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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