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CHAPTER 4

CHEMICAL NEUROTRANSMISSION AS THE MEDIATOR OF DISEASE ACTIONS

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Receptors and Enzymes as Mediators of Disease Action in the Central Nervous System

The reader should now know that enzymes make things and receptors make things happen, especially by activating genes. We have already discussed in Chapter 2 that the most powerful way known to change the functioning of a neuron with a drug is to interact at one of its key receptors or to inhibit one of its important enzymes. However, this is only one perspective in psychopharmacology, namely, that enzymes and receptors are the sites of drug action. A second and equally important perspective in psychopharmacology will be developed in this chapter. That perspective is that enzymes and receptors in their various neuronal pathways and circuits can also be the mediators of disease actions.
If receptors and enzymes are so important for explaining the actions of drugs on chemical neurotransmission, it should not be surprising that alterations of these same enzymes and receptors could disrupt brain function. That is, if the normal flow of chemical neurotransmission leads to the healthy growth, development, and implementation of normal brain functions, abnormal neurotransmission could therefore lead to behavioral or motor abnormalities expressed by patients who suffer from psychiatric and neurological disorders. Obviously, different aspects of neurotransmission would hypothetically be disrupted in different brain disorders. Given the vast complexity of chemical neurotransmission, there are certainly a lot of possibilities for sites of abnormally acting receptors and/or enzymes. Since these receptors and enzymes live in different neuronal pathways, when something happens to damage, misdirect, or remove a pathway, the resultant aberrant neurotransmission could be quite disruptive to normal brain functioning.

Psychopharmacology is a science dedicated in part to discovering where molecular lesions exist in the nervous system in order to determine what is wrong with chemical neurotransmission. Knowledge of the molecular problem that leads to abnormal neurotransmission can generate a rationale for developing a drug therapy to correct it, thereby removing the psychiatric and neurological symptoms of the brain disorder. This concept has proved to be quite complex to apply to specific brain disorders. The general nature of investigating the molecular basis of psychiatric disorders will first be discussed in a broad and general manner in this chapter. Later, once the reader is familiar with the general concepts outlined here, these scientific strategies will be applied in the subsequent chapters to many specific psychiatric and neurological disorders.

In particular, this chapter will discuss how diseases of the central nervous system (CNS) are approached by three disciplines: neuroscience, biological psychiatry, and psychopharmacology. We will then show how these three approaches can be applied to learning how modifications in chemical neurotransmission might lead to various brain disorders. Specific concepts that will be explained are the molecular neurobiology and genetics of psychiatric disorders, neuronal plasticity, and excitotoxicity. Also, the reader will learn how CNS disorders may be linked either to no neurotransmission, too much neurotransmission, an imbalance among neurotransmitters, or the wrong rate of neurotransmission.

**Diseases in the Central Nervous System: A Tale of Three Disciplines**

**Neurobiology**

Neurobiology is the study of brain and neuronal functioning, usually emphasizing normal brain functioning in experimental animals rather than in humans (Table 4—1). Obviously, one must first understand normal brain functioning and normal chemical neurotransmission in order to have any chance of detecting, let alone understanding, neurobiological abnormalities that cause psychiatric and neurological disorders. For example, neurobiological investigations have led to the clarification of certain principles of chemical neurotransmission, to the enumeration of specific neurotransmitters, to the discovery of multiple receptor subtypes for each neurotransmitter, to the understanding of the enzymes that synthesize and metabolize the neurotransmitters, and to the unfolding discoveries of how genetic information con-
Limited definition
The study of brain and neuronal functioning

Approach
Studies using experimental animals
Use of drugs to probe neurobiological and molecular regulatory mechanisms

Findings relevant to psychopharmacology
Discovery of neurotransmitters and their enzymes and receptors
Principles of neurotransmission
Genetic and molecular regulation of neuronal functioning
Neurobiological regulation of animal behaviors

trolls this whole process. The discipline of neurobiology uses drugs as tools to interact selectively with enzymes and receptors—and with the DNA and RNA systems that control the synthesis of enzymes and receptors—in order to elucidate their functions in the normal brain. Many of the lessons derived from this approach have already been discussed in the preceding chapters.

Biological Psychiatry

Biological psychiatry, on the other hand, is oriented toward discovering the abnormalities in brain biology associated with the causes or consequences of mental disorders (Table 4—2). Making such discoveries is proving to be very difficult. However, the importance of pursuing the causes of mental disorders is underscored by how frequent these illnesses are in our society and how limited current treatments for them can be. That is, as many as one in five persons may experience a mental illness during their lifetimes, and about 4% of the population has a chronic and severe mental disorder. Furthermore, currently available treatments in psychopharmacology are not strictly "curative" but are merely palliative, reducing symptoms without necessarily offering sustained relief. Better treatments of the future now depend on discovering the causes of mental illness. This is the central goal of biological psychiatry.

This discipline uses the results of neurobiological investigations of normal brain functioning as a basis for the search for the substrate of abnormal brain functioning in psychiatric disorders. Scientists have long suspected that abnormalities in brain enzymes or receptors are major contributors to the causes of mental illness and have been searching for an enzyme or receptor deficiency that could be identified as the cause of specific psychiatric disorders. Some of the earliest tools of biological psychiatry were less elegant than those of basic neurobiology, since practical and ethical considerations limit the manner in which patients and their CNS can be studied, compared with the techniques available for use in laboratories with experimental animals. Such tools available for use in humans include studies of enzymes, receptors, and genes in postmortem brain tissues and in peripheral tissues that can be ethically
Table 4-2. Biological psychiatry

**Limited definition**
The study of abnormalities in brain neurobiology associated with the causes or consequences of mental illnesses

**Approach**
- Studies using patients with psychiatric disorders
- Taking direction from psychopharmacological studies indicating that drugs with known mechanisms of action on receptors or enzymes predictably alter symptoms in a specific psychiatric disorder
- Search for abnormalities in receptors, enzymes, neurotransmitters, genes, or gene products that correlate with the diagnosis of a particular mental illness
- Biochemical measurements using blood, urine, cerebrospinal fluid, peripheral tissues such as platelets or lymphocytes, postmortem brain tissues, or plasma hormones after provoking hormone secretion by drugs
- Measurements of structural abnormalities using CT or MRI brain scans
- Measurements of functional or physiological abnormalities using PET, EEG, evoked potentials, or magnetoencephalography

**Findings relevant to psychopharmacology**
- Few strong biological findings demonstrating lesions in specific psychiatric disorders
- Example: discovery of changes in serotonin receptors and metabolites in depression, schizophrenia, and suicidal behavior
- Search for the genetic basis of specific neurological and psychiatric illnesses

Sampled in living patients, such as blood platelets or lymphocytes, whose enzymes, receptors, and genes are similar or identical to those in brain. Metabolites of neurotransmitters can be studied in cerebrospinal fluid, plasma, and urine. Metabolic rates and cerebral blood flow reflecting neuronal firing patterns, as well as the number and function of several neurotransmitter receptors, can be visualized in living patients by use of positron emission tomography (PET) scans. Receptors for neurotransmitters can also be studied indirectly by using selective drug probes, which cause hormones to be released into the blood that can be measured and therefore serve as a reflection of brain receptor stimulation. Structural brain abnormalities can be detected by computed tomography (CT) and magnetic resonance imaging (MRI). The latter modality can also detect functional changes in brain activity with a technique called functional MRI. Abnormalities in brain electrical activity can be measured with electroencephalography (EEG), evoked potentials, or magnetoencephalography.

Unfortunately, little progress has been made yet in defining the biological causes of mental illnesses by using these approaches. No single reproducible abnormality in any neurotransmitter or in any of its enzymes or receptors has been shown to cause any common psychiatric disorder. Indeed, it is no longer considered likely that one will be found, given the complexity of psychiatric diagnosis and the profound interaction of environmental factors with genetics in psychiatric disorders. More
recently, biological psychiatry has shifted from a strategy of pursuing a single unique biochemical lesion as the cause of each psychiatric disorder to the discovery and enumeration of risk factors that do not cause illness by themselves but contribute to the risk of a psychiatric disorder. This approach is sometimes called complex genetics because it is indeed complicated, as we shall see below.

The potential usefulness of this approach is underscored by findings from genetic studies of mental illnesses. Despite strong evidence from twin studies that genetic susceptibility exists for both bipolar disorder and schizophrenia, no specific gene has been unambiguously identified for the usual forms of any common mental disorder. Thus, it is already clear that the cause of major psychiatric disorders is not going to be a single abnormality in a major genetic locus of DNA, as already proved for Huntington's disease, sickle cell anemia, and cystic fibrosis. Rather, the genetics of major psychiatric disorders are likely to be at best contributors in multiple complex ways to these illnesses, just as is currently suspected for coronary artery disease, diabetes, and hypertension.

Methods to approach the complex genetics of mental illnesses are just evolving and include such techniques as linkage, linkage disequilibrium, and association studies to name a few. Rather than looking for a single major abnormality in DNA as the cause of mental disorders, the idea behind these methods is to identify multiple genes that each make a small contribution to the overall vulnerability to mental illness, perhaps only when other critical genetic vulnerabilities and critical environmental inputs are also present. If this approach does not prove to explain the causes of psychiatric disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), as appears likely, it may unravel the causes of simpler symptom complexes or even variations in personality.

Thus, biological psychiatry no longer deems it likely that any single abnormality in DNA in a psychiatric disorder leads to abnormalities in the synthesis of gene products that are sufficient on their own to cause mental illness. Rather, a whole list of abnormally acting genes and their corresponding gene products, triggered by both inherited and acquired risk factors, are hypothesized to act together or in just the right sequence to cause clusters of symptoms that appear in different psychiatric disorders. No wonder they call this field complex genetics!

Once the complete list of genes and environmental factors that comprise all the vulnerabilities to a psychiatric illness is determined, it will be necessary to understand how all the corresponding gene products participate in the neuronal functioning and especially the chemical neurotransmission that mediate the mental illness. The long-term hope, of course, is that by knowing this, a logical biochemical rationale can be found for reversing these abnormalities with drug therapies. The question of how this could lead to a rational drug therapy to halt, reverse, or compensate for these multiple simultaneous biochemical events leaves us in a complete quandary at present.

It might be possible to pursue treatments based on this knowledge if the abnormal gene products proved to be enzymes or receptors that could be stimulated or blocked by drugs. However, it is not likely to be this simple, as multiple simultaneous drugs acting to compensate for each genetic abnormality that contributes to the disease vulnerability might prove to be necessary. At any rate, the biological psychiatry hunt is on, but treatments based on this approach certainly do not appear to be right around the corner.
Limited definition
The use of drugs to treat symptoms of mental illness
The science of drug discovery, targeting enzymes and receptors

Approach
Studies in patients with psychiatric disorders
Serendipitous clinical observations
In clinical investigations, the use of drugs with known mechanisms of action to provoke biological or behavioral responses that would provide clues where abnormalities in brain functioning may exist in specific psychiatric disorders
In drug discovery, theory-driven targeting of enzymes and receptors hypothesized to regulate symptoms in a psychiatric disorder

Psychopharmacological results
In clinical investigations, the first observation is often a serendipitous discovery of clinical efficacy, after which the biochemical mechanism of action is discovered
In drug discovery, specific enzymes or receptors are first targeted for drug action. The earliest experiments use chemistry to synthesize drugs; experimental animals to test the biochemical, behavioral, and toxic actions of the drugs; and human subjects, both normal volunteers and patients, to test the safety and efficacy of the drugs
Discovery and use of antidepressants, anxiolytics, antipsychotics, and cognitive enhancers as well as drugs of abuse

Psychopharmacology
As mentioned previously, the discipline of psychopharmacology is oriented not only toward discovering new drugs and understanding the actions of drugs on the CNS, but also toward understanding diseases of the CNS by altering them through the use of drugs whose actions are known (Table 4—3). That is, if a drug with a well understood mechanism of action on a receptor or enzyme causes reproducible effects on the symptoms of a patient with a brain disorder, it is likely that those symptoms are also linked to the same receptor that the drug is targeting. Using drugs as tools in this manner can help map which receptors and enzymes are linked to which psychiatric or neurological disorder.

Since drug actions are much better known than disease actions at the present time, the use of drug tools in this manner has so far proved to be the more productive approach to understanding diseases as compared with the biological psychiatry approach of looking for abnormal receptors, enzymes, or genes. Indeed, much of what is known, hypothesized, or theorized about the neurochemical abnormalities of brain disorders is derived from the approach of using drugs as tools.

Therefore, in general, contemporary knowledge of CNS disorders, as will be discussed for specific entities in subsequent chapters, is in fact largely predicated on knowing how drugs act on disease symptoms, and then inferring pathophysiology by knowing how the drugs act. Thus, pathophysiology is inferred rather than proved, since we do not yet know the primary enzyme, receptor, or genetic deficiency in any given psychiatric or neurological disorder.

The discipline of psychopharmacology has therefore been useful, not only in generating empirically successful treatments for CNS disorders, but also in generating
the leading theories and hypotheses about psychiatric disorders. These theories, in fact, direct the biological psychiatry researcher where to look for proof of disease abnormalities. Thus, psychopharmacology is bidirectional in the sense that certain drugs, namely, those that have a known neurochemical mechanism of action and that are also effective in treating brain disorders, help to generate hypotheses about the causes of those brain disorders. The other direction of psychopharmacology is that in the case of a brain disorder with a known or suspected pathophysiology, drugs can be rationally designed to act on a specific receptor or enzyme to correct the known or suspected pathophysiology and thereby treat the disorder.

It would be advantageous for new drug development to proceed from knowledge of pathophysiology to the invention of new therapeutics, but this must await the elucidation of such pathophysiologies, which, as emphasized here, are yet largely unknown. Virtually all effective psychopharmacological drugs that have been discovered to date were found by serendipity (good luck) or by empiricism, that is, by probing disease mechanisms with a drug of known action but no prior proof that such actions would necessarily be therapeutic. Hopefully, a rational route from pathophysiology to drug development will become increasingly available as the molecular causes of such disorders are elucidated in coming years.

A new approach to selecting specific drugs for individual patients called pharmacogenetics is dawning in psychopharmacology. Although in its infancy, pharmacogenetics attempts to match the likelihood of a positive or negative clinical response to a given drug with the specific genetic makeup of the patient. The idea is that knowing the critical genetic information about a patient, not just the psychiatric diagnosis, could lead to a more rational decision as to which drug to prescribe for that patient.

Currently, there is no rational way to predict which antidepressant is more likely than another to work in any depressed patient or which antipsychotic would be best for a given schizophrenic patient. Such selections often are made by trial and error. Perhaps certain genetic characteristics will predict the likelihood of a better therapeutic response or better tolerability of one drug over another. To date, no such genetic factors are yet known that can assist the prescriber in selecting psychotropic drugs for individual patients.

How Synaptic Neurotransmission Mediates Emotional Disorders

Despite a frustrating lack of knowledge of specific pathophysiological mechanisms for various psychiatric disorders, a good deal of progress has been made in our thinking about mechanisms whereby synaptic neurotransmission can mediate disease processes. Discussed below are several general concepts relating to how psychiatric disorders are thought to be associated with modifications in synaptic neurotransmission.

Molecular Neurobiology and Psychiatric Disorders

A modern formulation of psychiatric disorders involves the integration of at least four key elements: (1) genetic vulnerability to the expression of a disease; (2) life event stressors that come that individual's way (divorce, financial problems, etc.); (3) the individual's personality, coping skills, and social support available from others;
Genetic Vulnerability. Geneticists no longer talk about inheriting a mental illness; they talk about inheriting vulnerability to a mental illness. Such vulnerability theoretically arises from a set of abnormally functioning genes, and some of this abnormal functioning is inherited. Since genes control all functions of the neuron, all psychiatric disorders at some level are genetic. However, that does not necessarily mean that all abnormal functions of genes are inherited. Some of the problems of gene function can arise from the person's experiences, from stressors arising in the environment, and from chemicals and toxins outside the brain. Vulnerability factors for psychiatric disorders are as yet poorly understood, multiple in number, and very complicated. Nevertheless, a few important principles of genetic vulnerability have been established.

For instance, if the rate of illness is greater among monozygotic (single-egg) twins than among dizygotic (two-egg) twins, then heredity is an important factor. At least two important examples of this, bipolar illness and schizophrenia, are well documented in psychiatry. The monozygotic twin of a schizophrenic has a 50% chance of having schizophrenia, whereas a dizygotic twin has only about a 15% chance. Similarly, the monozygotic twin of a person with bipolar illness has up to an 80% chance of being bipolar, whereas a dizygotic twin has only about an 8 to 10% chance. Despite this proof of genetic vulnerability, no specific gene has been established for these illnesses because it is now believed that there is no single genetic abnormality within the affected subject's DNA that by itself causes these or any other common psychiatric disorders.

Rather, the current thinking is that multiple sites in DNA within the genome must interact to produce most of the causation of a psychiatric illness. Such genes may act independently, additively, or even synergistically; they may also act at different critical times during brain development. There may be both positive and negative modifier genes, which if present also influence the likelihood that the illness will occur. Thus, unlike Mendelian disorders such as Huntington's disease, in which single genes contribute large effects (e.g., Fig. 4—1), in psychiatric disorders we are looking for many different genes, each of which contributes only a small effect or even no effect unless its effects coincide with the expression of other critical genes (Fig. 4—2). To make things even more complicated, different genes may be abnormal in different families with the same psychiatric illness. This situation is called heterogeneity.

The biochemical expression of vulnerability to a psychiatric disorder occurs when many different genes make many important proteins in the wrong amounts, at the wrong places, or at the wrong times. This in turn causes abnormal structures and functions of neurons. Even when all this happens in a manner to create the maximum amount of risk, there still may not be a psychiatric disorder unless nongenetic factors, especially from the environment, interact in just the right way to convert latent vulnerability into manifest disease. In such a case, only a conspiracy of several genetic and environmental risks produces an emotional disorder. Detection of a single conspirator without rounding up all the coconspirators is inadequate to explain the genetic basis of the disease.
**Life Events and the Two-Hit Hypothesis of Psychiatric Disorders.** One theory that tries to explain this combination of genetic vulnerabilities and environmental factors as the basis of many psychiatric disorders is the "two-hit" hypothesis. That is, in order to manifest an overt psychiatric disorder, one must not only sustain the first hit, namely all the critical genetic vulnerabilities, but one must also sustain a second hit of some type from the environment (Figs. 4—2 through 4—5). Thus, psychiatric disorders are increased in incidence in first-degree relatives of patients with a wide variety of psychiatric disorders but not to an extent that allows one to predict which specific individuals will or will not eventually develop a specific psychiatric disorder.

This supports the concept that one does not inherit the mental disorder per se; one inherits vulnerability factors for the mental disorder (the genetic first hits) (Figs. 4—2 through 4—5). The chance of actually manifesting a psychiatric illness apparently depends not only on whether one inherited all the necessary vulnerability factors but also on numerous other factors (i.e., second hits from nongenetic environmental sources) (Fig. 4—4).

Some mental disorders, such as schizophrenia or bipolar illness, may have a higher chance of being expressed in vulnerable individuals as compared with disorders such as depression, anxiety, or obsessive-compulsive disorder, which may more frequently lie dormant in the vulnerable individual (Fig. 4—5). Thus, genetic endowment gives
three risk factors are inherited and two risk factors come from the environment. In this case, these five factors combine to produce a hypothetical case of schizophrenia in a young adult. Thus, this individual inherited not only an aberrant enzyme (genetic risk factor 1) but also neurons with abnormal neuronal migration in utero (genetic risk factor 2), plus synapses that were incorrectly eliminated in adolescence (genetic risk factor 3). Compounding these inherited abnormalities in the biological functioning of the brain, there are neurodevelopmental problems due to bad parenting (environmental risk factor 4) and neuronal toxicities from ingesting drugs of abuse (environmental risk factor 5). When they are put all together in the right sequence, the result is schizophrenia.

an individual a certain degree of risk for a psychiatric disorder, and certain disorders may have more of a propensity to become manifest than other disorders, but genetic vulnerability alone is not enough to express overt psychiatric illness.

Childhood Development, Personality, Coping Skills, and Social Support as Factors in Psychiatric Illnesses. Several environmental interactions are hypothesized to affect the expression of information present in the genome and therefore may dictate whether a disorder remains only a latent possibility or breaks down into overt psychiatric pathology (Fig. 4—4). These include early life experiences, which cause a person to develop learned patterns of coping that together constitute his or her personality, or in some cases, personality disorder (Figs. 4-3 and 4—4). Also, there are adult life experiences, which an individual encounters from social interaction with the environment, including events commonly called stressful, such as divorce, death of a loved one, financial difficulties, and medical problems (Fig. 4—4).

Personality traits (Fig. 4—3) may themselves be genetically influenced (e.g., impulsivity, shyness) or environmentally determined by early childhood developmental
FIGURE 4 — 3. This figure demonstrates how life events from the environment test the postulated vulnerability genes for a psychiatric illness (in this case, several postulated genes capable of triggering depression if expressed in the critical manner). Life events, sometimes called stressors, challenge the organism, and this manifests itself as a biological demand on the individual's genome. Such stressors are modified by the individual and processed so that the nature of the biological demand may be similarly modified. That is, persons who have developed an adaptive personality with good coping skills and social support may be able to mitigate, blunt, or lessen the biological demand on their genetic code for latent depression. On the other hand, those who have developed an abnormal personality with poor coping skills may actually worsen, accelerate, or even recruit potentially damaging psychosocial stressors to play on the genome. Thus, personality and coping skills are either a filter or a magnifying glass through which psychosocial stressors pass on their journey to test and challenge the genome where a potential psychiatric disorder may or may not be waiting for a chance to be expressed.

experiences. Personality traits generate coping skills, which can either blunt or exacerbate the impact of adult life events on that individual's genome (Fig. 4 — 3). The ability of an individual to buffer stressors or even to grow and prosper when exposed to them versus breaking down into a mental disorder may be the product of which life events occur and how much coping skill and social support exist prior to being layered onto a genome. Also, that genome may be robust or vulnerable, and the particular vulnerability may explain why some people develop depression, others obsessive-compulsive disorder, and still others no disorder at all despite similar life experiences and similar personalities.

The nature of genetic risk may thus be quite different for different psychiatric disorders. Given comparable genetic material and comparable personalities and coping skills, it may be the severity of psychosocial stressors from the environment that determines how often a vulnerable individual develops a mental illness. According
FIGURE 4—4. This figure represents the two-hit hypothesis for psychiatric illnesses with a genetic component. In this hypothesis, inheriting a set of abnormal genetic risks (the first hit shown as the red genes on the black strands of DNA) is not sufficient for manifestation of a psychiatric disorder. One must also sustain just the right second hit from the environment, postulated to be life events such as a bad childhood or divorce or insults from the environment such as a virus or a toxin. Thus, those with just one hit do not develop the disorder, even though they have the identical genetic makeup as those who do develop the psychiatric disorder. What distinguishes those who ultimately develop an illness from those who do not is whether the individual at risk and vulnerable for the illness (i.e., having the red genes of vulnerability to a specific psychiatric disorder) also is exposed to just the right second hit (shown as inputs to the gene) necessary to trigger the abnormal genes into making their abnormal gene products and thereby causing the disease in that individual.

To this model, the more biologically determined disorders, with the more vulnerable genomes, would require only minor stressors for a person develop that mental illness to develop (e.g., schizophrenia in Fig. 4—5). On the other hand, a less vulnerable disorder such as depression might theoretically require moderate stressors to become manifest (Fig. 4—5). Finally, some stressors could be so severe (e.g., rape, combat, witnessing atrocities) that even a normal robust genome might break down to cause a mental disorder (e.g., posttraumatic stress disorder [PTSD] in Fig. 4—5).

Other Environmental Influences on Individuals and Their Genomes. Finally, the environment provides numerous potential biochemical influences on the genome, such as exposure to viruses, toxins, or diseases (Fig. 4—4). These, too, could contribute to the probability that genetic vulnerabilities for a psychiatric illness will become manifest.
Some disorders have a relatively high predisposition for manifestation in a vulnerable individual, whereas others have a relatively low predisposition, as shown in Figure 4—5. Thus, it may take only relatively minor or usual stressors for the set of schizophrenia vulnerability genes of a vulnerable individual to be activated into producing a disease (left panel). On the other hand, since fewer individuals with the postulated genetic potential for depression or bipolar disorder may actually manifest this disorder, it may take at least moderate or more unusual stressors for the vulnerable individual to have his or her set of bipolar disorder vulnerability genes activated into producing a disease (middle panel). Finally, even those with apparently normal DNA, with no known predisposition to any given psychiatric disorder, may decompensate under major and overwhelming stressors (such as rape or combat or natural disasters) to produce a breakdown of cellular functioning through the breakdown of normal DNA to produce yet other psychiatric disorders (right panel). This latter mechanism is one hypothesis for the development of posttraumatic stress disorder (PTSD), for example.

**Neuronal Plasticity and Psychiatric Disorders**

*Neurodevelopmental Disorders.* Neurons and their synapses must develop properly and then be adequately maintained or else a disorder in the functioning of the brain could result. First, the correct neurons must be selected in utero (Fig. 4—6), and then they must migrate to their predesignated locations (Fig. 4—7) for the brain to function properly. Epilepsy and mental retardation are disorders that in part may result from neurons getting lost and migrating to the wrong places during fetal development (Fig. 4—7). Abnormal neuronal migration may even contribute to the causes of schizophrenia and dyslexia.

Failure of neuronal migration could be caused by genes giving the wrong directions. Bad instructions could be inherited and thus be preprogrammed, or they could be acquired in utero, after the mother takes cocaine and alcohol or her uterus sustains radiation for some reason. One mechanism whereby the wrong genetic information or toxins such as drugs or radiation could cause abnormal neuronal selections would be for them to cause a “grim reaper” growth factor to be inappropriately turned on instead of a “bodyguard” growth factor (Fig. 4—6). This could cause the wrong cell to turn on its apoptotic suicide system (see Fig. 1—18). What may be left are puny cells with bad molecular “Velcro” (e.g., cadherins), which therefore cannot crawl along glia/fibers to get where they need to go. Thus, a neuronal migration disorder is begun by improper selection of neurons in the first place.
Neurons are formed in excess prenatally (top panel of neurons). Some are healthy and others may be defective. Normal neurodevelopment chooses the good neurons (left), but in a developmental disorder, some defective neurons may be chosen and thus cause a neurological or psychiatric disorder later in life when that neuron is called on to perform its duties (right panel).

Other neurodevelopmental problems could result from abnormal synaptogenesis. As discussed in Chapter 1, synapses are dynamic and constantly changing, being laid down, maintained, and in some cases removed. Many things influence this process of adding, maintaining, and removing synapses. If the neuron receives the wrong semaphore signal (from neurotrophic semaphorin molecules), it may sail its axonal growth tip into the wrong postsynaptic targets (cf. Figs. 4—8 and 4—9). Since the synapse is the substrate of chemical neurotransmission, information transfer in the brain is vitally dependent on axons innervating the correct targets.

Once innervation is complete, information transfer in the brain continues to be dependent on how the synapse is maintained, including the processes of branching, pruning, growing, or dying of neuronal axons and dendrites (see Chapter 1 and Figs. 1—21 through 1—23, as well as Fig. 4—10). If the process of synaptogenesis is interrupted early in development, the brain may not reach its full potential, as occurs in mental retardation, autism, and as is now hypothesized for schizophrenia (Fig. 4—6).
Neurons are formed in central growth plates (top panel) and then migrate out into the growing brain. If this is done properly (left panel), the neurons are properly aligned to grow, develop, form synapses, and generally function as expected. However, if there is abnormal migration of neurons (right panel), the neurons are not in the correct places, and do not receive the appropriate inputs from incoming axons, and therefore do not function properly. This may result in a neurological or psychiatric disorder.

Drug treatments themselves may not only modify neurotransmission acutely but also could potentially interact with neuronal plasticity. Harnessing the neurochemistry of the brain’s plasticity is an important goal of new drug development. For example, certain growth factors may provoke the neuron to sprout new axonal or dendritic branches and to establish new synaptic connections (see Chapter 1 and Fig. 1—22, as well as Fig. 4—10). If applied early enough in the course of a neurodevelopmental disorder, such treatments might be able to compensate for problems in cell selection, cell migration, or synapse formation. On the other hand, these problems are so anatomically discrete that it is hard to envision how one could program a drug for delivery only at the critical time during neurodevelopment and just at the critical places.
FIGURE 4 — 8. This figure represents the correct wiring of two neurons. During development, the incoming blue axons from all different parts of the brain are appropriately directed to their appropriate target dendrites on the blue neuron. Similarly, the incoming red axons from various regions of the brain are appropriately paired with their correct dendrites on the red neuron.

Neurodegenerative Disorders and Neurotrophic Growth Factors. Not only can psychiatric illness result if synapses are malformed early in life, but brain disorders can also occur if normal healthy synapses are inappropriately interrupted late in life. Thus, the brain may regress from the potential it had realized and result in various types of dementia (Fig. 4—10). A milder form of this may occur in "normal aging," if it
This figure represents simplistically a possible disease mechanism in neurodevelopmental disorders. In this case, the neurons do not fail to develop connections; the neurons also do not die or degenerate. What happens here is that the **synapse formation is misdirected**, resulting in the **wrong wiring**. This could lead to abnormal information transfer, confusing neuronal communications, and the inability of neurons to function, which are postulated to occur in schizophrenia, mental retardation, and other neurodevelopmental disorders. This state of chaos is represented here as a tangle of axons, where red axons inappropriately innervate blue dendrites and blue axons inappropriately pair up with red dendrites. This is in contrast to the organized state represented in Figure 4-8.
FIGURE 4—10. An undeveloped neuron may fail to develop during childhood either because of a developmental disease of some sort or because of the lack of appropriate neuronal or environmental stimulation for proper development (left arrow). In other cases, the undeveloped neuron does develop normally (right arrow), only to lose these gains when an adult-onset degenerative disease strikes it (bottom arrow).
can be considered normal to stop exercising the brain as one gets older. Just as neglect and abuse of other tissues contribute to breakdown of peripheral organ systems as they age, so could the lack of mental exercise lead to "rusty" and irritable synapses in the brain. Fortunately, challenging the brain throughout a lifetime by honing acquired skills and developing new ones may prevent this type of age-associated brain impairment.

Frank brain failure, however, can occur when neurons die and synapses are ruined. Two of the principal final common pathways for neuronal and synaptic destruction are necrosis and apoptosis, as discussed in Chapter 1 (see also Fig. 1 — 18). In neurological disorders, necrotic inflammatory demise of neurons can be triggered if they are poisoned by toxins and infections or hammered by physical trauma, or if their oxygen is choked off during a stroke, for example. More subtle loss of neurons occurs when apoptosis is activated inappropriately after the brain has developed, as may occur in Alzheimer's dementia, frontotemporal dementia, Lewy body dementia, and perhaps schizophrenia. Even if apoptosis can explain how neurons die in these illnesses, it is still a major mystery why they do this. Although neurological illnesses such as Alzheimer's disease and Parkinson's disease are classically considered to be the illnesses typified by neurodegeneration, there are now hints that a subtle form of neurodegeneration may be operative in the progressive course of schizophrenia and in the development of treatment resistance in depression, panic, and other psychiatric illnesses. Neurodegenerative phenomena may also play a role in the apparent "kindling" phenomena of various affective disorders, such as the development of rapid cycling in bipolar disorder, and in the increased risk of recurrence of depression during a shift in reproductive hormones in women who have had an affective episode associated with a previous shift in reproductive hormones.

Exploitation of normal neuronal plasticity to develop new drugs to halt degenerative diseases of the nervous system is only beginning to be investigated. Drugs are not yet available that can reliably turn on and direct the plasticity process. Theoretically, it should become possible to salvage degenerating neurons, to establish new synapses, and to reestablish preexisting synapses. Such possible modifications of degenerative nerve diseases are being pursued in several different ways.

First, the search is on for abnormal genes or abnormal gene products that might be mediating the breakdown of neurons. Once these are identified, it should theoretically be possible to stop the production or block the action of unwanted gene products. It should also be possible to turn on the production or provide a substitute for desirable but absent gene products.

Second, attempts are being made to make neurotrophic factors 'get on your nerves' to rescue degenerating neurons and halt the progression of neurodegenerative disorders (Figs. 4—11 through 4—13). This might be particularly effective if acquired deficiencies in neurotrophic factors were causing previously healthy neurons to degenerate. Hypothetically, the ideal cocktail of molecules could help nourish back to health all sorts of ailing neurons (Figs. 4—12 and 4—13). Applying knowledge of the actions of neurotrophic factors and recognition molecules that help guide sprouting axons might some day increase the odds that dysfunctional neurons in the mature nervous system can be salvaged or even that desirable synaptic connections can be facilitated.

It might in theory be possible to have growth factors get on your nerves by direct delivery of the growth factor if a delivery method could ever be devised. There are
FIGURE 4—11. Shown here is normal communication between two neurons, with the synapse between the red and the blue neuron magnified. Normal neurotransmission from the red to the blue neuron is being mediated here by neurotransmitter binding to postsynaptic receptors by the usual mechanism of synaptic neurotransmission.

numerous problems in using neurotrophic factors as therapeutic agents. Such a large number of neurons are responsive to them that systemic administration may well activate all kinds of axonal sprouts that are not desired. Perhaps high doses or chronic use could stimulate unwanted cell division of neurons or even increase the risk of cancer. Thus, local administration to the desired site of action or site-selective actions
FIGURE 4—12. Shown here and in Figure 4 — 13 is a conceptually more complex mechanism of compensation for the loss of a degenerating neuron. The ailing but not yet degenerated red neuron indicated here is no longer functioning to allow normal neurotransmission with the blue neuron (see box) and is about to die. Also indicated is the application of a growth factor to the degenerating neuron. This could be conceived as either a natural reparative mechanism that the dying neuron could activate (see Fig. 1—22 and Table 1 — 3) or a drug that could mimic this.

of systemically administered neurotrophic factors may be required if treatment is going to be safe.

To complicate the potential utility of growth factors for neurodegenerative disorders is that fact that many growth factors are large protein or peptide molecules,
FIGURE 4—13. This figure demonstrates how a degenerating neuron might be rescued by a growth factor. In this case, the dying neuron of Figure 4—12 is salvaged by a growth factor, which restores the function of neurotransmission to reactivate normal communications between the red neuron and the blue neuron (see box).

which are unable to survive intact when administered orally and unable to cross the blood-brain barrier when administered intravenously. This has led to several different approaches to delivering neurotrophic factors to their desired targets in the CNS.

First, the protein itself can be infused directly into the cerebrospinal fluid or implanted in a biodegradable, slow-release preparation. Second, the active protein can travel across the blood-brain barrier by hiding inside a "Trojan horse" molecule
FIGURE 4—14. Transplantation of a new neuron by neurosurgical techniques is another potential mechanism for replacing the function of a degenerated neuron. In this case, the turquoise transplanted neuron makes the same neurotransmitter as the formerly red neuron made (see Fig. 4—11) prior to degenerating here. Synaptic neurotransmission is restored when the transplanted neuron takes over the lost function of the degenerated neuron (see box). This has already been performed for patients with Parkinson's disease, in which transplanted fetal substantia nigra neurons can successfully improve functional neurotransmission of degenerated substantia nigra neurons in some patients.
that is normally translocated across this blood-brain barrier. Third, low molecular weight chemicals might be able to get into the brain and pharmacologically induce the formation of a trophic factor. This action, in fact, has been suggested for cholinesterase inhibitors, which not only increase acetylcholine levels but subsequently increase nerve growth factor. Finally, a high-tech idea is to transfer genes that produce the trophic factor directly into the brain by grafting cells that normally make it, by genetically engineering cells to make it, or by delivering the gene in a carrier virus. All of these possibilities are under active investigation.

A third long-term therapeutic approach to neurodegenerative disorders is transplantation of neurons. Neuronal transplantation is being investigated as a way to substitute new neurons for degenerated neurons (Fig. 4—14). This is not a Frankenstein-style transplant of an entire brain but rather a selective introduction of specific and highly specialized nerves, which produce specialized chemicals and neurotransmitters capable of compensating for and replacing the functions of the degenerated and destroyed neurons that caused disease in the first place. Transplantation of neurons into human brain is already occurring in Parkinson's disease, where dopamine-producing neurons have been successfully transplanted into the brains of patients with this condition. Experimental use of cholinergic neurons holds promise for the treatment of experimental models of Alzheimer's disease.

From Excitement to Brain Burn: Too Much Excitatory Neurotransmission Could Be Hazardous to Your Health

If Benjamin Franklin said "nothing in excess, including moderation" he may have anticipated contemporary thinking about excitatory neurotransmission. Excitatory neurotransmission with glutamate ranges from talking to neurons (Fig. 4—15), to screaming at them (Fig. 4—16), to strangling their dendrites, and even to assassinating them (Fig. 4—17).

Glutamate normally opens an ion channel so that the nerve can drink calcium (Figs. 4—15 and 4—18). Sipping calcium is exciting to a neuron and a normal reaction when glutamate is speaking pleasantly. However, when glutamate screams at a neuron, the neuron reacts by drinking more calcium (Figs. 4—16 and 4—19). Imbibing too much calcium may lead in part to excitatory symptoms such as panic, seizures, mania, or psychosis (Figs. 4—19 and 4—20). Too much calcium eventually will anger intracellular enzymes, which then generate nasty chemicals called free radicals. A small commune of free radicals can crash the chemical party in the postsynaptic dendrite and strangle it (Fig. 4—21). A mob of free radicals can kill the whole neuron, perhaps by triggering apoptosis (Fig. 4—22; see also Fig. 1—18).

Why would the neuron allow this to happen? It is possible that the brain needs this excitotoxic mechanism so that glutamate can act as a gardener in the brain, pruning worn out branches from dendritic trees so that healthy new sprouts may prosper (Fig. 1—23). However, this also equips the neuron with a powerful weapon, which can potentially be misused to cause various neurodegenerative conditions due literally to pruning neurons to death (Fig. 4—22). Such an excitotoxic mechanism could be activated if the genetic program controlling it is turned on or potentially by ingestion of toxins or toxic drugs of abuse. That is, when glutamate decides to act as an abusive bully for whatever reason, neurons may seize, panic, become manic, or become psychotic (Fig. 4—20). Furthermore, such symptoms of calcium intoxi-
FIGURE 4-15. The calcium ion is a key regulator of neuronal excitability and is constantly entering and leaving neurons through ion channels of various sorts that are conducting the normal business functions of the neuron. When this occurs at a normal rate, it modifies neuronal excitability but is not damaging to the neuron (but see Figs. 4-16 and 4-17).

FIGURE 4-16. Calcium may also rush into cells too quickly if its ion channels are opened too much, as is postulated to occur as a result of certain toxins, by stroke, or by neurodegenerative conditions (see Fig. 4-17).

FIGURE 4-17. If too much calcium gets into the neuron and overwhelms any sinks and buffers there, it can destroy the neuron and cause it to degenerate and die. This mechanism of excessive excitation is called excitotoxicity and is a major current hypothesis of the cause of various psychiatric and neurological disorders. This idea postulates that for such diseases, neurons are literally "excited to death."
FIGURE 4—18. Shown here are details of calcium entering a dendrite of the blue neuron when the red neuron excites it with glutamate during normal excitatory neurotransmission. This was shown in a more simplistic model in Figure 4—15. Glutamate released from the red neuron travels across the synapse, docks into its agonist slot on its receptor, and as ionic gatekeeper, opens the calcium channel to allow calcium to enter the postsynaptic dendrite of the blue neuron to mediate normal excitatory neurotransmission (see box).

cation may be followed by an unfortunate glutamate hangover in the form of destroyed dendrites, which can never be excited again (Fig. 4—21).

Other illnesses such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and even schizophrenia may hire glutamate as a
FIGURE 4—19. Shown here is what may happen when excitatory neurotransmission causes **too much neurotransmission**. This may possibly occur during the production of various symptoms mediated by the brain, including **panic attacks**. It could also occur during mania, positive symptoms of psychosis, seizures, and other neuronally-mediated disease symptoms. In this case, **too much glutamate** is being released by the red neuron, causing **too much excitation** of the postsynaptic blue neuron's dendrite. Extra release of glutamate causes additional occupancy of postsynaptic glutamate receptors, opening more calcium channels and allowing more calcium to enter the blue dendrite (see box). Although this degree of excessive neurotransmission may be associated with psychiatric symptoms, it does not actually damage the neuron (but see Figs. 4—20 and 4—21).
FIGURE 4—20. This figure represents the concept of an **electrical storm** in the brain in which **overexcitation** and **too much neurotransmission** are occurring during the production of various psychiatric symptoms, including those which occur during a panic attack. This may also be a model for other disorders of excessive behavioral symptoms that imply too much neurotransmission, including mania, positive manifestation of psychosis, and seizures.

Methodical undercover assassin, eliminating a whole subpopulation of predesignated neurons over a prolonged period of time. Such a systematic process would be consistent with the pace of these slow neurodegenerative disorders. In catastrophic brain diseases such as stroke and global ischemia associated with cardiac arrest, drowning, etc., a whole army of glutamate "hit men" may be hired as mass murderers. In this case, glutamate causes the massacre of an entire region of brain neurons by suddenly subjecting them to molecular mayhem.

Thus, glutamate's actions can range across a vast spectrum. It can be a friendly neuronal conversationalist or a screaming hypothetical mediator of neurological and psychiatric disorders. How might the symptoms and clinical course of various psychiatric disorders fit this model of excitotoxicity? Psychosis possibly shares some analogies with a seizure, in that excessive transmission of dopamine in the mesolimbic areas of brain may lead to symptoms of delusions, hallucinations, and thought disorder in various psychiatric disorders. Panic disorder may be analogous to a seizure in areas of the brain controlling emotions (such as the parahippocampal gyrus), leading to clinical symptoms characterized by a massive emotional discharge of panic, shortness of breath, chest pain, dizziness, feelings of impending death, or fear of losing control. Thus, disorders such as psychosis, epilepsy and panic disorder appear to involve excessive neurotransmission, which may help explain the mechanism by which they produce acute symptoms (Figs. 4—19 and 4—20).

Furthermore, these disorders seem to become more resistant to treatment the longer the disorder persists and the more poorly the symptoms are controlled, as if there were an underlying mechanism of destruction accompanying symptoms that are out of control (Figs. 4—21 through 4—23). Thus, excessive neurotransmission may itself be a cause of deficient neurotransmission. If seizures beget seizures, panic
FIGURE 4 — 21. If too much neurotransmission occurs for too long, it is hypothetically possible that this would lead to **dendritic death**. The mechanism for this may be tantamount to inappropriately activating the normal dendritic pruning process (indicated schematically as scissors snipping off the dendrite; see Figure 1 — 23 for a diagram of normal pruning). Thus, far too much glutamate release can cause too much opening of the gates of the **calcium** channel, activating an **excitotoxic** demise of the dendrite (see box).
begets panic, psychosis begets psychosis, and mania begets mania, these symptoms are obviously not good for the brain. The psychopharmacologist must therefore act to prevent symptoms, not only because symptom control may harness the disruptive influences of excessive neurotransmission on behavior, but also because symptom control may ultimately prevent the demise of the neurons mediating these very behaviors (Figs. 4—20 to 4—23). If these disorders of excessive neurotransmission are analogous to the brain "burning" during symptomatic crises such as a seizure, psychosis, panic attack, or mania, treatments might not only "put out the fire" but also salvage the underlying neuronal substrates, which are burning as the fuel for the fire.
FIGURE 4—23. Catastrophic overexcitation can theoretically lead to so much calcium flux into a neuron due to dangerous, wide-ranging opening of calcium channels by glutamate (see box) that not only is the dendrite destroyed, but so is the entire neuron. This scenario is one in which the neuron is literally excited to death. The same idea was represented more simplistically in Figure 4—17. Excitotoxicity is a major current hypothesis to explain the mechanism of neuronal death in neurodegenerative disorders, including aspects of schizophrenia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and ischemic cell damage from stroke.
Discovery of antagonists to excitotoxicity, such as exemplified by the glutamate antagonists, may portend the possibility of developing new drug therapies for neurodegenerative disorders. At least two approaches to controlling glutamate are showing promise. The first is to protect the neuron from drinking too much calcium by blocking glutamate receptors directly with antagonists. Thus, neurons are only allowed to quench their thirst in normal excitatory neurotransmission but not to guzzle so much calcium that they become excitotocically inebriated. If such compounds worked, they would be neuroprotective, since they would arrest glutamate before it could assassinate any more neurons. Another approach to developing treatments for illnesses that may be mediated by excitotoxicity is to rescue the cellular machinery once glutamate's cascade of doom has been activated. Thus, free-radical scavengers are being developed that neutralize the troublesome free radicals. Certain chemicals can do this, including vitamin E and experimental agents called lazaroids (so named because they purport to raise neurons from the dead, as the biblical Lazarus was raised).

**No Neurotransmission**

There are a myriad of known and suspected mechanisms by which diseases can modify chemical neurotransmission. These can vary from no transmission, as in the case of a degenerated or absent neuron, to too much neurotransmission from a malfunction of the synapse. One of the key consequences of loss of neurons in neurodegenerative disorders such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and Alzheimer's disease, is the fact that no neurotransmission occurs subsequent to neuronal loss (Fig. 4—24). This is a conceptually simple mechanism of disease action with profound consequences. It is also at least in part the mechanism of other disorders, such as stroke, multiple sclerosis, and virtually any disorder in which neurons are irreversibly damaged.

One of the earliest attempts to compensate for the dropout of neurons and the consequent loss of neurotransmission (Fig. 4—24) was simply to replace the neurotransmitter (Fig. 4—25). Indeed, this can happen in certain conditions such as Parkinson's disease, where loss of the neurotransmitter dopamine can be replaced. Even in this conceptually simple example, however, therapeutic replacement is in fact not so simple. Dopamine given orally or intravenously cannot get into the brain. Its precursor, L-DOPA, can reach the brain and be converted into dopamine. However, even the precursor needs help in practice, since coadministration of an inhibitor of L-dopa destruction is necessary for L-DOPA to work optimally.

**Other Mechanisms of Abnormal Neurotransmission**

Several other mechanisms can be conceptualized. These include the imbalance between two neurotransmitters required to regulate a single process. This has been theorized as the mechanism of many of the movement disorders, in which balance between the two neurotransmitters dopamine and acetylcholine is not normal. Another possible aberrancy is that of the wrong rate of neurotransmission, possibly disrupting functions such as sleep or biorhythms. We have already discussed how degenerative disorders involve loss of neurons and synapses, and the net result of the loss of key synapses is abnormality of the remaining wiring system of the brain.
FIGURE 4—24. This figure illustrates what happens in a conceptually simple disease in which a neuron dies, leaving behind **no neurotransmission**. The loss of the red neuron means that neurotransmission at the former site between the red and the blue neuron is now lost (but see Fig. 4—25).
FIGURE 4—25. One of the simplest pharmacological remedies for replacing the function of the lost neurotransmission from a degenerated neuron is to replace the neurotransmitter with a drug that mimics the former neuron's neurotransmitter. This is shown here with the yellow drug replacing the natural neurotransmitter that was formerly present when the red neuron was present and functioning (Fig. 4—11). This strategy is used, for example, when L-DOPA is used to replace the lost neurotransmission in Parkinson's disease when nigrostriatal dopamine neurons degenerate and die.
Summary

This chapter has reviewed how enzymes and receptors are not only the targets of drug actions but also the sites of disease actions. We have discussed how diseases of the CNS are approached by three disciplines: neurobiology, biological psychiatry, and psychopharmacology. We have also discussed how disease actions in the brain modify neurotransmission by at least eight mechanisms: (1) modifications of molecular neurobiology; (2) loss of neuronal plasticity; (3) excitotoxicity; (4) absence of neurotransmission; (5) excess neurotransmission; (6) an imbalance among neurotransmitters; (7) the wrong rate of neurotransmission; and (8) the wrong neuronal wiring.