Neuroscience and Biobehavioral Reviews 37 (2013) 1380–1402

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Translating the evidence for gene association with depression into mouse models of depression-relevant behaviour: Current limitations and future potential

Christopher R. Pryce[a,b,c,*], Federica Klaus[a,b]

[a] Preclinical Laboratory for Translational Research into Affective Disorders (PLaTRAD), Department of Psychiatry, Psychotherapy & Psychosomatics, Zurich University Hospital for Psychiatry, August Forel-Strasse 7, CH-8008 Zurich, Switzerland
[b] Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland
[c] Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

ARTICLE INFO

Article history:
Received 8 November 2012
Received in revised form 15 April 2013
Accepted 3 May 2013

Keywords:
Depression
Psychopathology
Aetio-pathology
Gene polymorphism
Gene–environment
Stress
Expression
Mouse model

ABSTRACT

Depression is characterised by high prevalence and complex, heterogeneous psychopathology. At the level of aetio-pathology, considerable research effort has been invested to identify specific gene polymorphisms associated with increased depression prevalence. Genome-wide association studies have not identified any risk polymorphisms, and candidate gene case–control studies have identified a small number of risk polymorphisms. It is increasingly recognised that interaction between genotype and environmental factors (G × E), notably stressful life events, is the more realistic unit of depression aetio-pathology, with G × E evidence described for a small number of risk polymorphisms. An important complementary approach has been to describe genes exhibiting brain region-specific expression changes in depression. Mouse models of depression informed by the human evidence allow for the study of causality, but to-date have also yielded limited insights into depression aetio-pathology. This review of the translational evidence integrates human and mouse research approaches and evidence. It also makes specific recommendations in terms of how future research in human and mouse should be designed in order to deliver evidence for depression aetio-pathology and thereby to inform the development of novel and improved antidepressant treatments.

Contents

* Corresponding author at: Preclinical Laboratory for Translational Research into Affective Disorders (PLaTRAD), Clinic for Affective Disorders & General Psychiatry, University of Zurich, August Forel-Strasse 7, CH-8008 Zurich, Switzerland. Tel.: +41 44 634 8921; fax: +41 44 634 8829.
E-mail addresses: christopher.pryce@bli.uzh.ch (C.R. Pryce), federica.klaus@bli.uzh.ch (F. Klaus).

0149-7634/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neubiorev.2013.05.003

1. Introduction

Major depressive disorder (hereafter depression) is the most prevalent disease of the central nervous system (CNS) and is one of the ten leading global causes of disease burden (Lopez et al., 2006). In the absence of a definitive understanding of its pathophysiology, depression is diagnosed exclusively on the basis of symptoms, course and outcome. According to the major diagnostic system for psychiatry (APA, 2000), depression constitutes one or both of the core symptoms, depressed mood (sadness, emptiness) and anhedonia (loss of interest or pleasure). The core symptoms must co-occur with at least four of the common symptoms, namely weight loss, insomnia, psychomotor retardation, fatigue, feelings of worthlessness/guilt, diminished ability to think/concentrate, recurrent thoughts of death or suicide, and suicide attempt/plan, for at least two weeks. Therefore, depression is a disease defined by a heterogeneous constellation of symptoms that are quite uninformative relative to the psychological dysfunctions that underlie them. The latter, in turn, are poorly understood in terms of their mediating pathophysiological processes at circuitry, cellular and molecular levels, and there is currently no pathophysiology input to the diagnosis. For the two core symptoms, depressed mood and anhedonia, neuropsychological dysfunction can be attributed, respectively, to hyper-sensitivity of the brain's punishment system and hypo-sensitivity of the brain's reward system (Pryce and Seifritz, 2011). Dysfunctional emotional-cognitive processing of punishing (aversive) stimuli/events is, at least in broad terms, a neuropsychopathology common to both depression and anxiety disorders e.g. generalized anxiety disorder. As would be expected therefore, there is a high prevalence of anxiety disorders in patients diagnosed with depression (APA, 2000).

Given the above situation, then an increased understanding of the genetics of depression is clearly vitally important. At the same time, it needs to be accepted that, given the heterogeneity of the disorder in terms of its diagnostic symptoms and the current absence of a pathophysiology basis to diagnosis, the obtaining of such increased understanding is bound to be extremely challenging. The heritability–liability estimate for depression, based on analysis of its relative concordance in monozygotic versus dizygotic twins, is 30–40%, with the remaining liability (60–70%) attributable to individual-specific environmental factors (Sullivan et al., 2000). Accordingly, aetiological models of depression emphasise the importance of both the genetic and the environmental contributions and indeed their interaction (Duncan and Keller, 2011). Gene–environment interaction (G × E) is itself complex and potentially includes additive, synergistic and protective effects. Furthermore, additional factors including the potential for G × E effects to be developmental-stage specific (Ansorge et al., 2007) and for their mediation by epigenetic mechanisms rather than specific DNA nucleotide sequences (Petronis, 2010), add to the complexity of understanding depression aetiology (see Section 2.6). One important consequence of these various levels of complexity has been the recognition that it will be essential to study aetiology in terms of specific markers or dimensions of depression in addition to – or quite possibly even instead of – its heterogeneous entirety. This will include analysis of the inter-relationships between genes and depression-relevant endophenotypes and between G × E and depression-relevant state markers or intermediate phenotypes, with both of these approaches conducted at the level of cells, neurocircuits and behaviour.

The present review aims to present the case that progress can be made in understanding the genetics of depression by focussing on those genes for which there is robust (e.g. with independent replication) evidence for association with depression and then studying these same genes in valid mouse models of depression. The review sets the scene by summarizing the current status of the evidence for the genetics (i.e. genetic aetiology) of depression[1]. This evidence is presented under the methodological sub-headings: genome-wide association studies, candidate gene case–control studies, gene–environment interaction studies, G × E – state marker and G – endophenotype studies, *post mortem* gene expression studies, and mediating mechanisms. For each gene for which one or more of these methods has provided robust evidence for an association with depression (specifically, with replication in the case of association studies), the current evidence for the impact of this gene in mouse models, is presented. The mouse evidence is presented in sections corresponding to those used to present the human data, with descriptions of the effects of manipulation of the relevant genes on depression-relevant behaviour and of the effects of depression-relevant environmental events on the brain expression of the relevant genes. Fig. 1 illustrates the approach used. This review of the current evidence is followed by a critical assessment of the experimental designs used and the evidence obtained to date. The review concludes with proposals for future experimental designs with the aim of maximizing the potential in mouse models for increasing understanding of

[1] As stated at the outset, here we are deploying the generic term depression to refer to major depressive disorder and are not addressing bipolar disorder.