The Neurobiology of Treatment-Resistant Depression

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Treatment-resistant unipolar major depression appears to be the rule rather than the exception. This view is supported by data from the STAR*D program, a multilevel treatment trial for major depression.1 Level 1 treatment was citalopram flexibly dosed from 20 to 60 mg/d (mean dose, 41.8 mg/d) for 12 weeks.1 Even though patients were naive to antidepressant treatment at study entry, only about one third achieved remission, a rate much lower than expected. Subsequent levels tested alternative treatment methods, including switching to another mono-therapy or combination strategies. Monotherapy options at level 2 included sertraline, venlafaxine, bupropion, or cognitive therapy; combinations included citalopram with bupropion, buspirone, or cognitive therapy. At level 3, patients were treated with nortriptyline, mirtazapine, or augmentation with triiodothyronine or lithium. Level 4 treatments included tranylcypromine or venlafaxine plus mirtazapine. Progressively higher proportions of patients remitted; remission was ultimately achieved in about two thirds of patients.2 However, a high proportion of patients eventually relapsed during a 1-year follow-up, representing another kind of treatment resistance. Thus, depression proved to be a difficult-to-treat condition even with multiple treatment options. These data are enlightening in several ways.

- First, it is clear that some people who do not experience remission via actions in 1 chemical system (eg, serotonin) may do so when another system is activated (eg, norepinephrine).
- Second, others seem to require effects on 2 or more systems in order to maximize response. This is consistent with the common practice of adding bupropion to an SSRI.
- Third, treatment resistance is a complex condition in which a treatment may achieve a good initial effect that is lost over time.

Hence, the neurobiology of treatment resistance is likely to involve multiple systems that vary among individuals. Pharmacokinetic causes of treatment resistance

The definition of treatment resistance hinges on the adequacy of both dosage and duration of treatment. To determine that a person has true treatment-resistant depression, a medication should be dosed through its therapeutic range until 1 of 3 outcomes occurs: (1) sustained remission; (2) a dose-limiting adverse effect (leading to a need to switch to an alternative medication); or (3) the maximum recommended dose is reached. Even meeting these criteria, resistance may occur for pure pharmacokinetic reasons. Polymorphic variants of CYP

Polymorphic variants of the genes for cytochrome P-450 (CYP) enzymes can yield widely varying plasma levels. The simplest of these effects are polymorphisms that lead to reduced activity of an enzyme such as CYP2D6 or CYP3A4. This can be associated with a much higher than expected plasma level of a given antidepressant drug, leading to unexplained sensitivity to adverse effects of 1 or more medications.3 This, in turn, may explain apparent treatment resistance that is related to adverse effects. Alternatively, some people are rapid or ultrarapid metabolizers via CYP enzymes. This is a result of a polymorphic variant of a CYP enzyme that yields increased activity or, in the case of CYP2D6, actual duplication of the alleles coding for this protein.4 Currently, there is an AmpliChip test available for both CYP2D6 and 2C19, both of which are involved in the metabolism of multiple antidepressant medications. (Information on the AmpliChip test is available at http://www.amplichip.us/?gclid=CMLxjIXW0o0CFQWSQAodcmCiaA; accessed July 5, 2007.) The multidrug-resistance gene

Another factor that may influence the effects of psychotropic drugs is p-glycoprotein (P-gp), also
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Depression appears to occur, in part, because of a failure of these regions to exert their normal effects, which may be responsible for incomplete response to antidepressants or loss of effect at a later time. Alternatively, certain drugs appear to inhibit the activity of P-gp, which would be expected to increase brain concentrations.

Inhibition of P-gp by antidepressants may exert inhibitory effects on hypothalamic-pituitary-adrenal (HPA) axis activity by decreasing glucocorticoid efflux. It has been proposed that reduced glucocorticoid efflux is associated with increased glucocorticoid receptor (GR) expression, which exerts inhibitory effects on HPA activation. Mouse knockout studies of P-gp have shown that intact P-gp is required for the actions of desipramine on GR expression. Hence, the relationship between polymorphisms of P-gp and the activity of antidepressant drugs is complex.

Other genetic polymorphisms

Polymorphic variants of other genes may also be associated with antidepressant drug response. For example, both coding and noncoding single nucleotide polymorphisms (SNPs) of the serotonin 2A gene (HTR2A) have been shown to be associated with reduced response to SSRIs. The largest of these studies was conducted by McMahon and colleagues using the STAR*D cohort. The study population comprised nearly 2000 patients who were divided between test and replication sets. A total of 768 SNPs from 68 genes were genotyped (a smaller subset were also characterized for polymorphic variants of HTR2A alone). The results showed a robust and reproducible association between response to citalopram and an SNP in intron 2 of the HTR2A gene. Whether this SNP specifically reduces the effect of citalopram, or whether it is in linkage disequilibrium with another SNP is unknown.

Other genetic variants have been found to be associated with antidepressant response, although the results have been variable. These have included SNPs of the genes for brain-derived neurotrophic factor (BDNF), the norepinephrine transporter, tryptophan hydroxylase 2, corticotrophin releasing hormone receptor 1, the glucocorticoid receptor, and the common promoter polymorphism of the serotonin transporter gene, among others. However, positive results have been in small-scale trials that have not been replicated; consequently, this area remains ambiguous.

Neuroanatomy and treatment response

Mood is regulated through a distributed network of brain areas, which involves functional connectivity between structures, such as the amygdala, anterior/subgenual cingulate, nucleus accumbens, hippocampus, thalamus, hypothalamus, and frontal cortex. These pathways are regulated by the 3 major monoamine neurotransmitters affected by antidepressants: serotonin (from the raphe nucleus), norepinephrine (from locus caeruleus), and dopamine (primarily from the ventral tegmental area). The functional connections between these structures mediate the experience of emotions. This complex interplay in brain regions is effective in regulating response to the external and internal environment. This is particularly true of conflicting choices, eg, approach versus avoidance of rewarding cues, or fight versus flight from threatening ones. However, it is also clear that these systems are prone to dysregulation, resulting in mood and anxiety disorders.

Antidepressants exert their effects via modulation of regulatory pathways involving norepinephrine, serotonin, and, indirectly, dopamine. Moreover, they have both rapid and sustained actions. The effect of SSRIs is largely suppressive to the actions of structures such as the locus caeruleus and amygdala, which may account for the global effect of these drugs on anxious symptoms related to anxiety and depressive disorders. However, antidepressants also exert longer-range effects by stimulating the synthesis of certain proteins such as BDNF, which may account for neuroplastic actions.

Because the effects are mediated in a complex way, they appear to be susceptible to failure, both acutely and chronically. Disruptions in the serotonin system, eg, may prevent SSRIs from exerting their typical effects. Alternatively, if BDNF is required for long-term "remodeling" effects in the brain, abnormalities of this protein or its receptor trkB, or an array of other factors that regulate its effect, may be responsible for incomplete response to antidepressants or loss of effect at a later time.

The frontal cortex and anterior cingulate have clear modulatory roles in the experience of emotion. Depression appears to occur, in part, because of a failure of these regions to exert their normal suppressive effects on limbic structures such as the amygdala. Depressive states appear to be
related to overactivity of more basal structures including the amygdala and to reduced activity of the frontal regions.\textsuperscript{32} Successful treatment appears to return these systems to their normal state. However, different types of treatment may produce their effects via different mechanisms. For example, one study examined the neural effects of cognitive-behavioral therapy (CBT) and the serotonin-norepinephrine reuptake inhibitor venlafaxine in patients with depression using positron emission tomography.\textsuperscript{33} Both treatments decreased glucose metabolism in the orbitofrontal cortex bilaterally and left medial prefrontal cortex and increased metabolism in the right occipital-temporal cortex. Venlafaxine enhanced the activity of specific regions that were reduced by CBT, which include the cingulate, thalamus, and insula. The opposite effect (up with CBT and down with venlafaxine) was shown in the inferior temporal cortex. Other studies suggest that antidepressants affect responses to fearful cues via direct effects on subcortical and frontal regions.\textsuperscript{34-36} The differential effects of antidepressants and psychotherapy on brain regional activity may account for why one is effective when the other is not.\textsuperscript{37,38}

Focal disruption of communication between regions may be effective in reducing depressive symptoms when neither medication nor psychotherapy is successful. This is the putative basis of the effects of deep brain stimulation or psychosurgery on the perception of emotion.\textsuperscript{39} In a preliminary study, Mayberg and colleagues\textsuperscript{39} showed that stimulation of the subgenual anterior cingulate reduced depressive symptoms in some patients with treatment-resistant depression.

**Conclusion**

Antidepressant treatments commonly fail to produce remission in depression. This reality may result from any of a number of mechanisms. These appear to include polymorphic variants of genes such as the 5HT$_{2A}$ receptor but also from unresponsive connectivity at a neuroanatomical level. Going forward, imaging, genetics, and other methods will dissect the elements of treatment response versus nonresponse and may result in new approaches and more effective matching of treatment to patient.

### References


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