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Approaches to dissecting mechanisms of adverse drug reactions in psychiatry: clozapine-binding sites in the bone marrow

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The advent of atypical or second-generation antipsychotics has represented a breakthrough in the treatment of schizophrenia. Those drugs, clozapine, risperidone, olanzapine, quetiapine, and ziprasidone, have relatively high serotonin to dopamine binding ratios. It is thought that increased serotonin input can stimulate dopamine activity in mesocortical pathways, and for this reason these drugs may be particularly effective. They are rapidly emerging as first-line treatment for schizophrenia.

Clozapine was the first atypical antipsychotic to hit the market. It has considerable advantages over conventional (typical) neuroleptics: it can work well in patients who are refractory to typical drugs and is effective not only for the positive symptoms of schizophrenia (hallucinations and delusions), but also for the negative symptoms (apathy and social withdrawal), which are not affected by the typical antipsychotics. Yet, the use of clozapine never reached its full potential because of the risk of adverse drug reactions (ADRs). Clozapine can cause life-threatening agranulocytosis in 0.9% of cases. This issue was succinctly described by Naheed and Green¹: 'Clozapine is a dibenzodiazepine derivative and a truly atypical anti-psychotic. Its therapeutic effects are probably mediated by dopaminergic and serotonergic activity. Although it appears to be the most effective antipsychotic drug for treatment-resistant schizophrenia, its general use is limited because of the risk of agranulocytosis.'

Clozapine can also cause metabolic disturbances, such as weight gain, diabetes mellitus, and serum lipid abnormalities.

The work of Pereira *et al.*, in this issue (pages 227–234), is focused on the effects of clozapine on the bone marrow. The authors used RT-PCR methods to detect the expression of a variety of mRNAs encoding various receptor types in human neutrophils, mononuclear, and bone marrow stromal cells. They found no sex differences. A summary of their results is presented in Table 3 in their article. Briefly, dopamine 2 (d2), d4, serotonin 7 (5ht7) receptor mRNA was present in neutrophils, mononuclear and stromal cells, but d3 receptor mRNA was only detectable in mononuclear cells. Mononuclear leukocytes and stromal cells expressed mRNA for 5ht2a receptors, but 5ht3 receptor was only detected in mononuclear cells; 5ht2a and 5ht3 receptor mRNA was absent in neutrophils. h1 (histamine 1) receptor mRNA was not detected in neutrophils but was found in mononuclear and stromal cells. Muscarinic 3 (m3) and m4 receptor mRNA were detected in all cells; m5 mRNA was only detectable in mononuclear cells. All receptors identified in neutrophils were also found in both mononuclear and stromal cells.

This work maps out the effects of clozapine on the expression of various receptor types and subtypes in bone marrow. The identification of potential binding sites can be of value for two reasons. On a biochemical level, it provides avenues of study on the mechanisms by which clozapine can affect bone marrow function. Moreover, these genes will be useful candidates in future pharmacogenomic studies of prediction of ADRs during the course of clozapine treatment. This type of study can bridge pathophysiology and genetics. A missing link in the pharmacogenomics of psychiatric disorders is the paucity of well-accepted pathophysiological pathways that can provide convincing candidate genes. Studies that increase our understanding of the mechanism of action of psychotropic drugs on peripheral tissues (where they act to cause ADRs) can provide us with new candidates for pharmacogenomic studies aimed at using genetic targets to predict, and hopefully reduce, ADRs in psychiatry.

REFERENCES

- 1 Naheed M, Green B. *Curr Med Res Opin* 2001; 17: 223–229.

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