the pathways and mechanisms that are associated with neuroprogression in BD. For instance, lamotrigine, lithium and VPA reduce oxidative stress (Cui et al., 2007; Eren et al., 2007; Kim et al., 2007a; Ng et al., 2008) and atypical antipsychotics also reduce oxidative stress, not only via dopamine antagonism (Berk et al., 2007c), but also via direct effects on oxidative defences (Fig. 2). Given this, it is likely that the glutathione precursor, N-acetyl cysteine (NAC) that prevents oxidative damage and has been shown to be efficacious in the treatment of BD (Berk et al., 2008a), may also have neuroprotective properties (Fig. 2). Similarly, lithium, VPA, lamotrigine, carbamazepine and atypical antipsychotics such as quetiapine share an effect of increasing BDNF, (Fig. 2) although these effects may be via secondary mechanisms (Bai et al., 2003; Martinowich et al., 2007; Chang et al., 2009). Further, when stimulated with lipopolysaccharide, monocytes from non-lithium treated bipolar patients showed trends towards low IL-1β and high IL-6 production resulting in a significant difference in the ratio of IL-1β to IL-6. Treatment with lithium reversed these changes, thus restoring the aberrant ratio (Knijff et al., 2007).

The protein bcl-2 has a key anti-apoptotic role and promotes cell survival. Mood stabilizers have been shown to increase bcl-2 levels in animal studies (Chen et al., 1999; Manji et al., 2000; Chang et al., 2009) and atypical antipsychotics have also been shown to increase bcl-2 levels (Bai et al., 2004). Lithium impacts on GSK-3, by directly inhibiting GSK-3α and -3β activity (Chalecka-Franaszek and Chuang, 1999; Manji and Lenox, 2000). VPA has been shown to suppress GSK-3 (Chen et al., 1999). There is, however, no evidence that other mood stabilizers, such as carbamazepine or lamotrigine, suppress GSK-3. GSK-3β is a component of the cell survival-promoting signalling pathway, which plays a critical role in multiple cellular processes, including metabolism, proliferation, differentiation, axogenesis and synaptogenesis (Gould et al., 2006). GSK-3 inhibits the transcription factors B-catenin and cyclic AMP response element binding protein (CREB), by phosphorylation, resulting in a decrease in the transcription of important genes involved in neuroprotection pathways (Gould et al., 2006; Boer et al., 2008). A number of studies have found that lithium not only directly inhibits GSK-3β activity, but also enhances inhibition of GSK-3β activity by the kinase Akt, which in turn promotes the

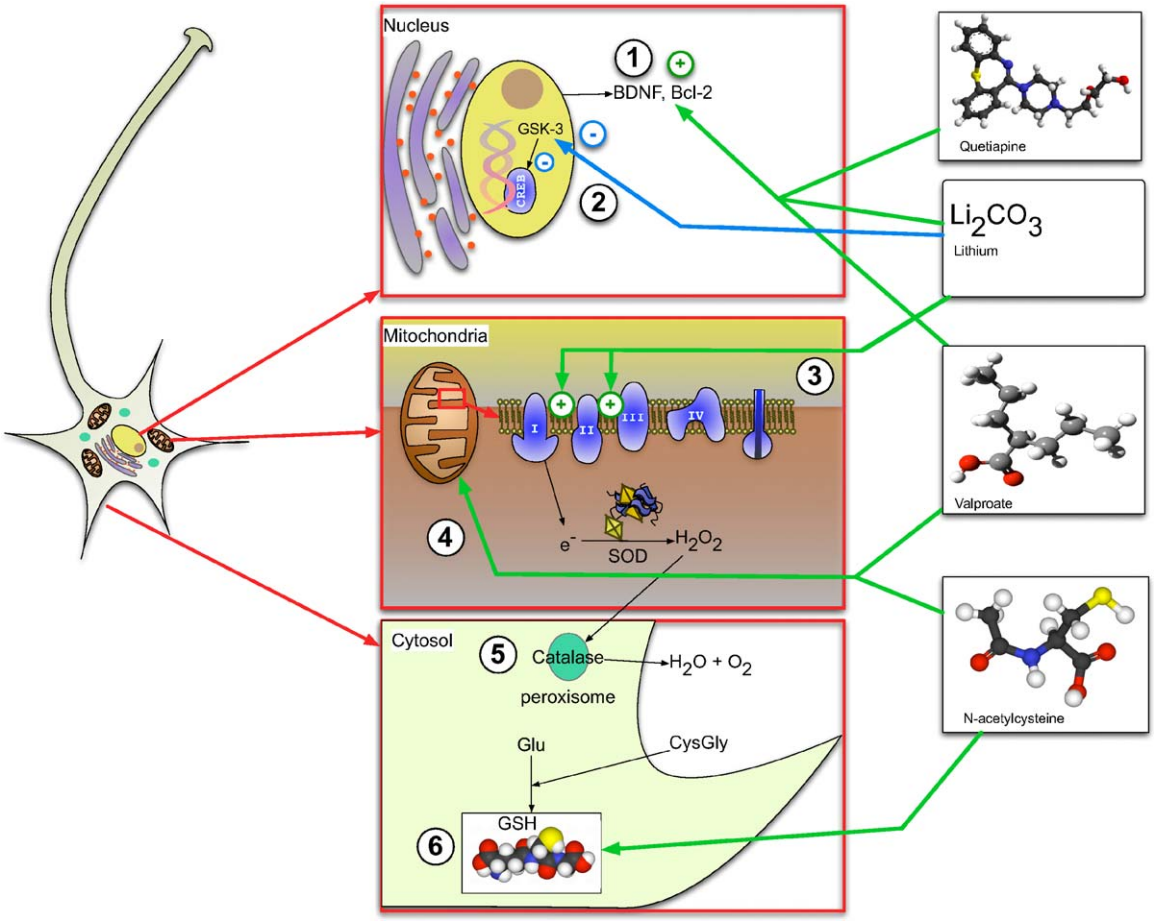


Fig. 2. Cellular loci of action of known and novel agents. (1) Production of neurotrophins, such as BDNF, and anti-apoptotic factor Bcl-2 have been shown to be reduced in exacerbations of BD. One of the targets of action for valproate, lithium and quetiapine are BDNF, by increased it expression. Valproate and lithium also have properties that boost Bcl-2 expression. (2) Glycogen synthase kinase-3 (GSK-3) is part of the survival signalling pathway, activate GSK-3 inhibits the transcription factors cyclic AMP response element binding protein (CREB), by phosphorylation, resulting in a decrease in the transcription of important genes involved in neuroprotection pathways. Lithium, play an important role in this pathway by suppressing GSK-3 activity, thereby facilitating CREB activation. (3) Lithium might increases activity of mitochondrial complex I, which can protect against reactive oxygen species production. (4) N-acetyl cysteine may reduce oxidative stress via protecting mitochondria against oxidative damage. Valproate can stabilize mitochondrial cell membranes, also promoting a protection against oxidative stress. (5) The activity of antioxidant enzymes superoxide dismutase (SOD) and catalase is increased in untreated manic and depressive episodes, suggesting an increased free radical production in these illness. (6) N-acetyl cysteine acts as a precursor for glutathione (GSH) that is essential to prevent the oxidative damage to biomolecules.

accumulation of β-catenin (Chalecka-Franaszek and Chuang, 1999; Grimes and Jope, 2001).

Mood stabilizers protect against excitotoxic apoptosis. Specifically, lithium has also been shown to increase N-acetyl aspartate, a marker of neuronal viability (Malhi et al., 2002; Malhi and Yatham, 2007; Forester et al., 2008), as well as grey matter volume in people with BD (Moore et al., 2000a,b). Similarly, atypical antipsychotics have been shown to increase neocortical grey matter in the disorder (Nakamura et al., 2007).

Atypical agents have impacts on many of these pathways. Clozapine and quetiapine alter the expression of key genes in mitochondrial pathways (Ji et al., 2009), and quetiapine appears to reduce oxidative stress in *in vitro* models, as well as reduce intracellular calcium, a component of the excitotoxic cascade. In *in vitro* studies, quetiapine and persopirone, but not ziprasidone reduce the TNF-α response to interferon gamma stimulation (Bian et al., 2008). Data from the CATIE study in schizophrenia suggests that some atypical agents, particularly olanzapine, are associated with a reduction in inflammatory markers (Meyer et al., 2009). Quetiapine increases BDNF expression in rat neocortex (Park et al., 2006), and reverses restraint stress induced reduction in hippocampal neurogenesis (Luo et al., 2005).

7. Novel neuroprotective strategies

7.1. N-acetyl cysteine

N-acetyl cysteine (NAC) is not only a precursor to the primary free radical scavenger, glutathione, but in addition has many other biological effects including increasing glutamate in the nucleus accumbens and anti-inflammatory properties (Dodd et al., 2008). NAC additionally enhances neuronal differentiation of mouse embryonic stem cells, and has been shown to enhance the extension of neuritogenesis (Qian and Yang, 2009). Similarly, it increases neuronal survival and the number of regenerating neurons after nerve graft (Welin et al., 2009). Intriguingly, NAC reverses mitochondrial toxicity. For instance, menadione, a mitochondrial toxin that induces apoptosis through increased peroxide and hence oxidative stress, adversely affects mitochondrial function because it induces collapse of the mitochondrial inner transmembrane potential and a decrease in inner membrane mass. This toxicity is reversed by NAC (Laux and Nel, 2001).

N-acetyl cysteine has been shown to modulate glutamate-cystine exchange and have beneficial effects in addiction where both oxidative stress and alterations in glutamate neurotransmission are present (Grant et al., 2007; LaRowe et al., 2007; Mardikian et al., 2007). NAC prevents the delayed adverse consequences of prenatal inflammation. For example, lipopolysaccharide-induced prenatal inflammation is attenuated by NAC. This inflammatory process reduces glutathione, increases reactive oxygen species and as a consequence, inhibits oligodendroglial cell development and myelination (Lante et al., 2007; Paintlia et al., 2008a,b). Increased levels of the pro-inflammatory cytokine IL-6 further increase levels of ROS (Behrens et al., 2008). Given the role of glutamatergic, oxidative and inflammatory pathways it is interesting to note that NAC appears to have some activity across these mechanisms.

Concordant with the accepted role of neurogenesis in depression, NAC shows antidepressant effects in the forced swim test, the benchmark screening test for antidepressant properties (Ferreira et al., 2008). In a proof-of-concept placebo-controlled design, NAC reduced depression and improved functioning and quality of life with large effect sizes (Berk et al., 2008a). It is therefore a potential neuroprotective candidate, with trials in the earliest stages of the disorder, with cognitive and structural endpoints both clinically and theoretically warranted.

7.2. Anti-inflammatory medications

Celecoxib, an anti-inflammatory COX-2 inhibitor has been studied in depressive or mixed episodes of BD using a double blind, randomized, placebo-controlled design. In this 6-week pilot RCT, treatment with celecoxib was associated with lower depression scores after 1 week compared to placebo. This suggests a potential antidepressant effect of COX inhibitors (Nery et al., 2008). Further, in schizophrenia, there is a suggestion that aspirin, with similar anti-inflammatory properties, may reduce the core symptoms of the disorder which, given the overlapping biomarker data in mood and psychotic disorders, is an intriguing lead (Laan et al., 2010).

Aspirin has established anti-inflammatory effects. In a study of 70 people with depression, aspirin together with fluoxetine conferred a greater reduction of oxidative stress parameters than fluoxetine monotherapy (Galecki et al., 2009). In a stroke model, aspirin has demonstrated neuroprotective effects (Kim et al., 2010). Aspirin has antidepressant properties in preclinical models (Brunello et al., 2006), and accelerates antidepressant effects. Clinically, aspirin has been suggested to shorten the onset of action of antidepressants (Mendlewicz et al., 2006). There are however negative epidemiological data on the link between aspirin and depression risk (Almeida et al., 2010). Of interest, a recent study has shown that in schizophrenia that aspirin reduces core symptoms of the disorder. Given the overlapping biomarker data in mood and psychotic disorders, this is an intriguing lead (Laan et al., 2010).

7.3. Omega-3 fatty acids

There is preliminary evidence for a role of omega-3 fatty acids in BD. As with major depression, seafood consumption has been inversely associated with prevalence rates of BD in epidemiological studies (Parker et al., 2006). There may be a correlation between decreased omega-3 consumption and increased prevalence of mood disorders. However, Jacka et al. (2010a,b) showed that fish consumption per se, not omega-3 fatty acid consumption was related to depression risk, suggesting the importance of whole diet rather than individual nutrients (Jacka et al., 2010b). This is possibly linked to the effect of eicopentaenoic acid (EPA) and docosahexaenenoic acid (DHA) on certain aspects of physiology that have been seen as key in BD. Both EPA and DHA have been shown to reduce pro-inflammatory cytokines and increase BDNF (Ross et al., 2007), as well as increasing glutathione (Berger et al., 2008), possibly countering relevant peripheral changes in BD (Kapczinski et al., 2008a, 2010; Brietzke et al., 2009a; Kauer-Sant'Anna et al., 2009). Oxidative stress may preferentially deplete key polyunsaturated lipids, potentially interacting with dietary insufficiency (Jacka et al., 2010a,b) and result in further vulnerability to illness. In schizophrenia, Amminger et al. (2010) have shown that omega-3 supplementation may reduce the rate of transition of high-risk individuals to a first-episode of illness (Amminger et al., 2010). In addition, depletion of key lipids including trans-vaccenic acid and nervonic acid, may both predict transition of at-risk individuals to illness, as well as treatment response.

Clinical studies conducted so far have been diverse and of varying quality (Montgomery and Richardson, 2008). Heterogeneity includes sample size, fatty acid used (EPA or DHA), dosage and duration of follow-up. Taken as a whole, however, the studies indicate beneficial effects of omega-3 for relieving depressive symptoms. Importantly, their relapse prevention effects apparently remain untested (Turnbull et al., 2008). One further interesting finding of recent systematic reviews is the possibility that omega-3 fatty acids may have greater efficacy for mood disorders than in schizophrenia, where the effects in established disorder are less robust (Ross et al., 2007).

7.4. Statins

Statins have potent anti-inflammatory and anti-oxidative properties that are thought to contribute to their efficacy in protection against cardiovascular disease, which shares many of the pathways discussed in this paper. There is epidemiological evidence that they may reduce the risk of the development of depression. Pasco et al. (2010) showed that in a community cohort individuals who were on statin therapy had an almost 80% reduced risk of developing a *de novo* episode of depression over a 10-year follow-up period (Pasco et al., 2010). Confirming this, Stafford and Berk (in press) showed a comparable reduction in risk for the development of depression over a 9-month follow-up period in a cohort of individuals who had an intervention for cardiovascular disease in those prescribed statins compared to individuals who did not receive statins (Stafford and Berk, in press).

8. Implications

In summary, we are now beginning to understand the underlying processes of neuroprogression in BD that include inflammatory cytokines, neurotrophins, mitochondrial dysfunction, oxidative stress and epigenetic effects. These parameters appear to be sensitive to the stage of illness, and indeed are the first biochemical indicators of the staging model in BD (McGorry et al., 2006; Berk et al., 2007d). While the interactions of these systems are beginning to be elucidated it remains difficult to say which mechanisms are the most important in the cascade of metabolic, immunological and neurochemical changes associated with BD disease progression. However, the importance of these mechanisms and their clear association with long the long-term course of BD cannot be understated. It is also becoming clearer that these pathways do not match the currently accepted DSM-IV classification, but instead appear to be shared across mood and psychotic disorders. However, at this early stage, the data do not suggest an alternate nosological plane of cleavage, although they do indicate that phenomenology as currently defined does not meaningfully link to these pathophysiological pathways. This suggests that treatment targets based on these pathways in one disorder may well be valid candidates in disorders with overlapping biomarker data, as has transpired in the case of antipsychotic treatment in BD. This further suggests that an acceleration of effort into conceptualising and validating novel biomarkers is potentially a high reward strategy.

This conceptualisation of the pathways to neuroprogression has a number of theoretical implications. Firstly, it is broadly concordant with the notion of allostatic load, originally proposed by McEwen (McEwen, 2004), and adapted to BD by Kapczinski (Kapczinski et al., 2008b). It implies that medical comorbidity and substance use interacts with the core neuroprogressive processes, to impact cumulatively on shared risk pathways. This is concordant with unpublished data that agents such as NAC, which are thought to act primarily on these neuroprogressive pathways, are more efficacious in individuals with those medical comorbidities (cardiovascular, endocrine) that also impact on inflammatory and oxidative pathways (Magalhaes et al., unpublished data). It is noteworthy that inflammatory and oxidative pathways are common risk factors for psychiatric disorders and those common medial disorders that are highly comorbid with psychiatric disorders such as cardiovascular disorders and osteoporosis (Pasco et al., 2006, 2008b; Williams et al., 2009). Elevated levels of markers such as CRP have been shown to be risk factors for depression, osteoporosis and cardiovascular disease in prospective designs. Addressing these shared vulnerability factors may theoretically contribute to secondary prevention of these comorbid medical disorders.

A further implication of this relates to predictors of response. To date, the field has lacked reliable biological predictors of response (Dodd and Berk, 2004). The study of aspirin in schizophrenia suggested that efficacy was greater in those with higher levels of inflammation (Laan et al., 2010). These embryonic data suggest that markers of oxidative or inflammatory stress may be predictors of response to therapies active on those pathways. The nascent field of theragnostics in psychiatry, predictors of treatment response and individualised medicine, may find support in this arena (Pene et al., 2009). This further reinforces the importance of biomarker research and its linkage to clinical trials.

9. Conclusions

The pathways explored in his review appear to be common targets of the otherwise diverse and seemingly unrelated treatments (lithium, valproate, atypical antipsychotics) that share efficacy in the treatment of BD. To date, it has been difficult to explain the shared efficacy of these superficially diverse therapies. These emerging data suggest that these common targets may be more central to the biological foundation of the disorder than hitherto appreciated. They additionally open the door to hypothesis driven rational drug development. These findings are concordant with the idea that neuroprotection is a viable therapeutic strategy, especially in the early stages of illness (Berger et al., 2007). This further supports the construct of early intervention, which suggests that the initiation of optimal therapy early in the trajectory of the disorder may reduce the disability associated with disease progression, and may modify the course of the disorder into a less malignant and more treatment-responsive pattern (Berk et al., 2008b).

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