Soc Psychiatry Psychiatr Epidemiol
DOI 10.1007/s00127-014-0927-8

COMMENTARY

Postnatal risk environments, epigenetics, and psychosis: putting the pieces together

Marija Kundakovic

Received: 4 May 2014 / Accepted: 22 June 2014

Abstract Postnatal environmental factors, such as early life adversity, cannabis use, and social stressors are associated with increased risk for psychotic disorders. Understanding mechanisms that underlie increased psychosis risk is of great importance for the development of novel preventive approaches and early interventions. In a timely review article, Pishva et al. discuss available evidence suggesting that postnatal environmental risk factors contribute to psychotic disorders via epigenetic mechanisms. While the evidence supporting this hypothesis is limited and primarily based on the epigenetic profiling of psychotic patients and animal models, further investigation in this area is warranted and may bring exciting results.

Keywords Postnatal environment · Epigenetics · Psychosis · Schizophrenia · Bipolar disorder

A psychotic disorder, such as schizophrenia or bipolar disorder, develops in an individual as a result of complex interactions of genetic and environmental factors. Many gene loci and genetic polymorphisms have been associated with increased risk for psychotic disorders yet genetic risk per se is not sufficient to induce psychopathology [1]. Adverse prenatal and postnatal environments substantially contribute to psychosis risk in genetically predisposed individuals; risk environments include early life adversity, growing up in an urban environment, cannabis use, and minority group position, among others [1]. The biological embedding of the environmental influence on the brain has started to be revealed and includes epigenetic mechanisms. Epigenetic modifications, such as DNA methylation and histone modifications, regulate gene expression in the developing and the adult brain and are responsive to environmental cues throughout life. Thus, the brain epigenome provides a plausible biological substrate through which the environment can shape brain structure and function over the life course and contribute to mental disorders.

In a timely review article, Pishva et al. [2] discuss available evidence suggesting that postnatal environmental risk factors contribute to psychotic disorders via epigenetic mechanisms. The authors first show the evidence that schizophrenia and bipolar disorders are associated with epigenetic dysregulation. The analyses of samples from psychotic patients have shown global epigenetic differences, changes in the expression of epigenetic machinery (proteins involved in epigenetic regulation) as well as epigenetic changes in specific psychosis-relevant genes, as compared to control subjects [3–5]. It is clear that epigenetic dysfunction can have functional consequences for multiple brain circuits and may contribute to behavioral and cognitive phenotypes associated with psychotic disorders. The authors then discuss the evidence from animal studies (with limited support in humans) showing that postnatal environmental risk factors associated with psychosis risk are able to induce lasting epigenetic changes. Indeed, environmental exposures, such as poor maternal care in early life as well as social defeat and drug use in adulthood have been shown to affect the brain epigenome resulting in lasting changes in gene expression and behavioral phenotypes. Finally, the authors provide an

Submitted as an invited commentary on a review paper by Pishva et al. (2014) regarding epigenetic mechanisms in psychotic disorders, in the journal *Social Psychiatry and Psychiatric Epidemiology.*

M. Kundakovic (✉)
Department of Psychology, Columbia University,
1190 Amsterdam Avenue, 406 Schermerhorn Hall, New York, NY 10027, USA
e-mail: mk3242@columbia.edu

Published online: 29 June 2014

integrative model that explains how genetic, epigenetic, and environmental factors may interact throughout life to bring about molecular and structural changes in the brain that result in psychotic disorders.

Although the authors provide strong arguments supporting an epigenetic link between the postnatal environment and later life psychosis, there are significant gaps in our current knowledge that warrant further investigation in this area. First, there is need to provide more direct evidence that an environmental risk factor (e.g. cannabis use) induces functional epigenetic changes in humans that contribute to psychiatric disorder. As the authors suggest, one of the best ways to tackle this question is to follow large, longitudinal birth cohorts and include tissue collection for epigenetic analyses [2, 6]. This approach would allow for the analyses of epigenetic changes over time and would provide the opportunity to relate epigenetic changes to specific environmental exposures as well as to the development of psychotic disorders. Even in this scenario (which, we hope, will be possible in the near future [6]), we encounter some problems. First, epigenetic marks are by definition tissue- and cell type-specific. Therefore, to be able to relate environmentally induced epigenetic changes to a brain disorder, we ideally need brain tissue. Since brain tissue is not accessible in living subjects, we need to focus on peripheral tissues, such as blood, saliva, or buccal cells. Luckily, there are studies showing some correlation between the epigenetic profiles in the brain and blood [7]. However, we need further studies to establish how to use epigenetic findings from peripheral tissues in the context of psychiatric disorders. In particular, combining epigenetic analyses of human postmortem brain tissues with the analyses of blood samples of psychiatric patients and control subjects will be very useful. Animal studies that allow direct correlations between the brain and blood epigenetic profiles within the same individual (and at the same point of time) would be ideal to complement the human data.

In addition, studies in humans are mainly correlational, and although some statistical methods may suggest causal relationships [5], animal studies are still essential to establish the causality between the effects of environmental factors on the epigenome and behavioral phenotypes. Using animal models, we will be able to dissect the effects of different environmental exposures on the brain (and blood) epigenome and link this to psychosis-related phenotypes. Of course, some of the risk factors, such as urban environment and minority group position, represent complex social constructs and are not easy to model in animals. However, those complex factors may act through mediators that are more accessible in rodent models [1]. For instance, the effect of minority group position on psychosis risk is not related to migration or any particular ethnicity; it is mediated by a chronic experience of an inferior position in the society. This experience can be successfully modeled in rodents using the "social defeat" paradigm [8]. Further dissecting of the risk factors that contribute to psychosis in humans will also lead to the development of better animal models and translational strategies to study these phenomena. Certainly, modeling of psychotic features in animals has also been very difficult. A more recent approach involves the use of several models (rather than one) that model different endophenotypes of schizophrenia or bipolar disorder, and this may be very useful in an effort to associate environmentally induced epigenetic changes to the development of psychotic disorders in humans.

In summary, there is limited, primarily indirect evidence suggesting that epigenetic mechanisms underlie the influence of postnatal environmental risk factors on psychosis risk. While substantial experimental evidence is still lacking, this field is very exciting and holds great promise for the development of novel preventive approaches and early interventions in psychiatry. Therefore, a global research effort combining well-designed human and animal studies with comprehensive epigenetic analyses of peripheral and brain tissues over time will likely prove to be very rewarding.

Conflict of interest There is no conflict of interest.

References

1. van Os J, Kenis G, Rutten BP (2010) The environment and schizophrenia. Nature 468(7321):203–212
2. Pishva E, Kenis G, van den Hove D, Lesch KP, Boks MP, van Os J et al (2014) The epigenome and postnatal environmental influences in psychotic disorders. Soc Psychiatry Psychiatr Epidemiol 49(3):337–348
3. Akbarian S (2010) Epigenetics of schizophrenia. Curr Topics Behav Neurosci 4:611–628
4. Grayson DR, Chen Y, Dong E, Kundakovic M, Guidotti A (2009) From trans-methylation to cytosine methylation: evolution of the methylation hypothesis of schizophrenia. Epigenetics 4(3):144–149
5. Kirkbride JB, Susser E, Kundakovic M, Kresovich JK, Davey-Smith G, Relton CL (2012) Prenatal nutrition, epigenetics and schizophrenia risk: can we test causal effects? Epigenomics 4:303–315
6. Mill J, Heijmans BT (2013) From promises to practical strategies in epigenetic epidemiology. Nat Rev Genet 14(8):585–594
7. Davies MN, Volta M, Pidsley R, Lunnon K, Dixit A, Lovestone S et al (2012) Functional annotation of the human brain methylome identifies tissue-specific epigenetic variation across brain and blood. Genome Biol 13(6):R43
8. Nestler EJ, Hyman SE (2010) Animal models of neuropsychiatric disorders. Nat Neurosci 13(10):1161–1169