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Letter to the Editor

Epigenetic mechanisms and the serotonin 2A receptor in schizophrenia

The decreased expression of the serotonin 2A receptor (HTR2A) and the biological consequence of this changed expression are key questions relating to the role of that receptor in the pathophysiology of the disorder (Dean, 2003); whether that receptor changes in the CNS of subjects with bipolar disorder is less clear (Dean et al., 2003; Lopez-Figueroa et al., 2004; Savitz and Drevets, 2012). Therefore, the recent paper published in this Journal suggesting that genotype, and changes in nucleotide methylation of the HTR2A gene, may be contributing to the altered expression of the gene in the CNS of subjects with schizophrenia and bipolar disorder (Abdolmaleyk et al., 2011) is significant. In the paper, the authors suggest that they have shown strong evidence for epigenetic fine-tuning of HTR2A with i) expression of the receptor being higher in individuals carrying the C allele of T102C (or G allele of −1438A/G polymorphism) compared with those with a TT genotype and ii) that the HTR2A promoter was hypermethylated at and around the −1438A/G polymorphic site and hypomethylated at the T102C polymorphic site in SCZ and BD compared with the controls. From these data, the authors propose that epigenetic dysregulation on or around the HTR2A gene may contribute to the changed expression of the receptor in schizophrenia and bipolar disorder early after the onset of the disease, when these changes in schizophrenia are more demonstrable (Dean, 2013). However, their data also suggests that changes in the gene sequence of HTR2A are also involved in regulating levels of HTR2A in the cortex.

These data are compelling and shed light on the factors that could lead to changes in the early steps in the translation of the HTR2A gene in the CNS of people with schizophrenia. However, it is now well recognised that there are many processes that lead to mismatches between changes in levels of mRNA and changes in levels of the protein encoded by that mRNA (Schwanhausser et al., 2011). Importantly, in most biochemical pathways, it is difficult to postulate a functional change without a change in the protein that drives that function (Nelson and Cox, 2005); this is relevant given recent findings suggesting that processes which can lead to mismatches between changes in levels of mRNA and protein have been shown to be altered in the CNS of people with schizophrenia (Middleton et al., 2002; Vawter et al., 2002; Altar et al., 2005; Beveridge et al., 2010; Boussman et al., 2010; Scar et al., 2013). In considering these factors with regards to the findings of Abdolmaleyk et al. (2011), their data clearly adds to other studies suggesting that levels of cortical HTR2A gene expression are decreased in people with schizophrenia compared with those in controls (Dean, 2003) and adds to the argument that the levels of these receptors are decreased in people with bipolar disorder. However, it is also important to fully challenge the hypothesis that it is both genotype and gene methylation that are the cause of changes in HTR2A levels in the cortex of subjects with schizophrenia. In that respect, it is significant that previous data shows that neither the T102C (Kouzmenko et al., 1997) nor the −1428A/G (Kouzmenko et al., 1999) genotype is associated with the steady state levels of HTR2A in the human cortex or the decrease in the levels of that receptor in subjects with schizophrenia. These latter data may suggest that it is the level of methylation of the DNA at either the −1438A/G or the T102C polymorphic site that is having more effect on the levels of cortical HTR2A protein in the cortex of people with schizophrenia. This hypothesis could have been addressed if measures of HTR2A protein had been presented; as these data were not reported in the paper, the possible relationship between methylation status and receptor levels remains a critical comparison that is required before any relationship between nucleotide methylation and cortical HTR2A can be interpreted as being of any physiological or pathophysiological relevance.

References

Letter to the Editor

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