

# Personalized Drug Therapy with Pharmacogenetics Part 2: Pharmacodynamics

Genetic differences among patients are likely to contribute to differences in their response to psychotropic medications, as well as their risk of developing adverse effects (Malhotra, Murphy, & Kennedy, 2004). The term pharmacogenetics refers to the use of molecular genetic approaches to investigate differences in drug response and tolerability. One approach to understanding pharmacogenetic differences is through the study

of pharmacokinetics, which was discussed in last month's Psychopharmacology article (Howland, 2006). The other main approach is through the study of pharmacodynamics (Evans & McLeod, 2003).

## PHARMACOGENETICS AND PHARMACODYNAMICS

When a drug is administered, it is absorbed and distributed to its site of action, where it interacts with its particular target(s),

undergoes metabolism, and is then excreted (Brunton, Lazo, Parker, Buxton, & Blumenthal, 2006). Pharmacodynamics refers to a drug's mechanism of action at its particular target(s), which includes its therapeutic effects and any adverse effects. Psychotropic drug targets typically are various enzymes, transporters, and receptors that regulate the synthesis, transmission, and/or degradation of different chemical neurotransmitters, such as

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serotonin (5HT) and dopamine (DA), in the brain.

The different enzymes, transporters, and receptors found in the brain each exist as a protein that is produced by a different gene. Therefore, for each person, these proteins are genetically determined, contributing to the known inheritance of mental disorders and inherited differences in drug effects (Evans & McLeod, 2003; Malhotra et al., 2004).

Variations in the genetic code for a particular gene are referred to as "genetic polymorphisms." Multiple genetic polymorphisms have been identified for some of the neurotransmitter enzymes, transporters, and receptors of particular interest in clinical psychopharmacology. Genetic polymorphisms may result in alterations of the amount, structure, binding, or function of these proteins, which could affect how drugs operate on them. Pharmacogenetic pharmacodynamics research examines genetic polymorphisms of various drug targets to determine whether they can predict drug therapy response or drug-induced adverse effects.

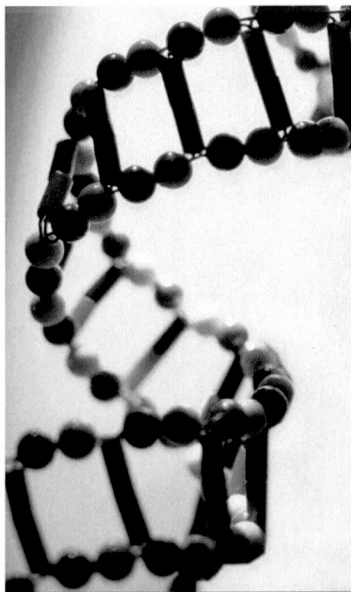
## RECENT STUDIES

### Transporter Proteins

Transporter proteins bind neurotransmitters after they have been released from a neuron (nerve cell) and transport them (before they are degraded) back into the neuron, where the neurotransmitter can be reused or recycled. The 5HT transporter (5HTT), which regulates the reuptake of 5HT into neurons, is the principal site of action of selective serotonin reuptake inhibitor (SSRI) antidepressant agents. The 5HTT is the best-studied transporter system in the brain and one of the most extensively studied drug targets in pharma-

cogenetics research (Serretti, Benedetti, Zanardi, & Smeraldi, 2005).

Multiple genetic polymorphisms of the 5HTT gene have been identified. One particular polymorphism that has been intensively studied is characterized as a "short" or "long" form of the



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5HTT gene. The short form is associated with decreased expression (i.e., decreased amount) of the 5HTT protein. A relatively consistent finding from many studies is that patients with depression who are carrying the short 5HTT polymorphism have a poor response to SSRI antidepressant agents such as fluvox-

amine (Luvox®), fluoxetine (Prozac®), and paroxetine (Paxil®) (Malhotra et al., 2004; Serretti et al., 2004).

Other studies have also found that patients with the short form of the 5HTT gene are more likely to experience adverse effects of SSRI agents. For example, Murphy, Hollander, Rodrigues, Kremer, and Schatzberg (2004) found that the short form was associated with significantly more adverse effects among patients treated with the SSRI paroxetine than among those patients taking the non-SSRI mirtazapine (Remeron®). In addition, a preliminary study by Mundo, Walker, Cate, Macchiardi, and Kennedy (2001) reported that depressed patients with bipolar disorder who had the short form of the 5HTT gene were more likely to develop hypomania or mania during treatment with antidepressant drugs than were those patients who had the long form. The 5HTT is being actively investigated in pharmacogenetics studies of other mood disorder therapies.

### Synthetic Enzymes

Synthetic enzymes regulate the production of different neurotransmitters within various neurons throughout the brain. Tryptophan hydroxylase (TPH) is of particular interest because it is the major enzyme that synthesizes 5HT in the brain (Zhang, Beaulieu, Sotnikova, Gainetdinov, & Caron, 2004), and 5HT plays a key role in mood disorders. Compared to the 5HTT, genetic polymorphisms of TPH have not been as well studied in pharmacogenetics research. Recently, a polymorphism that results in a loss of function of TPH activity was found to be associated with a poor response to SSRI drugs (Zhang et al., 2005).

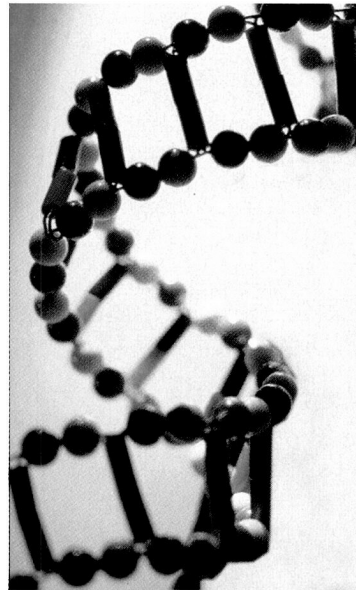
Other studies also found that TPH polymorphisms were associated with poor responses to SSRI drugs (Hassoun, Razi, & Malhotra, 2005; Serretti et al., 2005), although this finding was not replicated in a recent study (Serretti et al., 2004). Given the importance of 5HT regulation in the direct or indirect mechanism of action of many psychotropic drugs, more studies with TPH genetic polymorphisms are warranted.

### Neurotransmitters

Neurotransmitters bind to receptors located on neurons, causing some change in the function or activity of that neuron (e.g., increasing or decreasing its firing rate, stimulating the release of other chemical neurotransmitters). Many different receptor subtypes exist in the brain, and they are classified by their primary binding neurotransmitter (e.g., 5HT or DA), according to a standard nomenclature (Brunton et al., 2006).

The family of 5HT receptors is extensive and the best studied. The most important 5HT receptor subtypes include 5HT-1A, 5HT-2A, and 5HT-2C receptors. They are considered important because they are directly or indirectly relevant to understanding the mechanism of action of some antidepressant drugs, such as mirtazapine and nefazodone (Serzone<sup>®</sup>), as well as the unique clinical effects of atypical antipsychotic drugs, such as clozapine (Clozaril<sup>®</sup>) and risperidone (Risperdal<sup>®</sup>). For example, recent studies have found that some 5HT-2A receptor polymorphisms are associated with a poor response to SSRI antidepressant agents such as fluoxetine (Hassoun et al., 2005; Malhotra et al., 2004; Serretti et al., 2005). Other

studies have found that 5HT-2A receptor polymorphisms are associated with a poor response to the atypical antipsychotic agent clozapine (Malhotra et al., 2004). Some of these 5HT receptor subtypes have also been implicated in the development of adverse effects with antidepressant and an-



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tipsychotic drugs. For example, Murphy et al. (2003) found that a 5HT-2A polymorphism was more likely to be associated with side effects due to paroxetine than to mirtazapine. Finally, 5HT-2C receptor polymorphisms have been recently investigated for their potential role in increasing the risk of weight gain during treatment

with atypical antipsychotic drugs (Hassoun et al., 2005; Malhotra et al., 2004).

The family of DA receptor subtypes that have been identified includes DA-1, DA-2, DA-3, and DA-4 receptors. However, all known antipsychotic drugs bind to the DA-2 receptor subtype, and this may be most important for their antipsychotic efficacy. As a result, most pharmacogenetic studies of antipsychotic drug response have examined DA-2 receptor polymorphisms. These studies have found that certain DA-2 polymorphisms are associated with a poor response to haloperidol (Haldol<sup>®</sup>), risperidone, clozapine, and other antipsychotic agents (Hassoun et al., 2005; Malhotra et al., 2004). In addition, studies have investigated DA receptor polymorphisms and antipsychotic drug-induced adverse effects. For example, some DA-3 receptor polymorphisms have been found to be associated with an increased risk of akathisia and tardive dyskinesia (de Leon, Susce, Pan, Koch, & Wedlund, 2005; Evans & McLeod, 2003; Malhotra et al., 2004).

### CLINICAL APPLICATIONS OF PHARMACOGENETICS AND PHARMACODYNAMICS

Recently, the AmpliChip CYP450 Test (Roche Diagnostics) became commercially available for clinical use in the analysis of genetic polymorphisms in drug-metabolizing enzymes (Jain, 2005). Unfortunately, there are no comparable pharmacogenetic "drug target" tests commercially available. Developing genetic tests for the 5HTT seems to have the most promise. Most pharmacogenetics and pharmacodynamics work has focused on the effi-

cacy and tolerability of currently available antidepressant and antipsychotic drugs, but other studies are investigating drugs used in the treatment of mania, dementia, substance abuse, and attention-deficit/hyperactivity disorder (Evans & McLeod 2003; Hassoun et al., 2005; Malhotra et al., 2004; Nnadi, Goldberg, & Malhotra, 2005).

In addition, the availability of comprehensive genetic information (e.g., from the Human Genome Project) will elucidate the underlying genetic contributions to mental disorders. This information will be used to identify new drug targets, leading to the development of new pharmacogenetically engineered drug therapies. Molecular genetic methods are rapidly improving. It may be possible to collect a single blood sample from a patient, perform an analysis similar to that used in the AmpliChip Test, and test for genetic variations of genes that code for drug transporters, receptors, and other targets. This information can then be used in the rational selection of a drug therapy that is personalized for a particular patient, maximizing the therapeutic benefit and minimizing adverse reactions (Goldstein, 2003).

## CONCLUSION

The field of pharmacogenetics and pharmacodynamics is rapidly expanding and progressing. Future care of patients receiving drug therapy will depend more and more on pharmacogenetic technologies to help in choosing among currently available therapies and in developing new therapies. Understandably, patients and families will have many questions about the use of pharmacogenetic testing in their treatment,

including issues about confidentiality and ethics (Epstein, 2004). Nurses will have an important role in education and, therefore, need to understand these issues.

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