Bipolar Disorder: Molecular and Cellular Biology


Employing multiple models, methods and mechanisms in bipolar disorder research

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Abstract
BD (bipolar disorder) is a devastating condition, giving rise to debilitating mood swings and a greatly increased likelihood of suicide. Research into the origins, progression and treatment of BD has been slow, primarily due to lack of suitable model systems for BD research. However, the complexity of the neurological basis for mood, variability in patient populations and the lack of clear readouts for BD diagnosis also provide significant problems for research in this area. In this Biochemical Society Focused Meeting, held at Royal Holloway University of London, approx. 40 national and international delegates met to discuss current research into understanding BD. The talks presented at this conference covered research examining the genetic basis of the disorder, changes in patient populations, pharmacological actions of BD drugs and the development of new models systems for this research. The focus of these talks and the following papers is to help to unify and disseminate research into this important but poorly understood medical condition.

BD (bipolar disorder): a huge problem
BD comprises a group of cyclic mood disorders divided into three basic categories: bipolar I, also referred to as classic manic–depression, characterized by distinct episodes of major depression combined with episodes of mania; bipolar II, characterized by depression alternating with periods of hypomania (a less severe form of mania that does not include psychotic symptoms); and cyclothymia, a more mild form of BD producing oscillating high and low moods. The disorder is widespread, with estimates for bipolar I occurrence of ~1%, increasing to between 2.2 and 6.9% lifetime prevalence [1], including more mild forms. The origins of BD are based partially on genetic factors, since, for example, studies examining the inheritability of BD in first-degree relatives show an 8% co-inheritance, increasing to up to 93% in monozygotic twins [2]. These genetic studies suggest that a large number of genes may be necessary for BD inheritance, indicating the complex multifactorial basis for the disorder. Little is known regarding environmental triggers.
BD has considerable personal, societal and financial costs. Individuals with BD experience a wide spectrum of behavioural changes ranging from elation in mania to despair in depression. It also significantly increases mortality rate through suicide, where, for example, morbidity of patients with bipolar I has been reported to be 18% [3]. It has recently been recognized as one of the seven major common causes of human morbidity and mortality, and the World Health Organization has identified BD as the sixth leading cause of disability in the world among people aged 15–44 years [3a]. Financial costs for BD are difficult to estimate, since these include a large number of indirect costs, as well as direct costs such as loss of work time and hospitalization. In the U.K., the estimated annual cost of BD was £4.59 billion [3] and it was the most costly mental health disorder in a comprehensive Health and Productivity Cost Burden study performed in the U.S.A. [4]. Some studies have suggested that BD is either underdiagnosed [3] or increasing in frequency where the recent diagnosis of BD in those under 20 has increased 40-fold from 1994–2003 and has almost doubled in adults in the same period [5]. A variety of treatments for BD exist, including
lithium, VPA (valproic acid) and carbamazepine, with more recent treatments including lamotrigine, topiramate, gabapentin, olanzapine and risperidone; however, none of these fully controls BD cycling.

It is thus clear from the costly and widespread nature of this disorder that research must continue into BD, employing multiple models, methods and mechanisms to shed light on this complex medical condition.

**Multiple models**
Research into many medical conditions and health-related problems have used animals to reproduce the condition, enabling a better understanding of the aetiology and treatment of each case. A good example of this is epilepsy research, whereby a variety of methods have been developed to first initiate and then examine the progression and pharmacology of seizures, leading to a huge research effort and subsequent increase in understanding seizures. Research into BD has been seriously impeded by a lack of suitable models. To overcome this, scientists have adapted behavioural tests in animals, and have looked at biochemical changes in patient populations with BD, at genetic inheritance of disease markers and at pharmacological targets of BD treatments.

Standard neuropsychiatric research employs rodent models to analyse cell signalling, either in tissue culture or in vivo, but models for behavioural aspects of BD are scarce. Rodent-based behavioural models [6] employ measures for the manic pole of the disorder by assessing heightened vigour and goal-directed behaviour or psychostimulant-induced hyperactivity, and have employed the Forced Swim Test to simulate the despair aspects of depression. The potential development of new animal models may increase our ability to investigate BD [7]. It is hoped that these models will adequately simulate BD for research purposes on a behavioural level, ultimately enabling the transition of this knowledge to human subjects. On a molecular level, the analysis of cell signalling following BD drug treatment has made cautious advances in understanding, partially due to the complex nature of neuronal signalling and due to problems with manipulating mammalian brain cells for experimental purposes. To overcome this, a number of scientists have employed more simple biomedical models, including the simple sugar **Saccharomyces cerevisiae** [8,9] and the yeast **Dictyostelium** [10]. These systems have the advantage of being able to investigate BD for research purposes on a molecular level, the analysis of cell signalling following BD drug treatment has made cautious advances in understanding, partially due to the complex nature of neuronal signalling and due to problems with manipulating mammalian brain cells for experimental purposes. To overcome this, a number of scientists have employed more simple biomedical models, including the simple sugar **Saccharomyces cerevisiae** [8,9] and the yeast **Dictyostelium** [10]. These systems have the advantage of being able to examine novel compounds that may provide resilient laboratory-based methods for diagnosis. For example, blood-based biomarker assays could provide a fast and efficient method for diagnosis [15], in addition to other body fluids [16]. At this stage, it is unclear whether physical or cell signalling changes constitute the origin of the disorder and give rise to changes in cognitive function, although it is likely that pathogenic signalling changes are corrected by the action of BD treatments.

**Multiple drug mechanisms**
BD treatments have all been found serendipitously, with the most recently introduced medications having been originally prescribed for other condition such as epilepsy or psychosis. Since Cade identified the role of lithium in BD prophylaxis [17], the scientific community has been analysing the cellular targets of these treatments. Unfortunately, many have multiple targets and/or effects, and it remains unclear which target is the critical therapeutic one. In the case of VPA, although it has multiple cellular effects, no primary therapeutic target has even been suggested. To try to overcome this, the most common approach has been to find a signalling pathway targeted by multiple, structurally distinct, BD treatments, since these common targets would be likely to control the pathology of the disorder. The vast majority of these studies centre on lithium and VPA, with some studies including carbamazepine.

The first real advance in identifying common signalling pathways targeted by BD treatments was the inositol-depletion theory, proposed by Berridge et al. [18], who suggested that signalling dependent upon the simple sugar inositol was overactivated in BD, and attenuation of the levels of inositol by lithium stabilized mood swings. This remains a highly supported mechanism of action for BD treatments [19], and inositol-related signalling has been shown to be targeted by three structurally distinct BD treatments [11]. The initial focus of this theory, reduced inositol trisphosphate levels, has now broadened to include attenuating inositol phospholipids [10,20,21], and the reduction of these signalling components provides a range of cellular effects [22]. This work has also stimulated interest in the regulation of inositol transport into neurons [23], and research continues to examine novel compounds that may provide more potent treatments for this effect [24–26].

The second well-supported theory concerns the inhibition of an important protein kinase, GSK3 (glycogen synthase kinase 3) [27], an enzyme initially identified to regulate glycogen synthase, but subsequently found to play a central role in a large number of signalling pathways. GSK3 is inhibited directly by lithium [28], suggesting that it may be the therapeutic target in BD treatment. This idea is supported by studies showing that reduced activity of GSK3 gives rise to behaviour similar to lithium treatment [29], and the partial ablation of GSK3 activity in mice [29] or direct inhibition by specific inhibitors [30] mimics behaviour changes caused by lithium. Furthermore, elevating the level of the GSK3 substrate β-catenin (corresponding to GSK3
inhibition) also causes similar behavioural effects [31]. Support for this mechanism through other BD treatments is less clear, since VPA has also been proposed to act through both direct and indirect inhibition of GSK3 [32], although this effect may be variable [33].

A range of other targets have also been proposed to play a key role in BD prophylaxis. These include PLA2 (phospholipase A2) [34] and MAPK (mitogen-activated protein kinase) [35] signalling pathways, both targeted by VPA and lithium. In the case of several more recent treatments, such as lamotrigine, ion channel regulation remains a common theme [36].

Conclusions
Our slow advance in understanding the molecular and cellular biology of BD is derived from a number of factors including a lack of model systems, difficulties in recording and classifying BD, and unclear mechanisms of treatment. Integrating research approaches, and the development of improved diagnosis and new treatments will significantly advance our understanding of this important disorder.

References

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