British Journal of Pharmacology (2008) 155, 795–796

0007–1188/08 $32.00
www.brjpharmacol.org

COMMENTARY

Epigenetic biomarkers in psychiatric disorders

J Peedicayil

Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, India

The discovery of biomarkers in psychiatric disorders may help in the diagnosis, prevention and treatment of patients with these disorders. Here, I discuss the potential role of epigenetic biomarkers, that is, epigenetically altered genes and/or expression patterns of proteins or metabolites, in psychiatric disorders. Before epigenetic biomarkers can be clinically applied in these disorders, several issues need to be addressed. These include establishing a connection between biomarkers and the disease process; determining the predictive quality of the biomarkers; determining the effects of disease heterogeneity on the biomarkers; and identifying sample sources for the biomarkers that are easily accessible for testing.
British Journal of Pharmacology (2008) **155,** 795–796; doi:10.1038/bjp.2008.254; published online 23 June 2008

Keywords: biomarker; epigenetic; psychiatric disorder

Abbreviation: VLDLR, very-low-density lipoprotein receptor

Schwarz and Bahn (2008) in their recent review article in the *British Journal of Pharmacology* discuss the utility of biomarkers in psychiatric disorders. As they mention, although several molecular and structural abnormalities have been reported in psychiatric disorders, no diagnostic test or other application of clinical use has yet emerged. The authors emphasized that only the knowledge of disease mechanisms will facilitate the discovery of biomarkers that will help objective diagnosis, allow the identification of at-risk individuals, predict treatment success and revolutionize drug discovery approaches. They recommended a multi-omics approach for disentangling the complex nature of psychiatric disorders making use of transcriptomics, proteomics and metabolomics.

In this context, I will discuss the relevance of another 'omic' approach, not mentioned by the authors in their article, which may in the future provide useful biomarkers of clinical relevance to psychiatric disorders, that is epigenomics. Epigenomics is a new research area related to epigenetics, the study of heritable changes in gene expression not coded in the DNA sequence itself. Epigenetics involves three interacting molecular mechanisms as follows: DNA methylation, modifications of histones and RNA-mediated gene silencing (Peedicayil, 2007). Epigenomics is the description of these mechanisms across the genome.

There is increasing evidence that epigenetic mechanisms play a major role in the pathogenesis of psychiatric disorders (Peedicayil, 2007). For example, when large doses of the amino acid L-methionine are administered orally to patients with schizophrenia, there can be marked behavioural changes, especially when monoamine oxidase inhibitors are concurrently administered. This phenomenon is one of the bases for the postulation of the methylation hypothesis for the psychoses and is thought to be due to the methylation of DNA in genes in the brain (Peedicayil and Subbanna, 2007). Although this phenomenon may lack sufficient sensitivity and specificity to be used as a diagnostic test for schizophrenia, it is thought to be a viable lead in understanding the metabolic abnormality in this disorder (Peedicayil and Subbanna, 2007).

The study of epigenetic abnormalities in patients with psychiatric disorders is an active area of research. Several lines of evidence obtained from such research suggest that the *RELN* gene, encoding reelin, is epigenetically modified in patients with psychosis, resulting in decreased expression of reelin (Peedicayil, 2007). Reelin is an extracellular matrix glycoprotein that functions as a serine protease (Fatemi, 2005). It is involved in guiding neurons and radial glial cells to their correct positions in the developing brain and in neurotransmission, memory formation and synaptic plasticity in the adult brain (Fatemi, 2005). It acts on two receptors, the very-low-density lipoprotein receptor (VLDLR) and the apolipoprotein E receptor type 2 (Suzuki *et al* 2008). VLDLR, in addition to being involved in the systemic clearance of very-low-density lipoproteins, also binds and internalizes many extracellular ligands, such as proteases, protease inhibitors, peptide hormones and vitamin carrier proteins (D'Arcangelo *et al.*, 1999). VLDLR and apolipoprotein E receptor type 2 receptor are expressed at relatively high levels in the brain (D'Arcangelo *et al.*, 1999), and the reelin–VLDLR and apolipoprotein E receptor type 2 are expressed at relatively pathway is thought to be downregulated in the brain in patients with schizophrenia (Suzuki *et al.*, 2008).

Correspondence: Dr J Peedicayil, Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, Tamil Nadu 632002, India.
E-mail: jpeedi@cmcvellore.ac.in
Received 18 March 2008; revised 6 May 2008; accepted 30 May 2008; published online 23 June 2008

Recently, it was shown that levels of VLDLR mRNA in peripheral lymphocytes in drug-naive patients with schizophrenia were significantly lower than those of controls, indicating decreased expression of VLDLR in these cells in such patients (Suzuki *et al*., 2008). The authors of this study suggested that peripheral VLDLR mRNA may serve as a reliable biomarker of schizophrenia. Interestingly, Bahn's group had earlier detected higher plasma levels of very-low-density lipoprotein in patients with schizophrenia compared with unaffected subjects, suggesting a decrease in the metabolism/transport of very-low-density lipoprotein in the pathophysiology of this disorder (Tsang *et al*., 2006).

The application of epigenetics for the detection and diagnosis of psychiatric disorders is a new and potentially exciting area of research. The findings obtained, including those on the reelin/VLDLR pathway in schizophrenia, will have to be reproduced on larger sample cohorts to establish a potential connection to the disease process, and in terms of applicability as biomarkers, the predictive quality of the alterations will have to be evaluated. As Schwarz and Bahn (2008) discuss, psychiatric disorders can show marked heterogeneity. Hence, it would be necessary to know how epigenetic changes are affected by disease heterogeneity and other confounding variables, especially in patients with schizophrenia. Epigenetic changes may present a means to bypass difficulties that conventional protein and metabolite markers cannot address.

Another important issue in the discovery of epigenetic biomarkers in psychiatric disorders will be accessibility of samples. For diagnostic applications, epigenetic alterations in the brain would have to be reflected in peripheral body tissues/samples/cells in the form of epigenetically altered genes and/or expression patterns of proteins or metabolites (Maekawa and Watanabe, 2007). It remains to be seen how far epigenetic alterations in the brain translate to these peripheral locations. It is possible that epigenetic alterations, such as DNA methylation and histone modifications involving genes in the brain in psychiatric disorders, may not be reflected in genes in peripheral tissues (Peedicayil, 2007), and a study in humans comparing gene expression in the brain and the blood found the median non-parametric correlation to be about 0.5, suggesting only partial correlation (Sullivan *et al*., 2006). Proteins and metabolites have dynamic properties that are very valuable not only because they may be closely associated to an organism's phenotype, but also because they reflect the influence of environmental factors and allow for monitoring of disease progression. Epigenetic mechanisms are also thought to be dynamically regulated in response to environmental factors (Szyf, 2007).

In the light of the above, one hopes that peripheral analysis of epigenetically altered genes and expression patterns of proteins and metabolites may in the future find use as biomarkers in psychiatric disorders. This development, along with other biomarkers, may improve the care of patients with these disorders.

Conflict of interest

The author states no conflict of interest.

References

D'Arcangelo G, Homayouni R, Keshvara L, Rice DS, Sheldon M, Curran T (1999). Reelin is a ligand for lipoprotein receptors. *Neuron* **24**: 471–479.

Fatemi SH (2005). Reelin glycoprotein: structure, biology and roles in health and disease. *Mol Psychiatry* **10**: 251–257.

Maekawa M, Watanabe Y (2007). Epigenetics: relations to disease and laboratory findings. *Curr Med Chem* **14**: 2642–2653.

Peedicayil J (2007). The role of epigenetics in mental disorders. *Indian J Med Res* **126**: 105–111.

Peedicayil J, Subbanna PK (2007). Revisiting the methylation hypothesis for the psychoses. *Med Hypotheses* **68**: 721.

Schwarz E, Bahn S (2008). The utility of biomarker discovery approaches for the detection of disease mechanisms in psychiatric disorders. *Br J Pharmacol* **153** (Suppl 1): S133–S136.

Sullivan PF, Fan C, Perou CM 2006)). Evaluating the comparability of gene expression in blood and brain. *Am J Med Genet* **141B**: 261–268.

Suzuki K, Nakamura K, Iwata Y, Sekine Y, Kawai M, Sugihara G *et al*. (2008). Decreased expression of reelin receptor VLDLR in peripheral lymphocytes of drug-naive schizophrenic patients. *Schizophr Res* **98**: 148–156.

Szyf M (2007). The dynamic epigenome and its implications in toxicology. *Toxicol Sci* **100**: 7–23.

Tsang TM, Huang JT, Holmes E, Bahn S (2006). Metabolic profiling of plasma from discordant schizophrenia twins: correlation between lipid signals and global functioning in female schizophrenia patients. *J Proteome Res* **5**: 756–760.