EDITORIAL

Structural Plasticity: Cause, Result, or Correlate of Depression

The articles in this issue of Biological Psychiatry are derived from oral presentations at a conference, “Depression in the 21st Century: New Insight into Drug Development and Neurobiology,” held February 2–22, 2000 in Dana Point, California. The speakers represented a range of clinical practitioners, pathologists, and preclinical investigators, with strong focus on the neurobiology of mood disorders, as well as a few basic scientists like myself who had a strong interest in the field but little experience with directly relevant models. My comments here reflect a view of biological psychiatry from the perspective of a generalist observing a fast moving field, integrating basic observations in neurobiology with clinically defined problems.

Biological Psychiatry has emerged in parallel with, and as a result of, strong evidence that mood disorders have neurochemical consequences, in addition to the hypothesis that neurochemical alterations are causally related to mood disorders. The appreciation for the neurochemical basis of psychiatric disorders has led to a global hypothesis that a biochemical imbalance of neurotransmitter systems can cause disease. In addition, this hypothesis has led to effective strategies for pharmacologic intervention. Recent advances in molecular biology have led to the investigation of the cellular and molecular mechanism underlying the observed neurochemical imbalance.

More recently, evidence has accumulated supporting the persistence of “structural plasticity” in the adult brain. The plasticity is reflected both in the birth of new cells in the adult brain and in the death of genetically healthy cells in response to the individual’s interaction with the environment. Of converging relevance to mood disorders is the recent observations that lithium has a robust effect on structural plasticity and synaptic interaction could directly contribute to a loss of neurotrophic action and thus cell survival and synaptic efficacy, a truly vicious cycle. Duman et al compellingly and thoroughly summarize the intracellular signaling cascades that may be responsible for these actions, drawing from preclinical and clinical data, much from their own results. Manji et al (2000) present an interesting set of data that take as a starting point the clear mood-stabilizing effects of lithium and valproate. The link between structural changes and these drugs comes from the recent observations that lithium has a robust effect on the expression of Bcl-2, an antiapoptotic protein, as well as neurotrophic activity, by influencing intracellular signaling. These findings provide for clear hypotheses to test for the direct action of the mood stabilizers on structural maintenance and repair. Kaufman et al (2000) take the specific example of child abuse and the subsequent elevated rates of major depression and other psychiatric disorders in adulthood to summarize the more recent evidence for mechanisms that could account for long-term changes in the brain due to early experience. Evidence is...
presented for short changes in several components of the hypothalamic–pituitary–adrenal axis, the monaminergic systems, and the γ-aminobutyric acid system as being potential causes of long structural changes due to early experience. Identification of these systems suggests clear targets for intervention to facilitate recovery from early stress.

Several reviews summarize the recent evidence for structural changes in patients with affective disorders using standard pathologic methods, as well as newly developed imaging techniques. Importantly, Sheline (2000) summarizes her important results showing that with high-resolution three-dimensional magnetic resonance imaging detectable changes are reported in several areas in association with early-onset major depression, with the most consistent changes occurring in the volume of the hippocampus. Though at present the nature of the volume loss is not known, this is critical information. Corroboration of these findings was presented by Rajkowska (2000), who showed that, in postmortem studies, neuronal and glial histopathology related to major depression and bipolar disorder in both the prefrontal cortex and the hippocampal gyrus. The prefrontal cortex changes detected in postmortem tissue are further corroborated by Drevets (2000) with neuroimaging studies using cerebral blood flow that reveal persistent physiologic abnormalities in the orbital and medial prefrontal cortex in patients with mood disorders. New developments in neuroimaging tracers have made it possible to ask very specific questions about the function of specific neurotransmitter systems. In particular, Fujita et al (2000) summarize the recent findings with the new 5-HT2A and 5-HT1A receptor imaging tracers to study serotonin neurotransmission in depressive disorders. Although the results are not fully consistent at present, the variability likely reflects the heterogeneity in what are now considered more homogeneous disorders. The use of imaging techniques to reveal heterogeneity is dramatically demonstrated in the article by Mayberg et al (2000), in which they examine the differences in brain glucose metabolism using 18fluorodeoxyglucose positron emission tomography in hospitalized unipolar depressed patients treated with fluoxetine. They report clear and interesting differences between patients who respond to fluoxetine and those who do not, which appear to be associated with a failure of adaptive neural changes in the nonresponsive group, once again revealing perhaps a physiologic basis for heterogeneity.

Clearly, this is an exciting field of study, and the evidence supporting structural changes in major depression is likely to have significant impact on diagnosis, treatment, and therapy. A clearer understanding of the cellular and molecular mechanisms underlying structural plasticity will be essential for the further rapid and rational development in this field. What seems to be happening is that the clear hypothesis of the importance of structural changes in mood disorders is forcing the development of new methods, particularly in imaging and cell and molecular biology, to test the validity of this hypothesis.

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References


