EDITORIAL

New Directions in Psychiatric Therapeutics

There are three time-honored domains of psychiatric therapeutics: talk therapy, drug therapy, and electricity therapy. It is doubtful that any of the specific treatments within these domains address the basic causes of any psychiatric disorder. Indeed, all currently available treatments for psychiatric disorders are derivatives in one form or another of serendipitous discoveries, usually from therapeutic efforts in other areas of medicine. Many of the popular biologic theories about the origins of psychiatric illness evolved from pharmacological studies of the mechanisms of action of available psychiatric therapies. Thus, the biogenic amine hypotheses of depression followed elucidation of the aminomimetic properties of antidepressant drugs. The dopamine hypothesis of schizophrenia was based primarily on the antidopaminergic properties of antipsychotic drugs. Given the fact that psychiatric drugs were not developed based on fundamental knowledge about disease pathogenesis, it is not surprising that these various theories, like the drugs that they were based on, have proved inadequate.

The landscape for the next generation in psychiatric therapeutics is changing rapidly. Two developments in the basic science of psychiatry are leading to dramatic insights about pathogenesis of illness and fundamental mechanisms of causation. The first is the demonstration at the cellular and neural systems level of neuroplasticity related to stress and to learning and memory, in terms of altered signal processing, synaptic architecture, and neuronal connectivity. This has changed how psychiatric researchers think, from traditional static models of too few or too many receptors or transporters, to dynamic concepts of long-term cellular adaptations to changes in the extracellular milieu. Thus, physiologic and psychologic stress leads to a complex pattern of molecular and synaptic modifications in critical brain circuitries related to processing of emotions and cognition with potentially long-term implications for behavior and pharmacology. Drugs can be conceived as molecular switches that target specific nodes in the pathways mediating relevant neuroplasticity events. In all areas of psychiatry, adverse environmental experience, especially during development when plasticity is least constrained, and the result-

ing molecular ramifications are being viewed as fundamental to understanding the pathogenesis of psychiatric disorders.

The second breakthrough comes from the success of psychiatric genetics in identifying genes that likely represent valid susceptibility factors for major mental disorders. There appear now to be at least five and maybe 10 genes implicated as causative factors for schizophrenia (Harrison and Weinberger),¹ and probably three or four genes implicated in affective disorders. This is a stunning development because genes represent basic mechanisms of disease, may ultimately lead to modifications in diagnosis away from pure phenomenology, and identify molecular pathways that may contain druggable targets. Indeed, in the context of the search for genes for common complex medical disorders such as hypertension, obesity, and diabetes, it could be argued that the search in psychiatry, although clearly operating on a much smaller financial scale than other areas of medicine, has been the most successful discovery effort of all in complex medical genetics.

Genes will profoundly change psychiatry, ultimately impacting on psychiatry in more fundamental ways than in any other field of medicine. This is because the basic biology and pathogenesis of psychiatric disorders is especially obscure; there are no pathognomonic or diagnostic pathologies, and no objective biologic signs. The field is based on clinical phenomenology, and genes will change this forever. Moreover, genes also tell us what psychiatric disorders are at a basic cellular level. Of the genes so far implicated in schizophrenia (Harrison and Weinberger),¹ only two relate directly to popular theories of abnormal neurotransmitter function: COMT implicates dopamine directly, and GRM3 implicates glutamate directly. All the others involve more fundamental molecular processes of neural development and plasticity. Although the path from genetic discovery to molecular pathogenesis to novel drug target identification is difficult and uncertain, it is concrete and objective, which is a sea change in the therapeutic approach to psychiatric disorders.

A striking illustration of how genes, developmental neuroplasticity, and adverse environmental experience interact in the pathogenesis of a psychiatric disorder and its treatment is the story of the gene that encodes the serotonin transporter protein (*SLC6A4*). A common variant in the promoter region of the gene has been identified

Address correspondence and reprint requests to Daniel R. Weinberger, M.D., Genes, Cognition and Psychosis Program, IRP, NIMH, National Institutes of Health, Room 4S-235, 10 Center Drive, Bethesda, MD 20892.

that affects expression of the transporter (5HTTLPR), such that so-called “s” alleles have less expression and activity than “l” alleles. Although there are other variants in this gene that also affect serotonin transporter (SERT) function and probably modify the impact of the 5HTTLPR variant, the story of the associations of the 5HTTLPR variant is illustrative. The HTTLPR gene has been studied very extensively in clinical association with various psychiatric phenotypes, such as depression and related temperamental traits, with mixed results at best (Glatt and Freimer).² The picture changed suddenly with the demonstration using functional magnetic resonance imaging in normal individuals that the s allele was strongly associated with the response of the human amygdala to environmental stimuli that represent potential danger or threat (Hariri et al.).³ This suggests that although the gene might be only weakly related to a clinical phenotype that is difficult to quantify and reliably characterize, it is relatively strongly related to an objective, quantifiable biologic response that might underlie the clinical phenomenology. This finding has been replicated now by several other groups. A large epidemiologic study in New Zealand took this a step further and showed that the s allele, although not itself associated with depression, was associated with risk for depression in the context of adverse environmental events, especially if they occurred early in life (Caspi et al.).⁴ These results, which also have been replicated by several other groups, argue that a genetic variation in serotonin signaling biases during brain development toward neuroplastic changes in critical emotion processing systems that increase the probability of a depression emerging in the context of experiential stress during adult life.

Basic neuroscience experiments have shown that the response of the amygdala to environmental threat is critically regulated by cortical inputs, especially from medial prefrontal and cingulate cortices, which account for extinction of amygdala activation and fear behaviors. Subsequent neuroimaging studies of the 5HTTLPR variant showed that the amygdala over response was related to abnormal development and function of this critical circuitry involving the amygdala and its connections with prefrontal and cingulate cortices (Heinz et al.; Pezawas et al.).^{5,6} Serotonin appears to be critical for the shaping of connections between the amygdala and the rostral cingulate and early developmental changes in this wiring are linked to early serotonin signaling. Indeed, experiments in animals confirm that both pharmacologic and genetic alterations in early serotonin signaling imprint a lifetime of anxiety phenotypes (Ansorge et al.; Gross and Hen).^{7,8} Finally, the s allele of 5HTTLPR also impacts on the response to selective serotonin reuptake inhibitors (SSRIs), presumably because the molecular adaptations to a lifetime of genetic variants in SERT signaling have

changed the response characteristics of serotonin synapses. The broad implications of this work for understanding the genetic, environmental, and molecular complexity of psychiatric disorders and their treatment is the impetus for this issue of *NeuroRx*.

This issue of *NeuroRx* contains a collection of papers from leaders in areas of neuroplasticity and neurogenetics related to the search for new strategies in psychiatric therapeutics. The papers deal with several emerging areas: 1) new treatments for mood and anxiety disorders based on an elaboration of the neural circuitries and cellular molecular cascades implicated in these disorders; 2) a sophisticated revision of our understanding of how antipsychotic drugs work, based again on a clarification of the neural circuitries implicated in psychosis and on the cellular effects of dopamine within these circuitries; 3) targeting of cognition in psychiatric disorders because of compelling evidence that cognition dysfunction is a reliable predictor of treatment outcome and long-term disability, with new strategies for improving cortical, especially prefrontal function; and 4) using genetic information to guide treatment, the emerging field of pharmacogenetics in psychiatry. It should be obvious to the reader that the molecular and systems neuroscience of psychiatry has undergone a dramatic revision and has become scientifically sophisticated. Although these papers represent only the first steps in a long path to the next generation of therapeutics, the race is on.

Daniel R. Weinberger

E-mail: daniel.weinberger@mail.nih.gov

Guest Editor

REFERENCES

1. Harrison P, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 10:40–68, 2005.
2. Glatt CE, Freimer NB. Association analysis of candidate genes for neuropsychiatric disease: the perpetual campaign. *Trends Genet* 18:307–312, 2002.
3. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. *Science* 297:400–403, 2002.
4. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301:386–389, 2003.
5. Heinz A, Braus DF, Smolka MN, et al. Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nat Neurosci* 8:20–21, 2005.
6. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz K, Kolachana BS, Egan MF, Mattay VS, Weinberger DR: 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci* 8:828–834, 2005.
7. Ansorge MS, Zhou M, Lira A, Hen R, Gingrich JA. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science* 306:879–881, 2004.
8. Gross C, Hen R. The developmental origins of anxiety. *Nat Rev Neurosci* 5:545–552, 2004.