From neuroprogression to neuroprotection: implications for clinical care

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Neuroprogression in bipolar disorder is associated with neuroanatomical changes and cognitive decline. Here, we discuss how the biochemical foundation of this process relates to clinical care.

Clinical evidence of neuroprogression in bipolar disorder

Abundant evidence supports the construct of stage-related changes during the course of illness in individuals with bipolar disorder. There is evidence that the illness itself is self-perpetuating. Each episode of illness increases the risk of future recurrence. For example, there is a well replicated reduction in the inter-episode duration with recurrence — as the number of episodes increases, the inter-episode duration decreases.[1-4] Bipolar disorder is nevertheless pleomorphic, presenting and developing differently in different individuals. Although progressive changes in illness presentation over time are a common feature of the illness, some individuals have a malignant course from an early stage while a few return to functionality despite multiple recurrences.

Although early diagnosis and treatment is essential for optimal treatment outcomes,[5] frequently there is a substantial gap between the onset of the first features of bipolar disorder and the introduction of appropriate treatment.[6] Of concern, this delay is associated with a progressive reduction in the probability of response to treatment, so that both lithium[7,8] and cognitive behaviour therapy appear to be less useful if used later in the illness.[9] A more recurrent pattern of illness is also associated with higher rates of comorbidity, particularly substance abuse,[10] poorer social adjustment,[11] more hospitalisations,[12] greater suicide risk[13] and forensic complications. Persistence of illness, especially in young people, is associated with failure to meet age-specific developmental tasks, which further compounds the complex interaction between clinical, biological, social and developmental processes.[14]

Neuroimaging and cognitive evidence of neuroprogression in bipolar disorder

The observed clinical progression in bipolar disorder is reflected by growing evidence of stage-related structural brain changes in affected individuals, leading to the identification of structural abnormalities in established forms of the illness. The fact that these structural abnormalities are not consistently found at illness onset, but are more commonly found in chronic and more recurrent forms of the disorder, raises the possibility of neuroprogressive changes over time. Individuals with a first episode of mania have been shown to have ventricular size comparable to control individuals, whereas individuals with recurrent illness showed ventricular enlargement.[15] Progressive loss of grey matter thickness with chronicity has also been described.[16] There is, however, data showing that "ultra-high risk" individuals who have not yet manifested a first episode of threshold mania already show amygdala and insular volume reductions (A B, unpublished data), as well as pituitary enlargement.[17] As such, it is possible that both early neurodevelopmentally mediated differences[18] and ongoing neuroprogressive changes occur, and that these are regionally specific. These findings are controversial as negative data have also been published.[19-21] Further investigations with more rigorous designs, such as prospective and treatment studies, are required.

Cognitive impairment is also a core feature of bipolar disorder[22] and contributes to the disability associated with the disorder. It has been suggested that this is related to the number of illness episodes experienced.[23,24] In a study of cognitive functioning, patients with bipolar disorder who had experienced one or two illness episodes displayed minimal cognitive divergence from controls. In contrast, individuals who had longstanding illness manifested significant reductions on most measures of cognition when compared with both controls and early-episode patients.[25] A staging model for bipolar illness has been described,[5,26] which provides a theoretical framework for clinical observations in which individuals are seen to progress from an at-risk stage to a prodrome, a first episode, single and multiple recurrences, and potentially a stage of treatment resistance.

The biochemical foundation of neuroprogression

In the kindling model, it has been suggested that multiple episodes of illness have the potential to result in long-term alterations in neuronal systems.[27] Part of this hypothesis is a failure of endogenous compensatory mechanisms during progression of the illness.[28] Similarly, the allostatic load hypothesis describes a

ABSTRACT

- Bipolar disorder follows a staged trajectory in which persistence of illness is associated with a number of clinical features such as progressive shortening of the inter-episode interval and decreased probability of treatment response.
- This neuroprogressive clinical process is reflected by both progressive neuroanatomical changes and evidence of cognitive decline.
- The biochemical foundation of this process appears to incorporate changes in inflammatory cytokines, cortisone, neurotrophins and oxidative stress. There is a growing body of evidence to suggest that these markers may differ between the early and late stages of the disorder.
- The presence of a series of tangible targets raises the spectre of development of rational neuroprotective strategies, involving judicious use of current therapies and novel agents. Most of the currently used mood stabilisers share effects on oxidative stress and neurotrophins, while novel potentially neuroprotective agents are being developed. These developments need to be combined with service initiatives to maximise the opportunities for early diagnosis and intervention.

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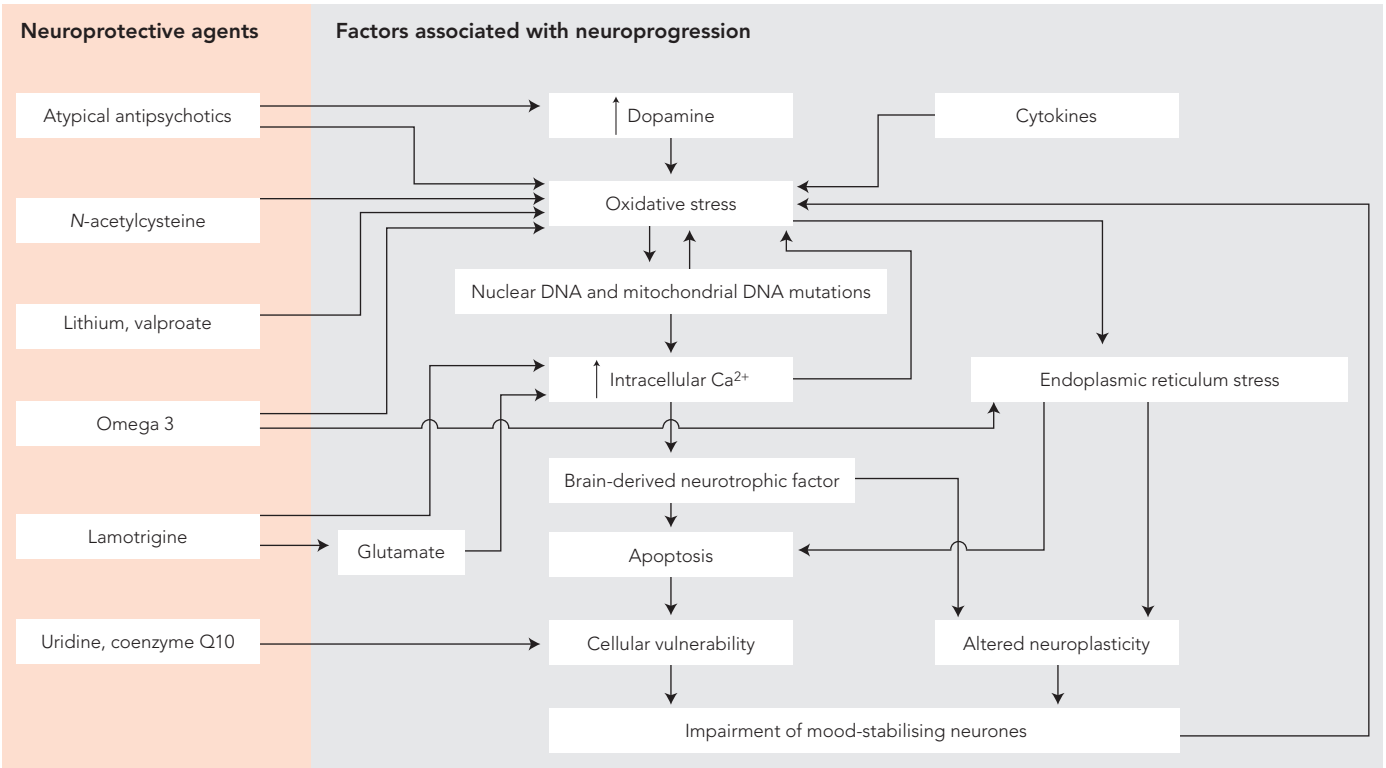
Neuroprogression and neuroprotection in bipolar disorder*



*Arrows represent mechanisms of action. Figure adapted with permission from: Kato T, Kapczinski F, Berk M. Mitochondrial dysfunction and oxidative stress. In: Yatham LN, Maj M, editors. Bipolar disorder: clinical and neurobiological foundations. Hoboken, NJ: John Wiley and Sons, 2010.[30] ◆

process of progressive "wear and tear", in which genetic load, life stressors and aggravating factors such as substance use combine.[29] This sets up a vicious cycle that aggravates the innate neuropathology of the disorder and further disrupts the brain circuits responsible for mood modulation and cognition, further increasing vulnerability to future episodes of illness. There are many biochemical components of neuroprogression (Box), which are additionally affected by environmental stress and medical comorbidity. Core components include the monoamines, inflammatory cytokines, oxidative stress, endoplasmic reticulum stress, neurotrophins including brain-derived neurotrophic factor (BDNF), and cortisone.[28,30-32] The latter is consistent with the pituitary enlargement identified at the earliest stages of psychosis, as noted above.[17]

Cytokines

Cytokines are intimately involved in mood regulation. Infusion of pro-inflammatory cytokines is perhaps the best human model of depression, and elevated levels of cytokines are known to be associated with both depression and mania.[32] Certain components of the inflammatory process may be state dependent. In mania, elevation of pro-inflammatory cytokines such as IL-6 resolve with clinical remission, while tumour necrosis factor-α (TNF-α) does not change with remission.[33] Recent studies have demonstrated activation of inflammatory cytokines and chemokines during both depression and mania, but more prominently during acute mania.[34-36] These changes are not consistently present during euthymia and, therefore, could be related to the episode-related cognitive decline in bipolar disorder.[29] There is evidence that stage of illness has an impact on cytokines. It has been shown that although the pro-inflammatory cytokines IL-6 and TNF-α are elevated in both early- and late-stage disorder, the anti-inflammatory cytokine IL-10 increases only in the early stage of the disorder.[37] TNF-α levels, while elevated throughout the course of the disorder, are higher in the later stages. The increased inflammatory state that appears later in the disorder might be a result of progression of the primary underlying process or a consequence of failure of adaptive homeostatic mechanisms occurring as part of neuroprogression. Some changes such as increased pituitary volume occur earlier in the trajectory, suggesting that there may be multiple interacting processes.

Oxidative stress and mitochondrial dysfunction

Many lines of evidence link bipolar disorder to a fundamental abnormality in oxidative energy generation.[38] Both brain and somatic energy generation are altered in bipolar disorder.[39] High rates of deletions in mitochondrial DNA are seen,[40] as is reduction in the activity of complex 1 of the mitochondrial chain.[41] Mitochondria are intracellular organelles that play a crucial role in ATP production, and hence energy production, and also serve as calcium buffers and regulators of apoptosis.[42] In addition to energy, reactive oxygen species (ROS) are generated in the mitochondria, which are detoxified by antioxidant enzymes. When mitochondrial and cytoplasmic enzymatic antioxidant systems are overwhelmed by elevated levels of ROS, oxidative damage may

occur to DNA, lipids (cell and organelle membranes) and proteins (receptors, transcription factors and enzymes).[43]

There is now abundant evidence that there is an increase in oxidative stress in bipolar disorder, which includes reduction in brain glutathione and changes in levels of antioxidant enzymes (including superoxide dismutase, catalase and glutathione peroxidase).[44] Oxidative stress, inflammatory biomarkers and neurotrophins may be interrelated, such that oxidative stress is associated with decreased BDNF in acute manic episodes.[45] In addition, there is evidence of stage-dependent oxidative changes. The activity of key enzymes in the glutathione pathway — glutathione reductase and glutathione *S*-transferase — is increased in late-stage patients compared with early-stage patients and controls.[46] 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 phenomenon of the staging process. Of interest, many of the alterations in biomarkers are commonly observed in those chronic medical illnesses that are frequently comorbid with mood disorders. This suggests that there may be shared mechanistic pathways between psychiatric and common medical disorders. With all biomarkers, the extent to which peripheral changes reflect central changes is uncertain.

Increased lipid peroxidation, a consequence of uncompensated oxidative stress, is consistently documented in bipolar disorder.[47-49] Oxidative damage results in damage to membrane phospholipids, leading to alteration in fluidity and aggregation of oxidised protein, which may result in impairment of mood-stabilising neurones, and can ultimately lead to neuronal cell death by apoptosis (Box).

Neurotrophins

Neurotrophins such as BDNF play a key role in neuronal survival and proliferation. Alterations in neurotrophins are well documented in bipolar disorder. BDNF is decreased in acute episodes of mania and depression, and correlates with severity of illness, seemingly independent of medication status.[47,48] Supporting BDNF as a state marker, manic patients who respond to treatment have been shown to experience a sharp increase in their serum BDNF after the resolution of symptoms.[50] Together, these data support the notion that part of the neuroprogression in bipolar disorder may be related to a decrease in BDNF levels in acute episodes,[51] with a cumulative effect as the disorder progresses.[29] Supporting a stage-dependent change in neurochemistry in bipolar disorder, levels of BDNF have been shown to be normal in the early stages of the disorder and decreased in the later stages.[37] Decreases in BDNF levels have similarly been documented in disorders such as schizophrenia and depression, as have increases in BDNF after response to treatment; these findings suggest that increased BDNF levels may be a marker of state change rather than a direct pharmacological effect.

Neuroprotective effects of mood stabilisers

One of the conundrums in understanding bipolar disorder is that, at first glance, many of the agents that are useful in managing the disorder share few properties. However, established mood stabilisers affect the pathways and mechanisms that are associated with neuroprogression in bipolar disorder. Both lithium and valproate reduce oxidative stress.[52] Atypical antipsychotics reduce oxidative stress, not only via dopamine antagonism, as dopamine is an oxidative stressor,[53] but also via direct effects on oxidative defences.[30] *N*-acetylcysteine, a glutathione precursor, may also provide neuroprotection by preventing oxidative damage.[54,55] Similarly, lithium, valproate and atypical antipsychotics such as quetiapine share an effect of increasing BDNF.[56,57] Concordant with the pathological role of inflammatory cytokines, it seems that lithium decreases inflammatory cytokines.[58] The protein bcl-2 has a key anti-apoptotic role and promotes cell survival. Both lithium and valproate increase levels of bcl-2 in animal studies.[59,60] Atypical antipsychotics also increase bcl-2 levels.[61] Lithium affects glycogen synthase kinase-3 (GSK-3).[62,63] GSK-3β is a component of the signalling pathway that promotes cell survival, which plays a critical role in multiple cellular processes, including metabolism, proliferation, differentiation, axogenesis and synaptogenesis.[64] Although there is significant evidence to suggest a neuroprogressive deterioration with chronic illness and that treatment may be neuroprotective, direct experimental evidence (particularly in early-stage illness) needs to be gathered. Prospective studies are required to demonstrate the course and treatment response of the neuroprogressive process.

Elevated intracellular calcium is documented in bipolar disorder,[65] and may contribute to the excitotoxic process that is mediated at least in part by glutamate.[66] Mood stabilisers protect against excitotoxic apoptosis in vitro, and may have theoretical benefits in this regard. Lithium has also been shown to increase *N*-acetyl aspartate, a marker of neuronal viability,[67-70] as well as grey matter volume in patients with bipolar disorder.[71]

Conclusion

In summary, the biochemical processes underpinning neuroprogression in bipolar disorder could include inflammatory cytokines, neurotrophins and oxidative stress. These factors appear to be sensitive to stage of illness, and they provide preliminary biochemical evidence that is concordant with the staging model of bipolar disorder.[26,72] They are also common targets of the otherwise diverse and seemingly unrelated treatments that share efficacy in the treatment of bipolar disorder, and they open the door to hypothesis-driven rational drug development. In addition, the biochemical processes of neuroprogression in bipolar disorder are concordant with the idea that neuroprotection is a viable therapeutic strategy, especially in the early stages of illness.[73] This further supports the construct of early intervention, which suggests that initiation of optimal therapy early in the trajectory of the disorder may reduce the disability associated with disease progression and modify the course of the disorder into a more benign and treatment-responsive pattern. These concepts ideally need to be combined with service initiatives to maximise the opportunities for early diagnosis and intervention.

Competing interests

Michael Berk has received funding for research from Stanley Medical Research Foundation, MBF, the National Health and Medical Research Council (NHMRC), beyondblue, Geelong Medical Research Foundation, Bristol-Myers Squibb (BMS), Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma and Servier, and honoraria for speaking engagements from AstraZeneca, BMS, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Pfizer, Sanofi-Synthelabo, Servier, Solvay and Wyeth, and has served as a consultant to AstraZeneca, BMS, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Servier.

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Gin Malhi has served on international and national pharmaceutical advisory boards, received funding for research and has been in receipt of honoraria for talks at sponsored meetings worldwide involving AstraZeneca, Eli Lilly, Janssen-Cilag, Organon, Pfizer and Wyeth.

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